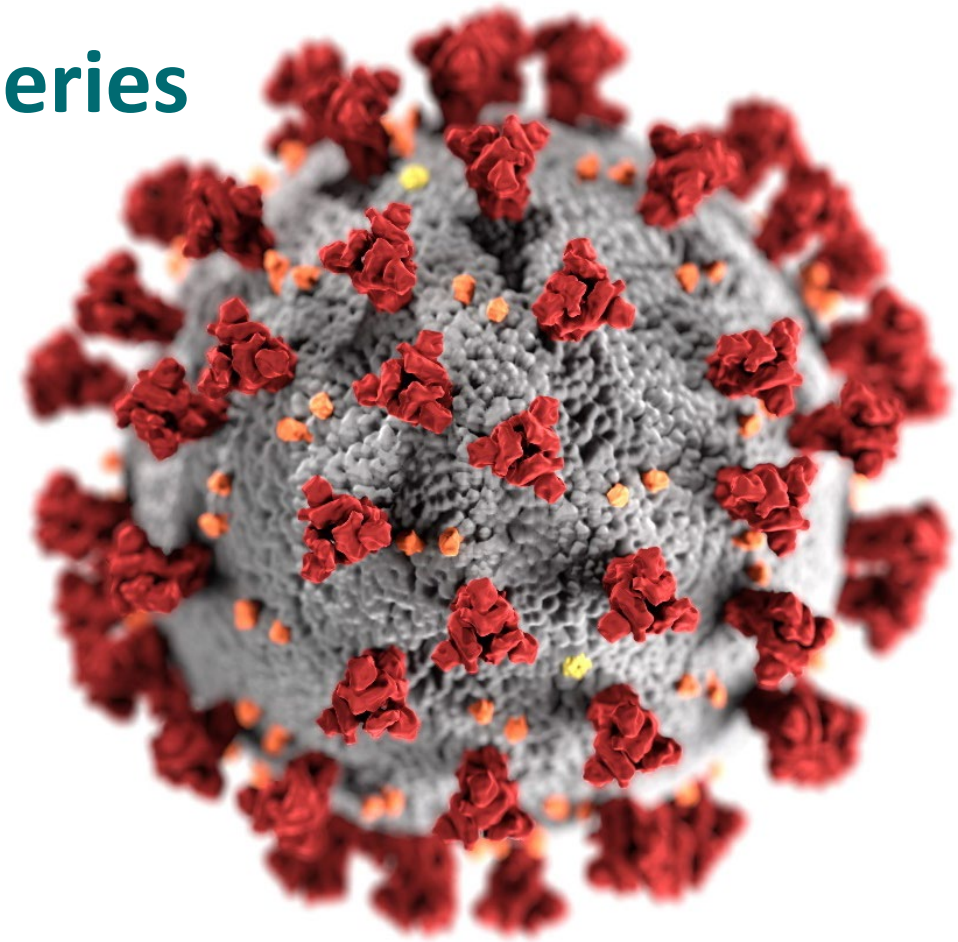
Considerations for Bivalent Primary Series



Sara Oliver, MD, MSPH
ACIP Meeting
February 24, 2023

cdc.gov/coronavirus

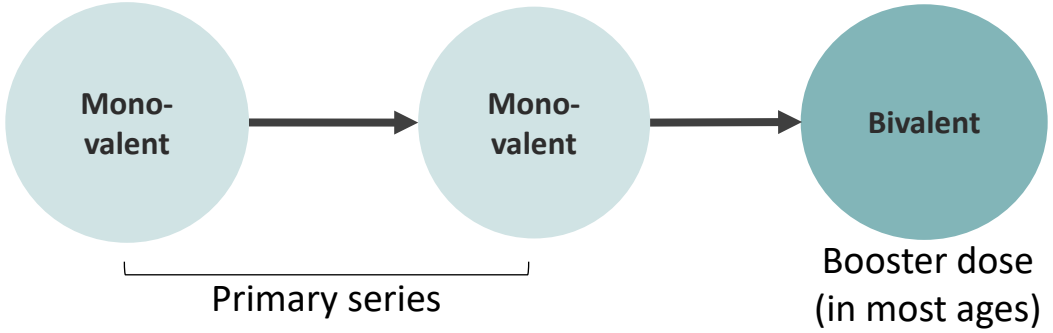
Question for consideration

- Does ACIP support **harmonizing** the vaccine strain composition for mRNA COVID-19 vaccines across both primary series and booster doses:
  Changing the primary series from monovalent (Original) to bivalent (Original plus Omicron BA.4/5) for all ages?

Current recommendations

(Simplified representation)

People ages 6 months and older*

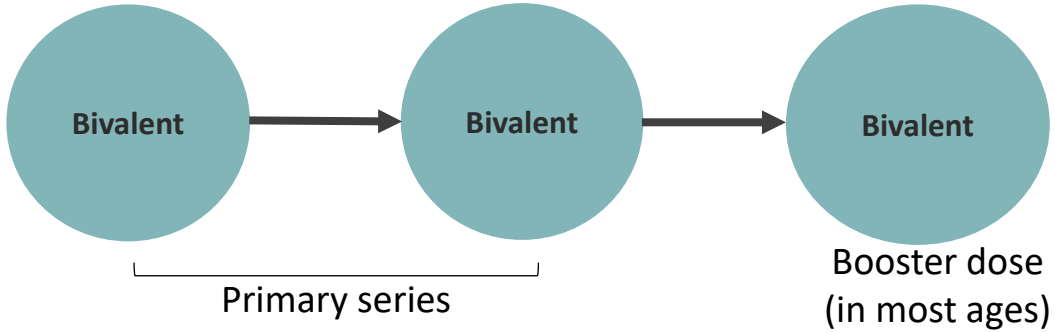


***Ages** and **vaccines** as authorized by FDA and recommended by ACIP/CDC

For children ages 6 months-4 years of age who start a Pfizer-BioNTech primary series, the third dose in a 3-dose primary series is a bivalent dose

Future proposed recommendations

People ages 6 months and older*



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

For children ages 6 months-4 years of age who start a Pfizer-BioNTech primary series, 3-dose primary series still needed

Policy considerations for bivalent primary series

- Policy on bivalent primary series will be coordinated with **FDA** for regulatory action, and **CDC/ACIP** for recommendations for use

Considerations for Bivalent Primary Series

U.S. COVID-19 Vaccination Coverage (%) of Total Population by Age Group — February 8, 2023

Coverage / Age (years)	<2	2-4	5-11	12-17	18-24	24-49	50-64	≥65
At least 1-dose	7.6	10.3	39.7	71.9	81.9	85.2	95.0	95.0
Completed primary series	3.7	5.5	32.6	61.6	66.5	72.0	83.7	94.2
1st monovalent booster*	-	-	3.3	16.6	27.2		45.3	64.6
2nd monovalent booster *	-	-	-	-	-	-	10.6	25.3
Bivalent booster**	0.2	0.3	4.0	7.0	6.7	11.2	20.3	40.8
Unvaccinated	92.4	89.7	60.3	28.1	18.1	14.8	—†	—†

