CDC Advisory Committee on Immunization Practices (ACIP) Meeting Report

Date: April 20, 2022

The ACIP met today to consider recommendations for a second booster dose of mRNA COVID-19 vaccines. On March 29, 2022, FDA authorized a second booster dose of either the Pfizer-BioNTech or Moderna COVID-19 vaccine for individuals 50 years or older and for immunocompromised 12 years and older to be given at least 4 months after receipt of a first booster dose. The Moderna vaccine was limited to individuals 18 years of age or older. That day, CDC issued Emergency Use Instructions stating that for both mRNA vaccines, people 18-49 years who received Janssen vaccine as primary and booster doses may receive a second booster dose using mRNA vaaccine at least 4 months from first Janssen booster dose. There was no vote scheduled for today's meeting; the ACIP heard updates on effectiveness and safety with review of issues surrounding second boosting now and for future vaccines.

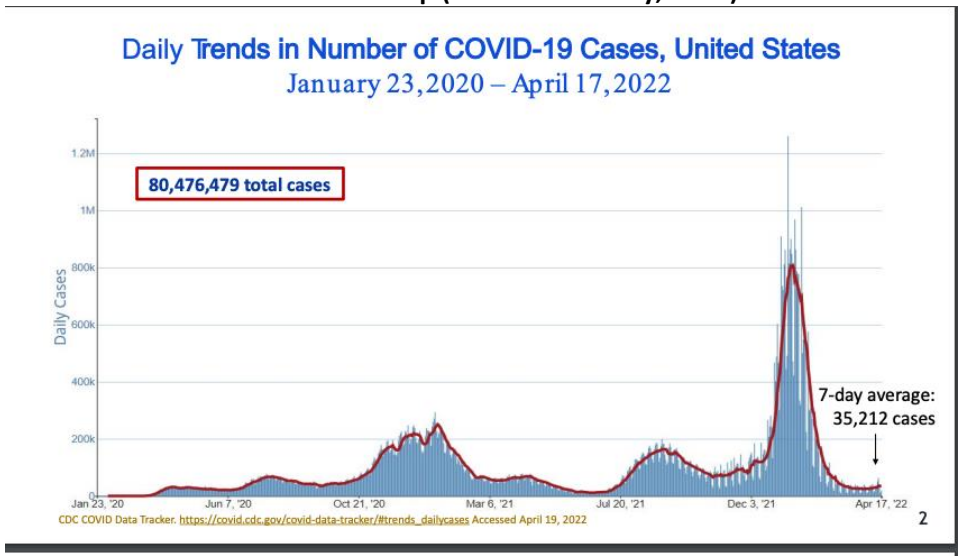
The first presentation reviewed the work of the Working Group. The second was an update re: vaccine effectiveness and presented data split by not immunocompromised vs. immunocompromised and by increasingly severe types of disease (infection, ED/urgent care, hospitalization and critical illness/death). For the mRNA vaccines against Omicron, there was limited protection against infection after dose 2 with fast waning (28% to 11%) in non-immunocompromised, higher protection with some waning (74%-54%) against against ED/UC visits, highest protection with some waning (81%-64%) against hospitalization. A third dose gave some protection with waning (65%) against infection, some protection with limited waning (88%-75%) against ED/UC and highest protection with limited waning (86%-79%) against hospitalization. Booster increased protection across all outcomes and VE remains high among non-immunocompromised 4-6 mo. after boost.

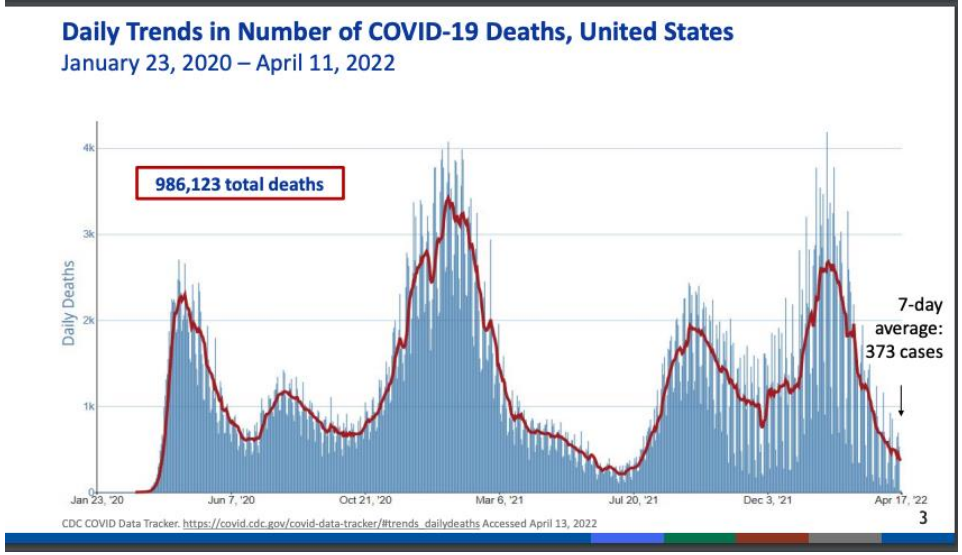
The third presentation on safety reported VSD, VAERS and v-safe data, mainly post-mRNA dose 3. The only signal in VSD was in for myocarditis/pericarditis; they did chart reviews on 271 cases with 51% being verified on review. There were marked differences in presentation between 12-39yo and 40+yo: younger group had mostly myocarditis and myopericarditis with onset <7days after first boost while 40+ yo had mostly pericarditis with cases spread out over 21 days. Rate ratios were elevated for 12-39yo but not higher than after primary series of 2 mRNA vaccines. Rate ratios for 40+ years were elevated but less so. Update on VAERS with 41+MM first boost vaccinations in males (93+MM total booster doses) revealed 110 myocarditis and 38 pericarditis cases with similar difference in timing as for VSD. Reporting rates exceed background for 12-29yo but were lower than following primary series. Disease severity was similar to that following primary series, most recovered at last f/u. No unusual or unexpected findings in v-safe data.