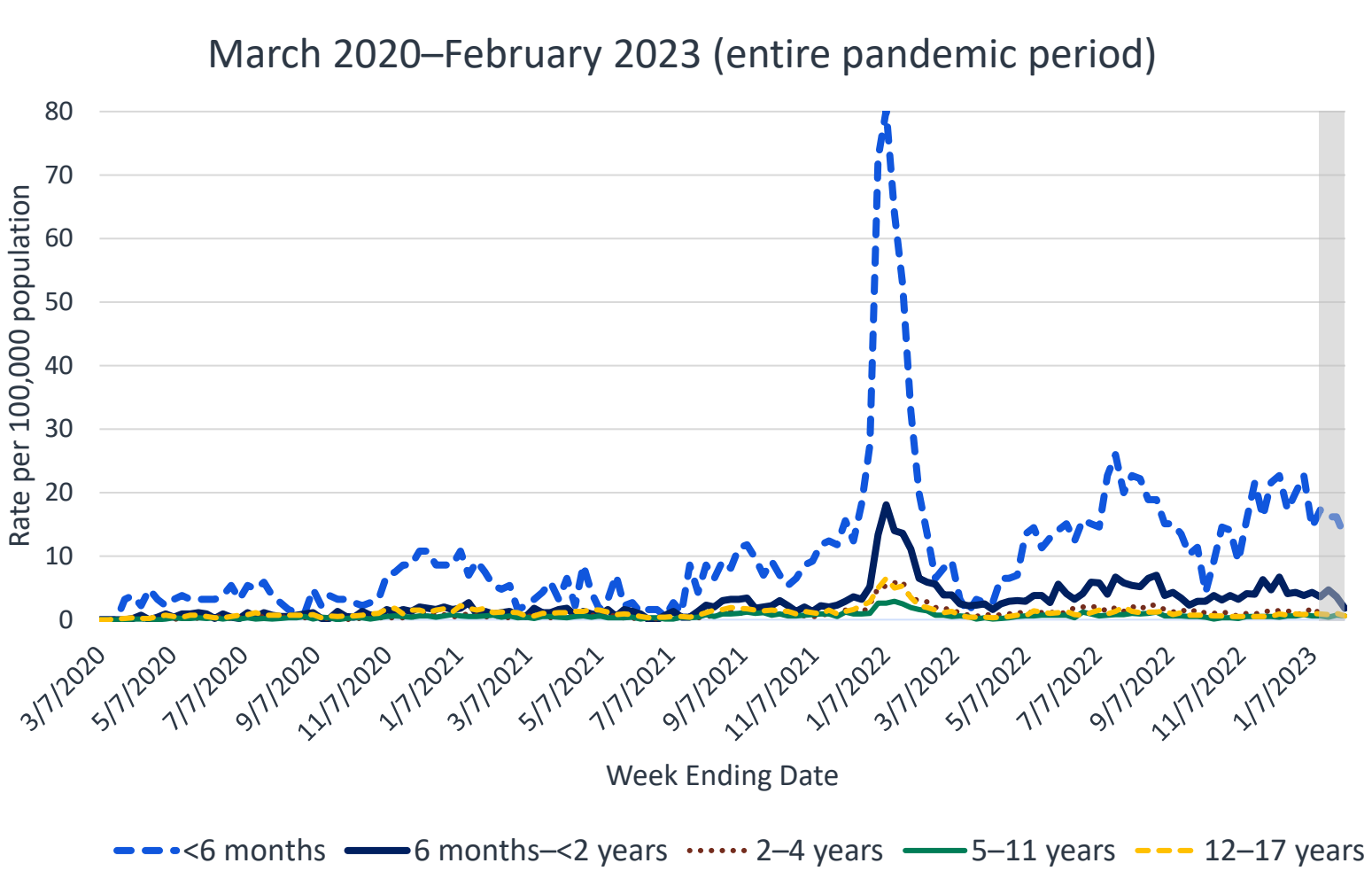
*Monovalent booster dose coverage as of August 26, 2022

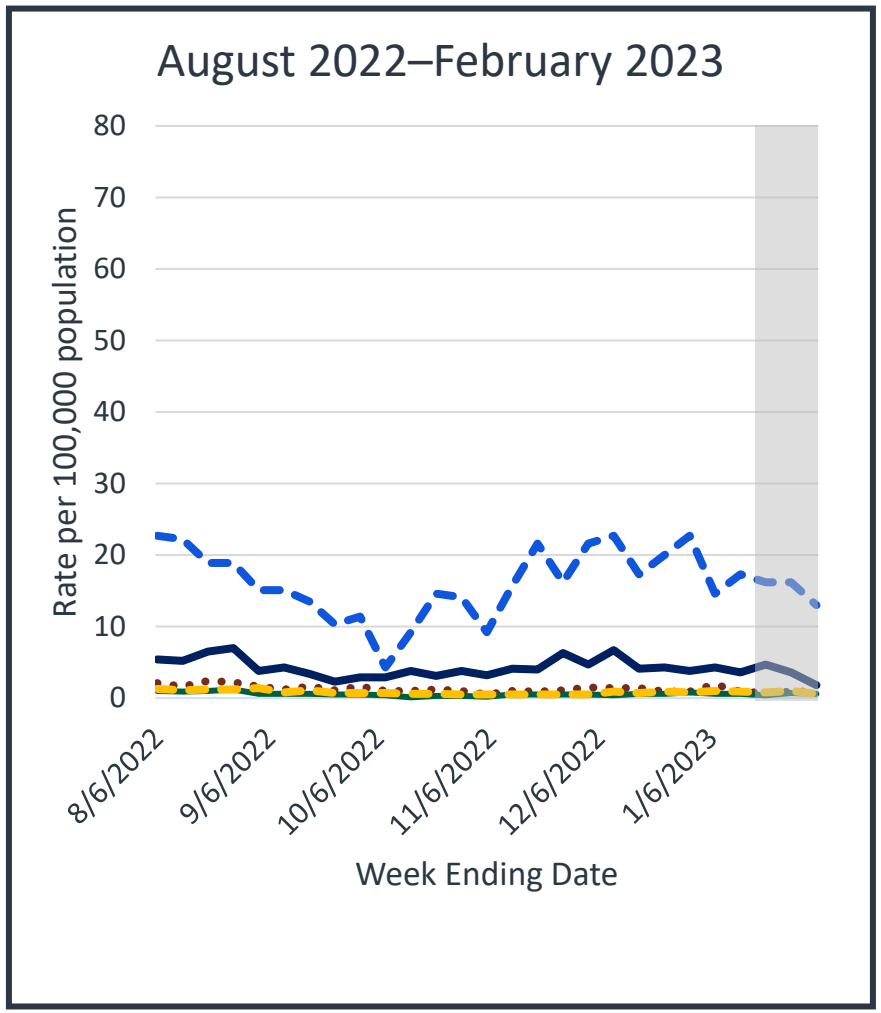
** Bivalent booster coverage is independent of 1st and 2nd dose monovalent coverage

†Note: Coverage is capped at 95%

Source: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Updated February 10, 2023

Weekly Population-Based Rates of COVID-19-Associated Hospitalizations among Children and Adolescents Ages ≤17 Years — COVID-NET, March 2020–February 2023

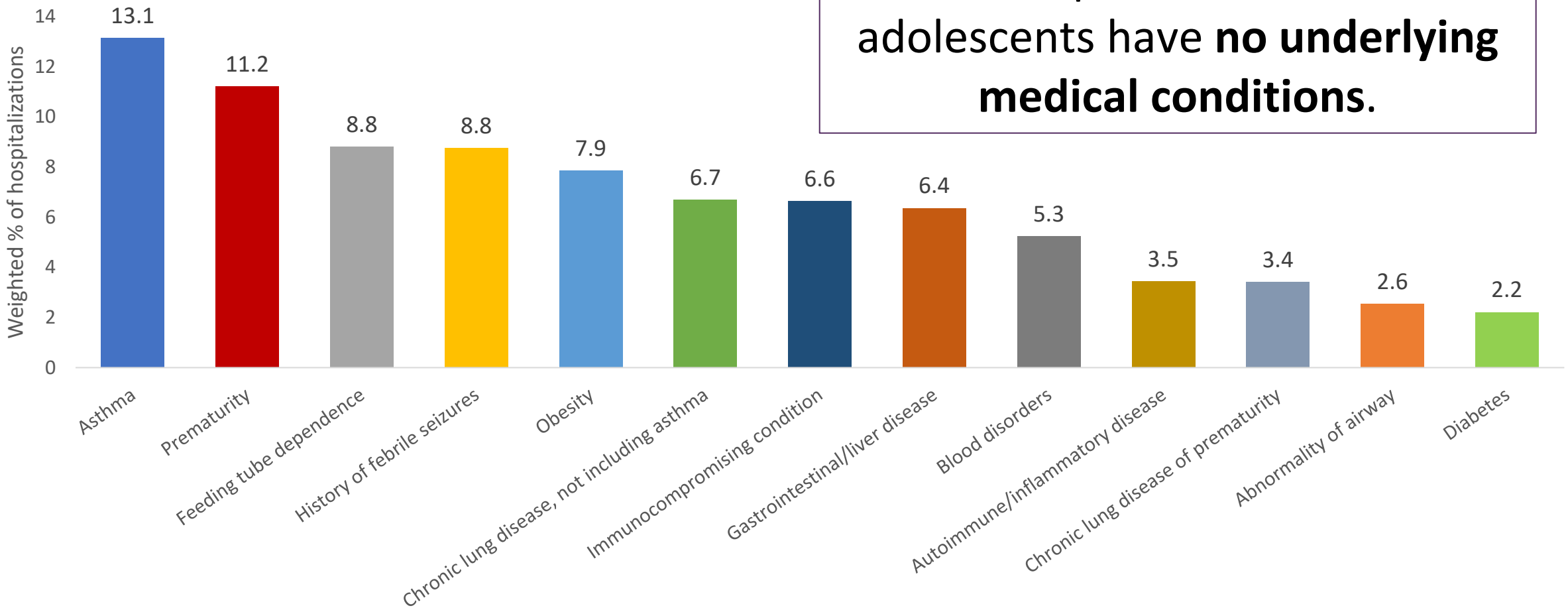




Gray boxes indicate potential reporting delays. Interpretation of trends should be excluded from these weeks.

Underlying Medical Conditions among Children and Adolescents Ages ≤17 Years — COVID-NET, June–November 2022

49% of hospitalized children and adolescents have **no underlying medical conditions**.



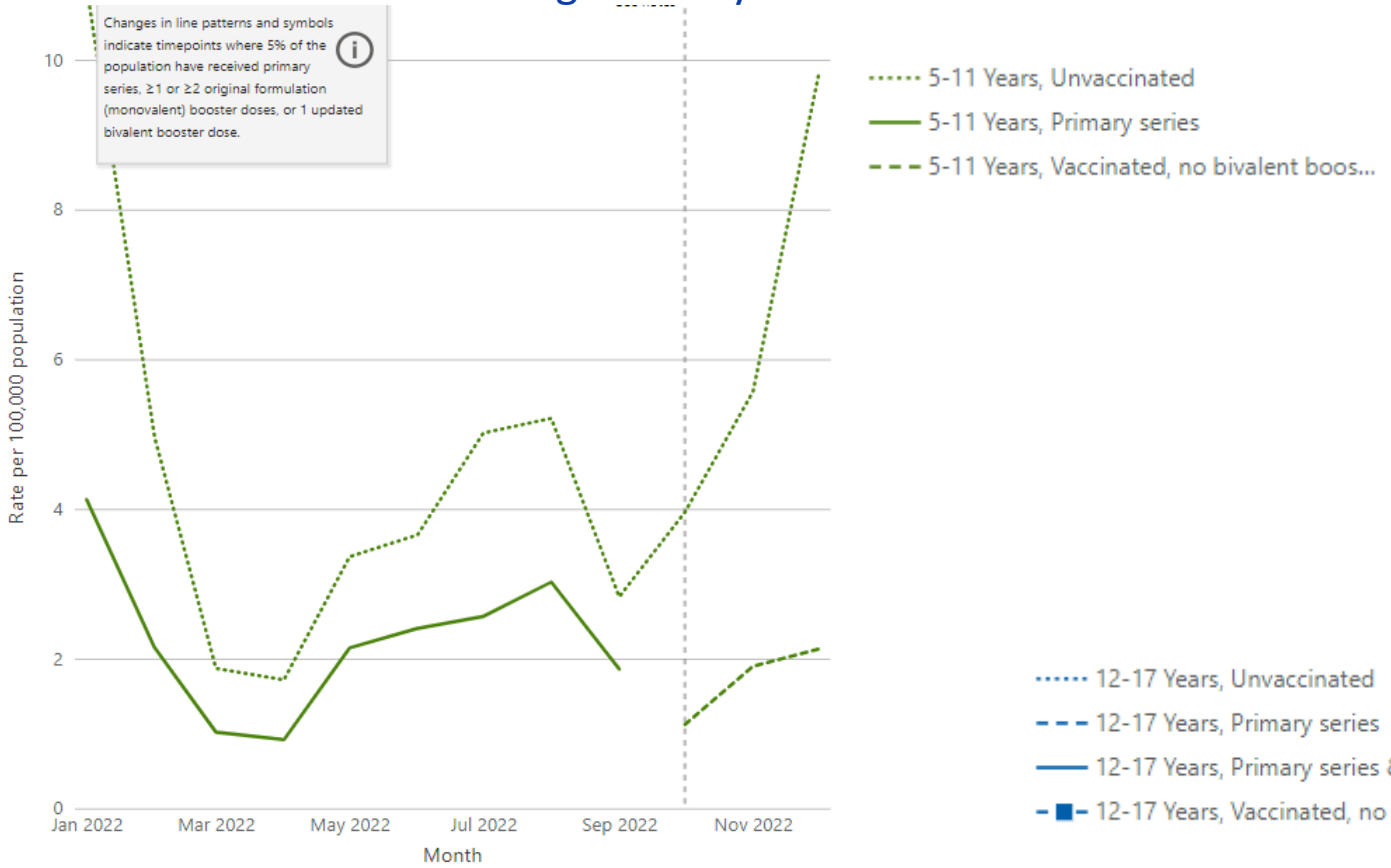
Data are limited to hospitalizations where COVID-19 is a likely primary reason for admission.

Age-adjusted rates of COVID-19-associated hospitalization by vaccination status and receipt of booster dose in children and adolescents

COVID-NET, December 2021 - December 2022

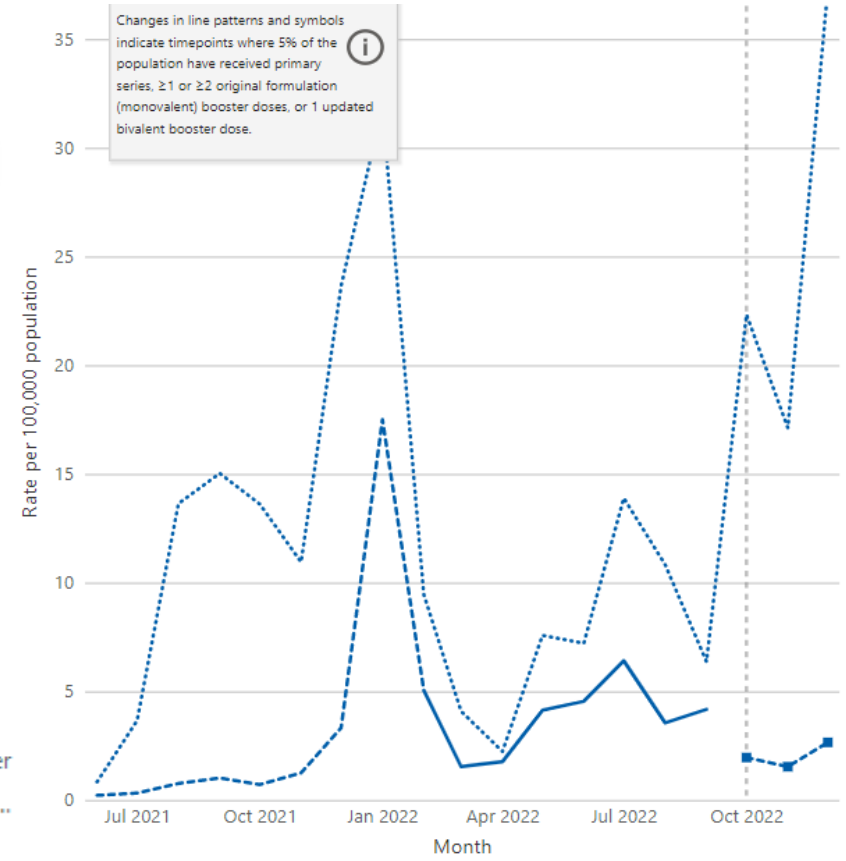
Hospitalization rates by vaccination status

Children ages 5-11 years



Hospitalization rates by vaccination status

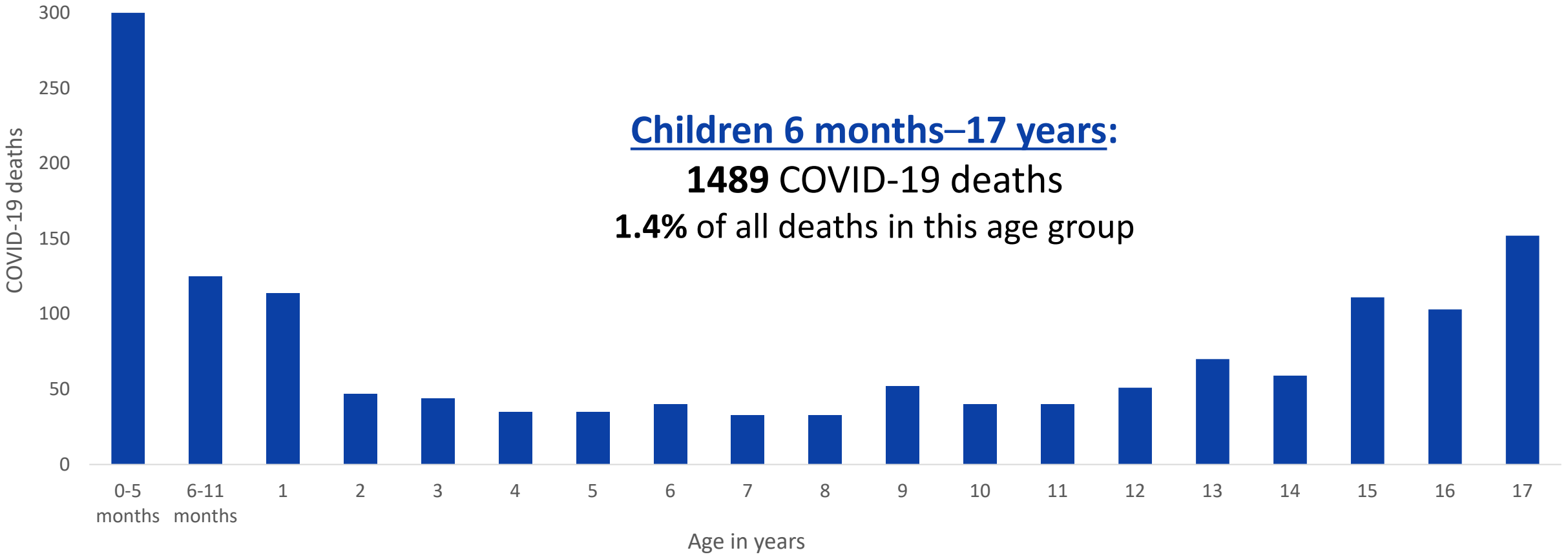
Adolescents ages 12-17 years



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed February 10, 2023

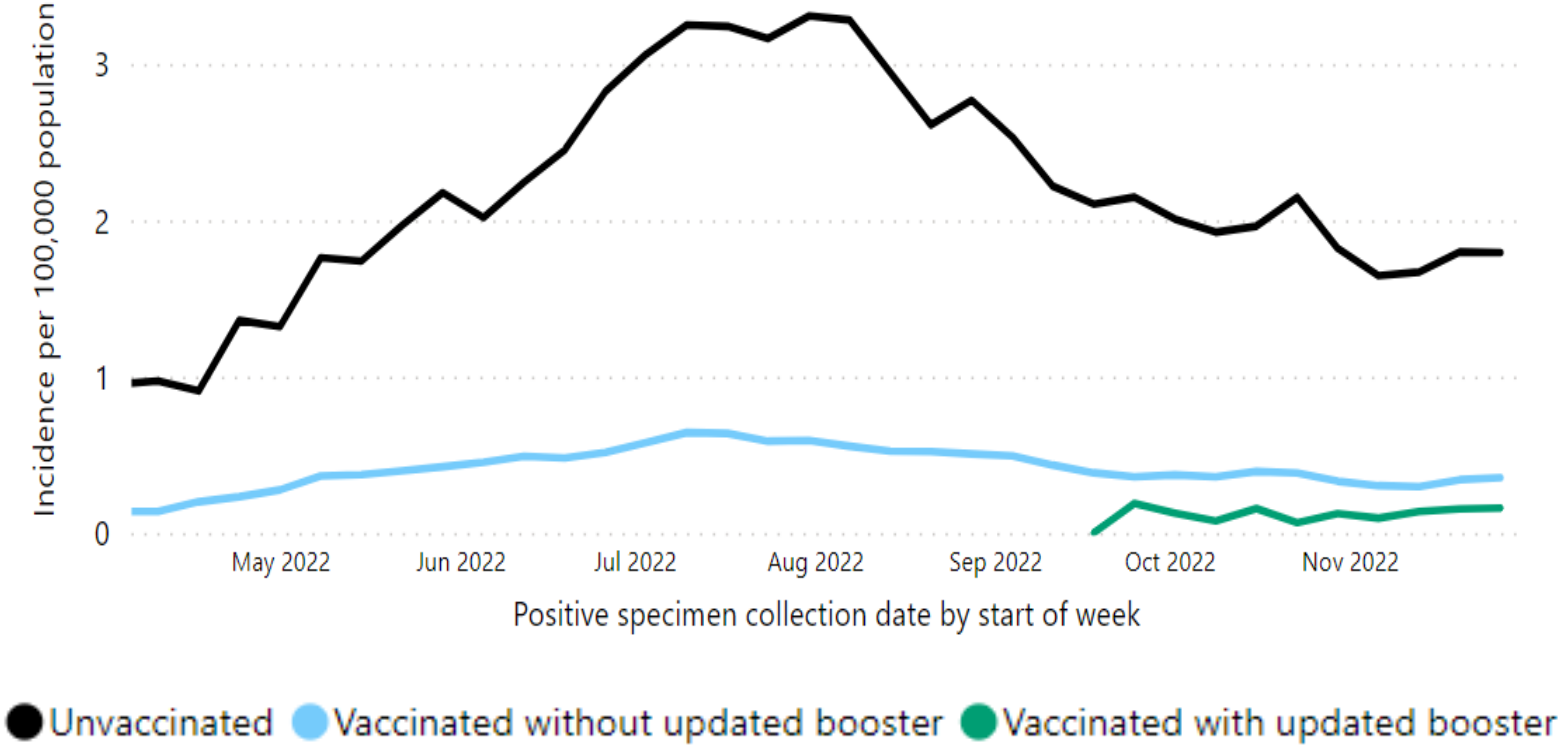
COVID-19 deaths in children and adolescents by age based on death certificate data, National Center for Health Statistics

January 1, 2020–February 11, 2023



Source: https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-Counts-by-Age-in-Years/3apk-4u4f/data. Accessed February 16, 2023

Death rates by vaccination status and receipt of bivalent booster doses among people ages 5 years and older April 3 – December 3, 2022 (23 U.S. Jurisdictions)



In November 2022, people ages 5 years and older with **bivalent booster** had **12.7 times lower risk of dying** from COVID-19, compared to **unvaccinated people** and **2.4 times lower risk of dying** from COVID-19 than people **vaccinated without a bivalent booster**

*Includes either a booster or additional dose. Updated booster = Bivalent booster

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed February 10, 2023

Considerations for Bivalent Primary Series

Public Health Problem

- Children and adolescents can develop severe COVID-19. **Nearly 1500** children and adolescents have died from COVID-19 since the beginning of the pandemic
- Half of the hospitalized children and adolescents had **no underlying medical conditions**
- During all periods, COVID-19 hospitalizations and mortality were consistently **higher** among **unvaccinated persons** than among persons who had completed a primary series and/or an updated booster
- Many children remain **unvaccinated** for COVID-19

Considerations for Bivalent Primary Series

Moderna BA.1 bivalent primary series among children ages 6 months – 5 years

- Ongoing, Phase 3, open-label study (unpublished, data obtained from sponsor)
- Children ages 6 months – 5 years in United States
  - Original primary series (historical control): 4,792 participants received 25 ug of mRNA-1273
  - BA.1 bivalent primary series: 179 participants received 25 ug of mRNA-1273.214 (12.5 ug original strain and 12.5 ug Omicron BA.1 strain)
- Median follow-up for the original vaccine was 102 days post Dose 1 and for the BA.1 bivalent vaccine was 85 days post Dose 1
- Baseline SAR-CoV-2 positive was **8**% for the original vaccine and **63**% for the BA.1 bivalent vaccine

Immunogenicity of Moderna BA.1 bivalent primary series among children ages 6 months – 5 years

		Bivalent Vaccine		Original Vaccine		
Outcome	Time point	N	GMT[a] (95% CI)	N	GMT[a] (95% CI)	**GMR**[b] (95% CI) – Bivalent vs. Original
BA.1 Neutralizing Antibody	Pre Dose 1	58	49.2 (30.4, 79.6)	402	5.9 (5.5, 6.2)	
	Day 57		**1889.7** (1430.0, 2497.2)		**74.3** (67.7, 81.7)	**25.42** (20.14, 32.07)[c]
Original Strain Neutralizing Antibody	Pre Dose 1	66	35.6 (24.0, 52.7)	594	9.6 (8.9, 10.4)	
	Day 57		**1432.9** (1054.5, 1947.0)		**1732.5** (1611.5, 1862.5)	**0.83** (0.67, 1.02)[d]

GMT = geometric mean titer; GMR = geometric mean ratio; CI=confidence interval

[a] GMTs were estimated using an analysis of covariance (ANCOVA) model with neutralizing antibody values at Day 57 as the depend variable and a group variable (mRNA-1273.214 vs mRNA-1273) as the fixed variable, adjusted by age group and by baseline SARS-CoV-2 infection status. The GMT value at Day 57 was estimated by the geometric least square mean (GLSM) from the model.

[b] GMRs were estimated by the ratio of the GLSMs with a 2-sided 95% CI from the model

[c] Met the pre-specified superiority success criterion (lower bound of the 95% CI > 1.0)

[d] Met the pre-specified non-inferiority success criterion (lower bound of the 95% CI > 0.667)

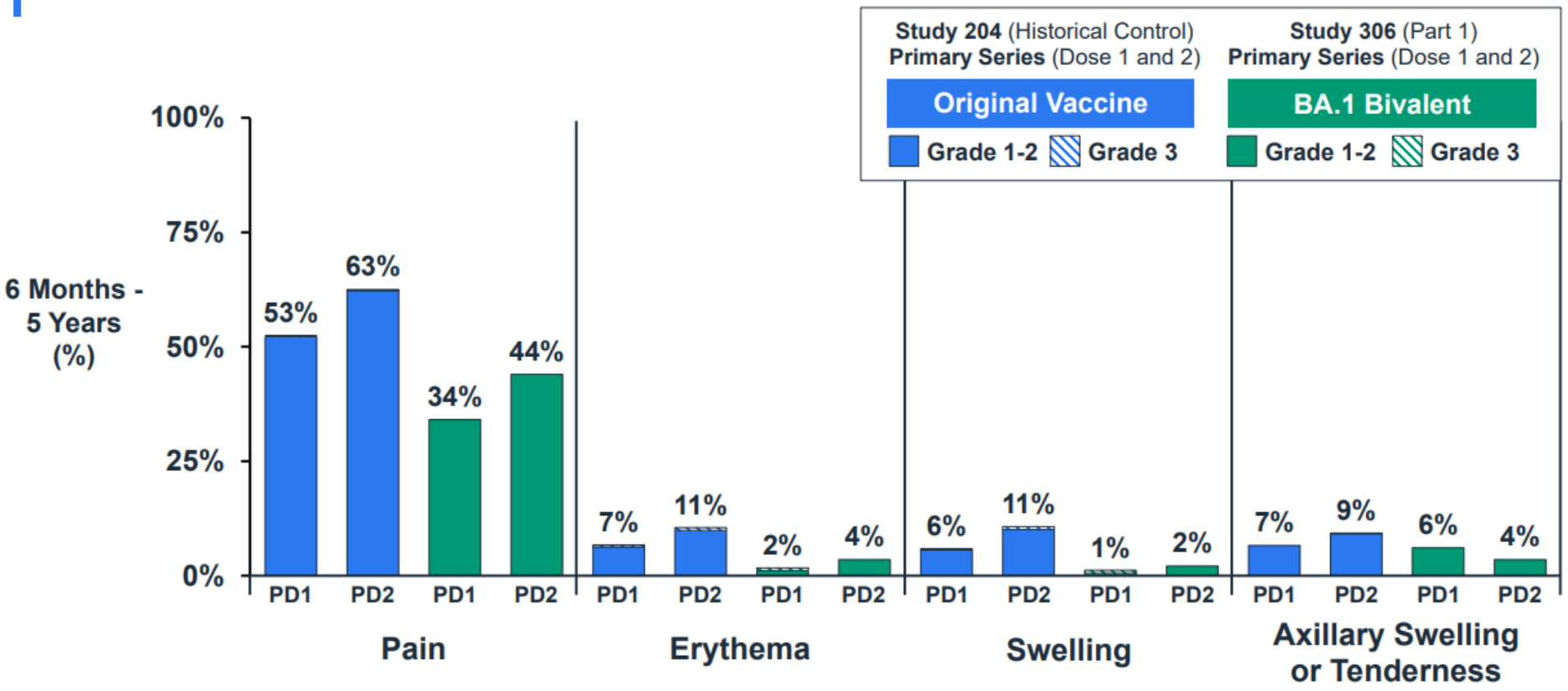
Safety of Moderna BA.1 bivalent primary series among children ages 6 months – 5 years

- 142 patients received two doses of the bivalent vaccine
- Percentage of patients reporting solicited local or systemic events was **similar to** or **less** than percentages seen after original vaccine, however this may be a result of the larger percent of seropositive participants in the bivalent vaccine group
- Pain, axillary (or groin) swelling or tenderness, and erythema were the most common local events
- Irritability/crying, sleepiness, and fatigue were the most common systemic events
- There were no Grade 4 solicited adverse events reported
- There was one serious adverse events (SAE) of asthma exacerbation reported after the first dose that was assessed as unrelated to vaccination by the investigator

Safety of Moderna BA.1 bivalent primary series among children ages 6 months – 5 years

Local Reactions Following BA.1 Omicron Bivalent Primary Series

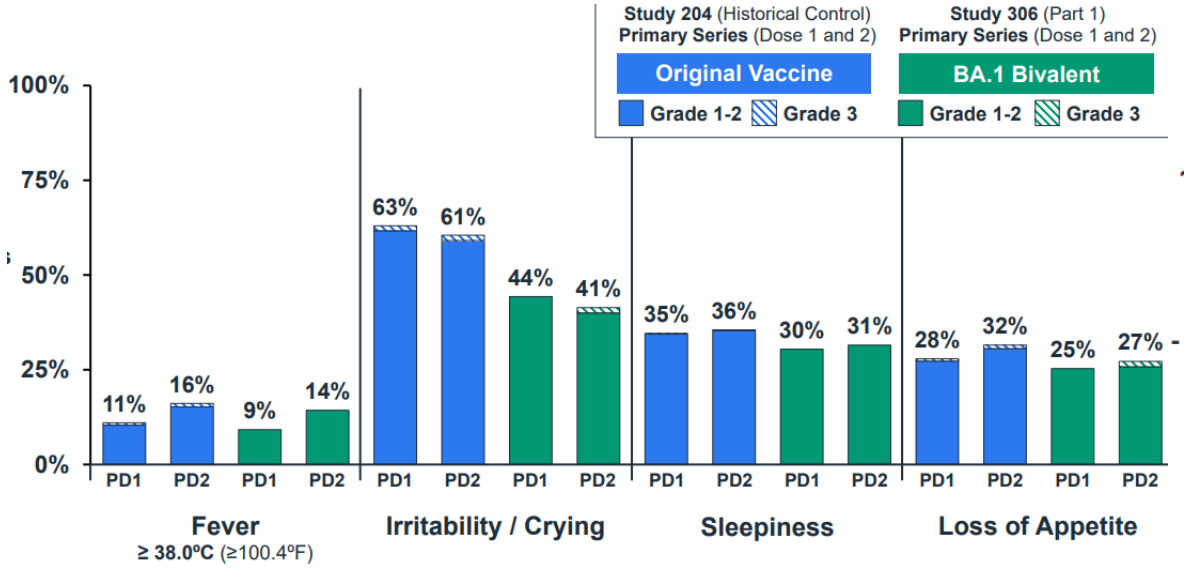
Study 306, Part 1: 6 Months - 5 Years (Solicited Safety Set)



From Jan 26, 2022 VRBPAC meeting: https://www.fda.gov/media/164810/download

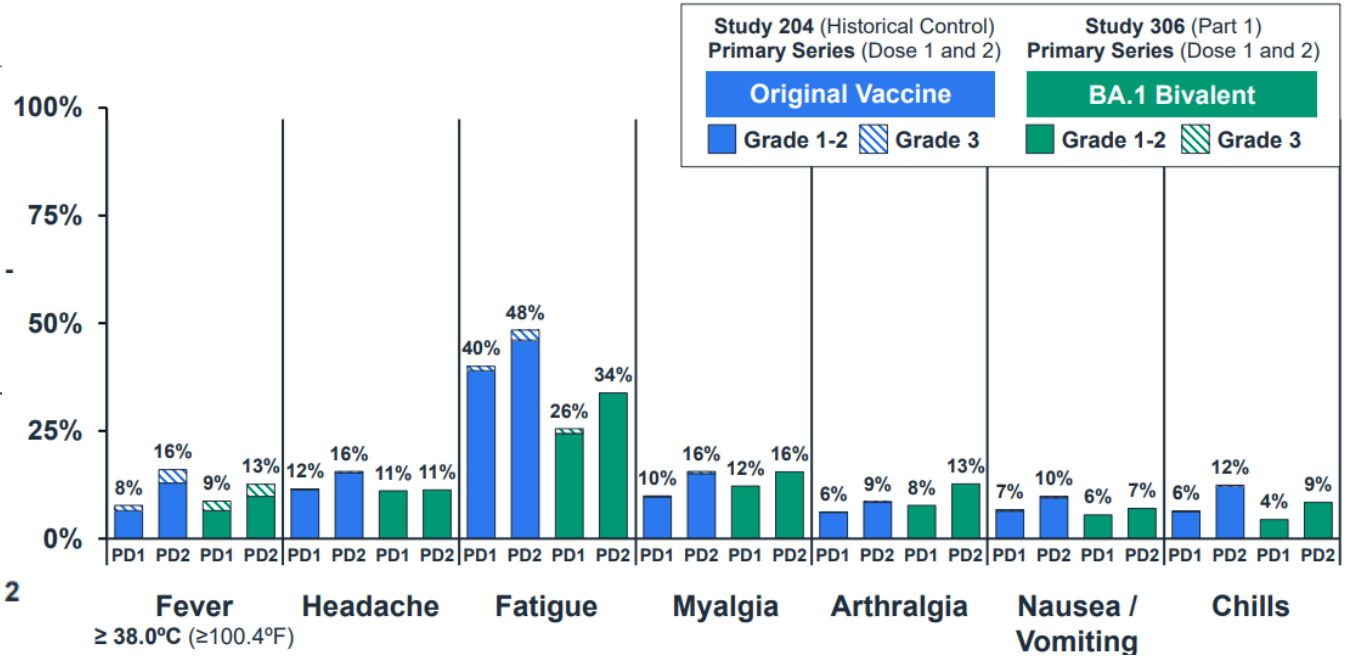
Safety of Moderna BA.1 bivalent primary series among children ages 6 months – 5 years

Systemic reactions 6–36 months



No Grade 4 events reported among participants receiving BA.1 Bivalent
10 events of Grade 4 fever reported with Original Vaccine– 4 postdose 1, 6 postdose 2

Systemic reactions 37 months–5 years



No Grade 4 events reported among participants receiving BA.1 Bivalent
5 events of Grade 4 fever reported with Original Vaccine– 1 post dose 1, 4 post dose 2

From Jan 26, 2022 VRBPAC meeting: https://www.fda.gov/media/164810/download

Considerations for Bivalent Primary Series:
Imprinting

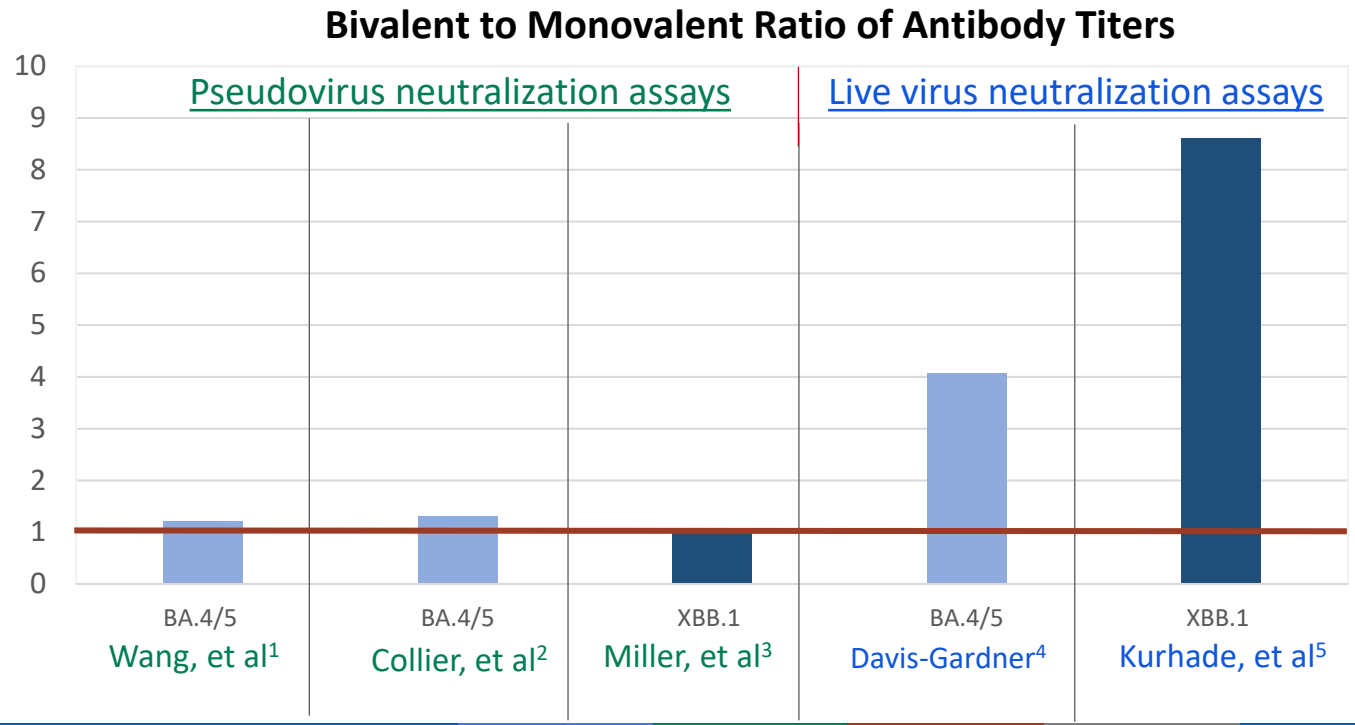
- Concern that initial exposure to one virus strain may primes B-cell memory and limit the development of memory B cells and neutralizing antibodies against new strains
- Prior infection and/or vaccine history likely has impact on subsequent immune response[1-3]
- **Affinity maturation** occurs: the ability of memory B cells to mature over time, especially when exposed to newer strains[4-5]
  - Variant-specific vaccines can also initiate **new** variant-specific immune responses[6-7]
- Clinical impact of different immune responses by prior exposure, or how it may differ by infection and vaccine, requires additional research
- Vaccines continue to be able to provide a **broad boost** in antibody responses
- Imprinting concerns related to **incremental benefit** of updated variant-specific vaccines

1. Immune boosting by B.1.1.529 (Omicron) depends on previous SARS-CoV-2 exposure | Science
2. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution (nature.com)
3. Protective Effect of Previous SARS-CoV-2 Infection against Omicron BA.4 and BA.5 Subvariants | NEJM
4. Affinity maturation of SARS-CoV-2 neutralizing antibodies confers potency, breadth, and resilience to viral escape mutations – ScienceDirect
5. The germinal centre B cell response to SARS-CoV-2 | Nature Reviews Immunology
6. SARS-CoV-2 Omicron boosting induces de novo B cell response in humans | bioRxiv
7. Molecular fate-mapping of serum antibody responses to repeat immunization (nature.com)

Comparing monovalent and bivalent vaccines

Antibody data

- Several studies compared antibody titers with recent Omicron sub-lineages for both the bivalent and monovalent vaccines; most studies ranging from ~21-42 days after bivalent vaccine
- **Ratio** of antibody titers from bivalent vaccine to monovalent vaccine shown
- Overall, most studies show improvement in neutralizing antibodies for Omicron sub-lineages with a bivalent vaccine (ratio >1)
- Clinical impact is unknown for specific ratios or antibody levels
- Neutralizing antibodies at a single time do not convey the entire immune response



1. https://www.biorxiv.org/content/10.1101/2022.10.22.513349v1.full.pdf
2. https://www.nejm.org/doi/full/10.1056/NEJMc2213948
3. https://www.nejm.org/doi/full/10.1056/NEJMc2214314
4. https://www.biorxiv.org/content/10.1101/2022.10.31.514636v1
5. https://www.nature.com/articles/s41591-022-02162-x

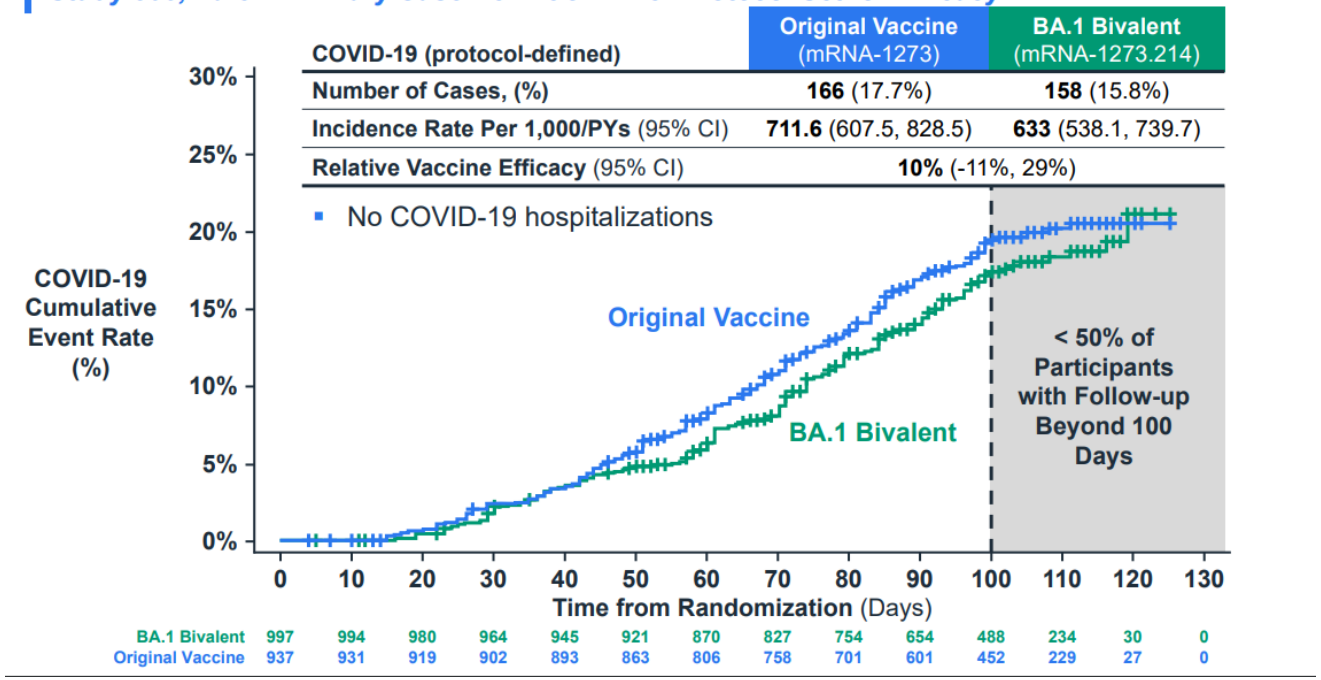
Comparing monovalent and bivalent vaccines

Clinical data

- Unable to directly compare clinical outcomes for monovalent and bivalent vaccines in the U.S. due to timing of authorizations
- Study in the UK found ~**10%** increase in relative VE for COVID-19 infections
- Unable to estimate differential impact for prevention of severe COVID-19

Cumulative Incidence Curve of COVID-19 ≥14 Days Following Receipt of Omicron BA.1 Bivalent or Original Vaccine Booster

Study 305, Part 2: Primary Case Definition – Per Protocol Set for Efficacy



https://www.fda.gov/media/164810/download

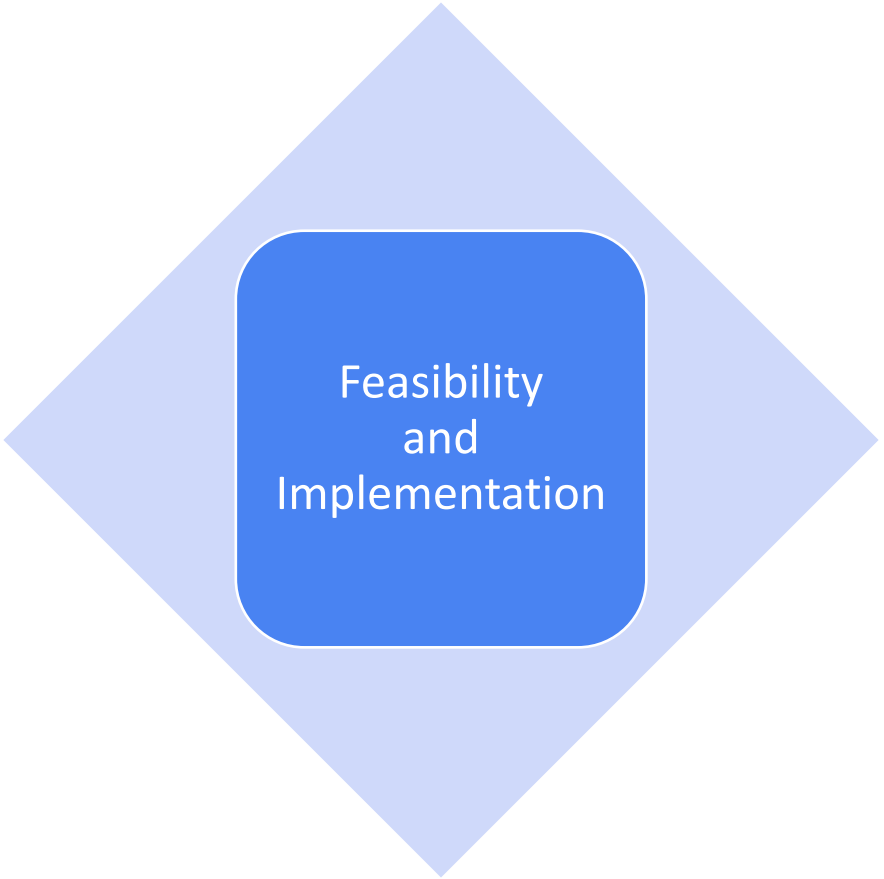
A Randomized Trial Comparing Omicron-Containing Boosters with the Original Covid-19 Vaccine mRNA-1273 | medRxiv

Considerations for Bivalent Primary Series

Benefits and Harms

- Bivalent COVID-19 vaccines are able to **induce an immune response** when given either as a primary series or a booster dose
- Limited data to directly compare COVID-19 outcomes after receipt of a monovalent or bivalent vaccine
- COVID-19 vaccines have a high degree of safety. Initial safety data from bivalent primary series trial are encouraging but study was not powered to assess rare adverse events

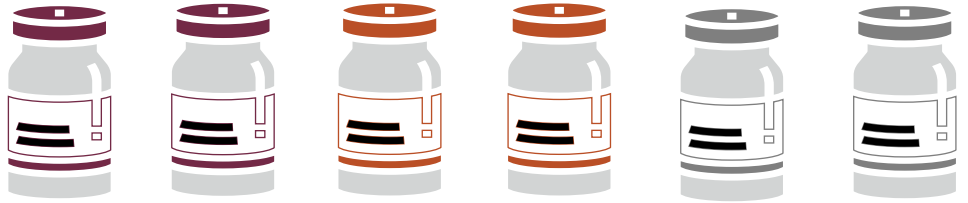
Considerations for Bivalent Primary Series



Number of mRNA COVID-19 vaccine products currently

Moderna: 5 products

Pfizer-BioNTech: 6 products



11 TOTAL Products!

Possible number of mRNA COVID-19 vaccine products with a bivalent primary series

Moderna: 2 products

Pfizer-BioNTech: 3 products

Could be reduced to 5 total products

Would eliminates look-alike vials for Moderna and Pfizer-BioNTech

Considerations for Bivalent Primary Series

Feasibility and Implementation

Transition to bivalent primary series could:

- Improve **storage space**
  - Providers have limited storage space
  - In addition to monovalent and bivalent products, Vaccines for Children (VFC) stock required to be duplicate and separate
- **Reduce errors**
  - Would eliminate ‘look-alike’ vials
  - Currently, one of the most common administration errors reported is providers giving a bivalent vaccine as a primary series
- Allow for **continued access** to primary series
  - Majority of current monovalent vaccine stock expires within the next few months

Considerations for Bivalent Primary Series

Resource Use

- Work is ongoing to evaluate cost effectiveness in preparation for a transition to commercialization of COVID-19 vaccine
- Bivalent COVID-19 vaccines already purchased and delivered; transition of current primary series recommendations from monovalent to bivalent vaccines unlikely to have significant impact on resource use

Summary

Considerations for Bivalent Primary Series

Summary

- Receiving a **COVID-19 vaccine primary series** continues to be important for prevention of COVID-19 severe disease, hospitalization, and death
- Many children and adolescents remain unvaccinated for COVID-19
- COVID-19 vaccines recommendations that are **simple to implement** may remove some barriers to uptake
- Harmonizing the primary series and booster doses could simplify the presentations, reduce administration errors, and allow continued access to primary series for unvaccinated populations

- The Work Group was **supportive** of a transition of the mRNA COVID-19 vaccine primary series from monovalent (original) to bivalent (original plus Omicron BA.4/5)

Acknowledgments

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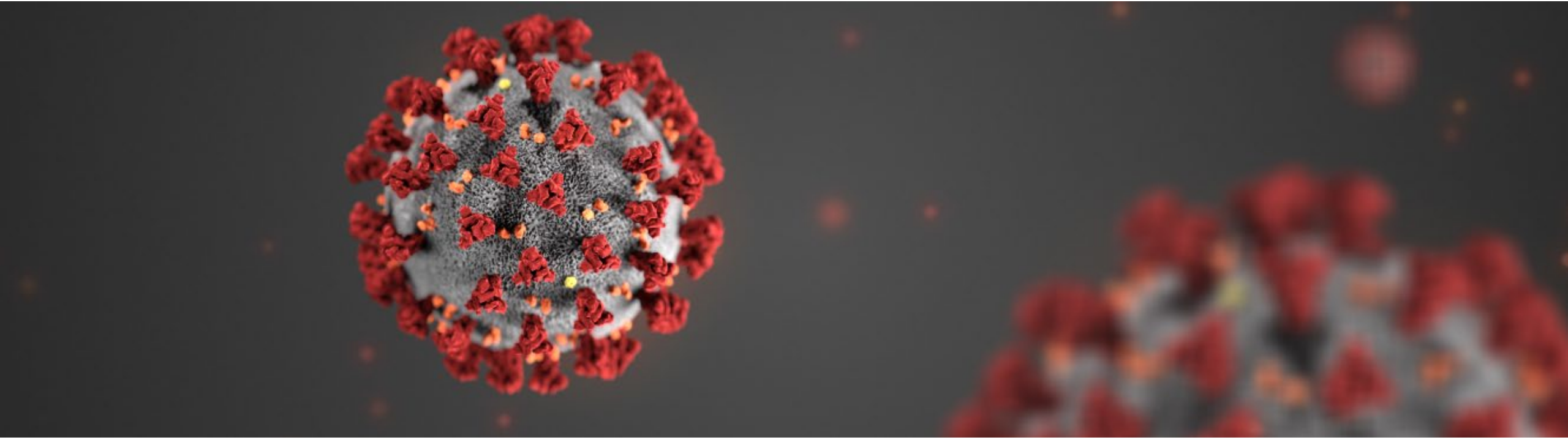
- Ruth Link-Gelles
- Megan Lindley
- Sierra Scarbrough
- Jefferson Jones
- Aron Hall
- Barbara Mahon
- Data Analytics and Visualization Task Force
- Coronavirus and other Respiratory Viruses Division
- National Center for Immunization and Respiratory Diseases

Question for ACIP

- Transition to bivalent primary series can only occur after FDA regulatory action and updates to CDC recommendations

- What are ACIP thoughts on a **transition** of the mRNA COVID-19 vaccine primary series from monovalent (original) to bivalent (original plus Omicron BA.4/5)?

Note: “Monovalent” and “bivalent” designations are based on the currently authorized products.
For future vaccines, focus would be harmonization of products across primary series and booster doses.



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

Thank you

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

Comparing monovalent and bivalent vaccines

Antibody data

References for data:

1. https://www.biorxiv.org/content/10.1101/2022.10.22.513349v1.full.pdf
2. https://www.nejm.org/doi/full/10.1056/NEJMc2213948
3. https://www.nejm.org/doi/full/10.1056/NEJMc2214314
4. https://www.biorxiv.org/content/10.1101/2022.10.31.514636v1
5. https://www.nature.com/articles/s41591-022-02162-x

Wang, et al[1]

Antibody titers measured 24-26 days after vaccine

Pseudovirus neutralization assay	Bivalent BA.4/BA.5 N=19	Monovalent N=21	Ratio
Ancestral SARS-CoV-2 antibody titers (ID_{50})	8488	12054	0.70
BA.4/BA.5 neutralizing antibody titers (ID_{50})	1649	1366	1.2

Collier, et al[2]

Antibody titers measured ~21 days post-dose for bivalent and ~32 days post-dose for monovalent group

Pseudovirus neutralization assay	Bivalent BA.4/BA.5 N=15	Monovalent N=18	Ratio
Ancestral SARS-CoV-2 antibody titers (ID_{50})	40575	21507	1.89
BA.4/BA.5 neutralizing antibody titers (ID_{50})	3693	2829	1.31

Miller, et al[3]

Antibody titers measured ~21 days post-dose for bivalent and ~32 days post-dose for monovalent group

Pseudovirus neutralization assay	Bivalent BA.4/BA.5 N=15	Monovalent N=18	Ratio
Ancestral SARS-CoV-2 antibody titers (ID_{50})	40515	21507	1.89
XBB.1 neutralizing antibody titers (ID_{50})	170	175	0.97

Davis-Gardner, et al[4]

Timing post-vaccine differed (monovalent: 70-100 days post vaccine; bivalent: 16-42 days post vaccine)

Live virus neutralization assay	Bivalent BA.4/BA.5 N=12	Monovalent N=12	Ratio
Ancestral SARS-CoV-2 antibody titers (ID_{50})	2312	1812	1.27
BA.5 neutralizing antibody titers (ID_{50})	576	142	4.06

Kurhade, et al[5]

Antibody titers measured at different time points (monovalent: 23-94 days post vaccine; bivalent: 14-32 days post vaccine)

Live virus neutralization assay	Bivalent BA.4/BA.5 Without infection N=29	Monovalent N=25	Ratio
Ancestral SARS-CoV-2 antibody titers (ID_{50})	3620	1533	2.36
BA.4/BA.5 neutralizing antibody titers (ID_{50})	298	95	3.14
XBB.1 neutralizing antibody titers (ID_{50})	35	15	2.33

Live virus neutralization assay	Bivalent BA.4/BA.5 WITH infection N=23	Monovalent N=25	Ratio
Ancestral SARS-CoV-2 antibody titers (ID_{50})	5776	1533	3.77
BA.4/BA.5 neutralizing antibody titers (ID_{50})	1558	95	16.4
XBB.1 neutralizing antibody titers (ID_{50})	103	15	8.58