The last presentations were on VaST assessment, EtR Framework, CDC guidance for second booster dose and framework for future COVID doses and next steps. These provided material for committee discussions. A selection of slides from the various presentations can be found in the attached pdf. The full set of slide presentations can be found HERE.

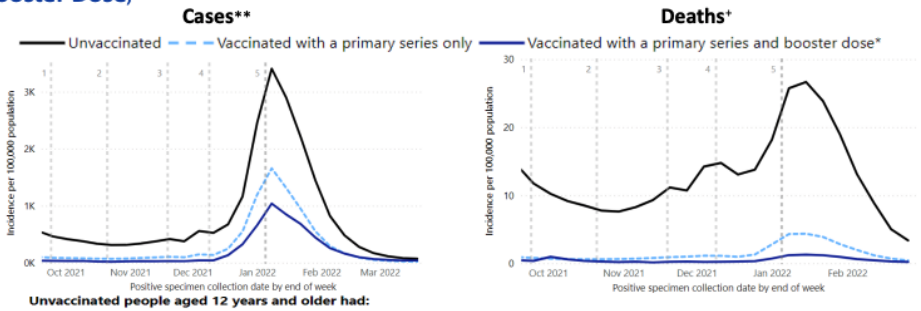
Report created by: Cornelia L. Dekker, MD

1. **ACIP COVID-19 Vaccines Work Group (Matthew F. Daley, Chair)**





Age-Adjusted Rates of COVID-19 Cases & Deaths by Vaccination Status and Receipt of Booster Dose,*



Unvaccinated people aged 12 years and older had:

3.1X *Risk of Testing Positive for COVID-19* **AND** **20X** *Risk of Dying from COVID-19* **in February, and**

2.0X *Risk of Testing Positive for COVID-19* **in March,- compared to people vaccinated with a primary series and a booster dose.**

*This includes people who received booster doses and people who received additional doses.
** Data from September 19, 2021 – March 19, 2022 (24 U.S. jurisdictions)
+ Data from September 19, 2021 – February 26, 2022 (23 U.S. jurisdictions)
CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed April 19, 2022

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FDA updates

FDA authorizes second booster dose of two COVID-19 vaccines

- On March 29, 2022: FDA authorized a second booster dose of either the Pfizer-BioNTech or Moderna COVID-19 vaccine for older people and immunocompromised individuals
  - A second booster dose of the Pfizer-BioNTech COVID-19 vaccine or Moderna COVID-19 vaccine may be administered to individuals 50 years of age and older at least 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.
  - A second booster dose of the Pfizer-BioNTech COVID-19 vaccine may be administered to individuals 12 years of age and older with certain kinds of immunocompromise at least 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.
  - A second booster dose of the Moderna COVID-19 Vaccine may be administered to individuals 18 years of age and older with certain kinds of immunocompromise at least 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine

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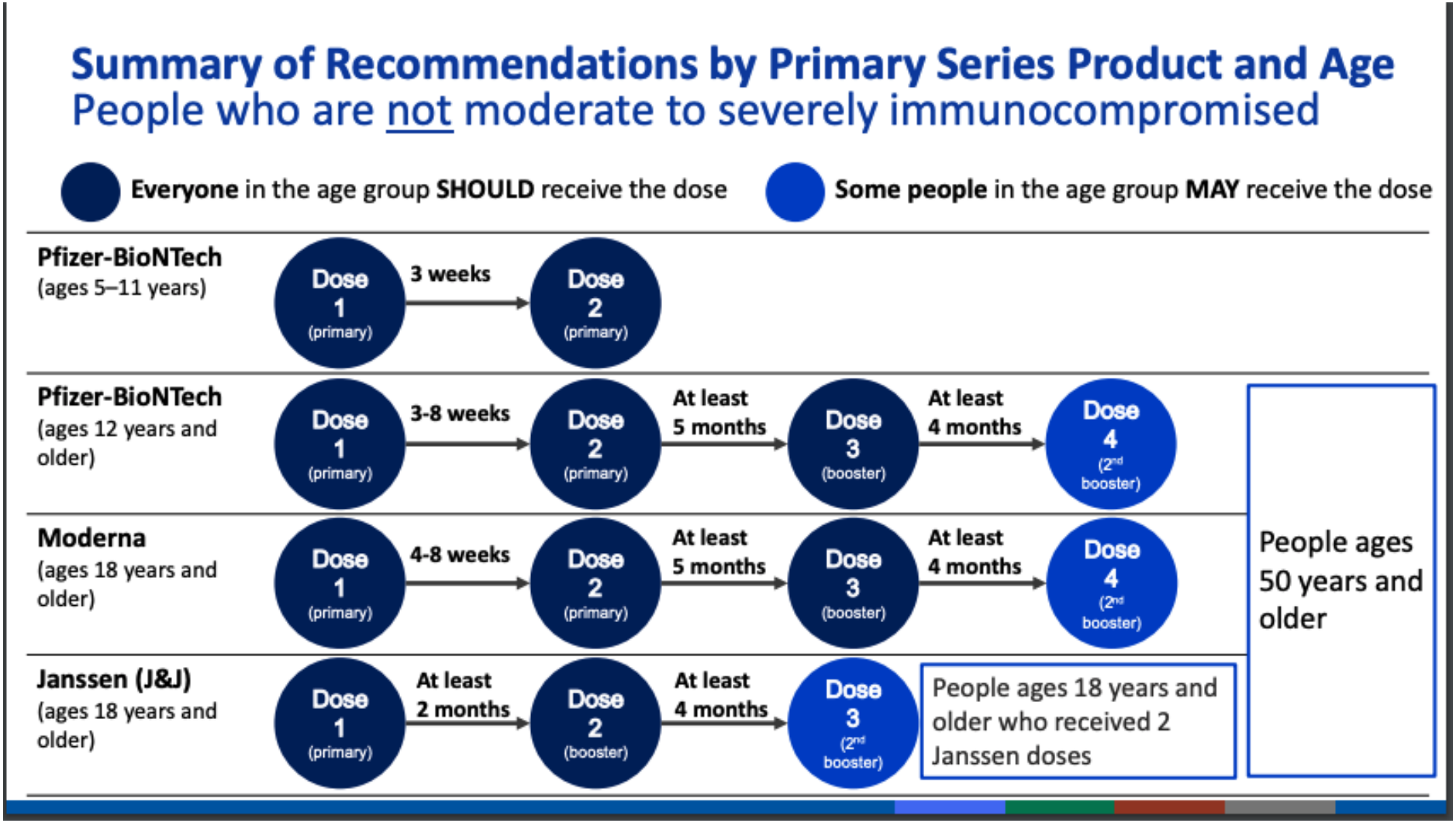
https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-second-booster-dose-two-covid-19-vaccines-older-and


Summary of Recommendations by Primary Series Product and Age
People who are not moderate to severely immunocompromised
Everyone in the age group SHOULD receive the dose
Some people in the age group MAY receive the dose
Pfizer-BioNTech
(ages 5–11 years)
Dose 1 (primary)
3 weeks
Dose 2 (primary)
Pfizer-BioNTech
(ages 12 years and older)
Dose 1 (primary)
3-8 weeks
Dose 2 (primary)
At least 5 months
Dose 3 (booster)
At least 4 months
Dose 4 (2nd booster)
Moderna
(ages 18 years and older)
Dose 1 (primary)
4-8 weeks
Dose 2 (primary)
At least 5 months
Dose 3 (booster)
At least 4 months
Dose 4 (2nd booster)
Janssen (J&J)
(ages 18 years and older)
Dose 1 (primary)
At least 2 months
Dose 2 (booster)
At least 4 months
Dose 3 (2nd booster)
People ages 18 years and older who received 2 Janssen doses
People ages 50 years and older

Agenda: Wednesday April 20, 2022

▪ **Updates on vaccine effectiveness of COVID-19 booster dose**	Dr. Link-Gelles (CDC)
▪ **Updates on safety of COVID-19 booster dose**	Dr. Klein (KPNC)
	Dr. Shimabukuro (CDC)
▪ **VaST assessment**	Dr. Talbot (ACIP, VaST chair)

Break

▪ **Updates to the EtR Framework: COVID-19 vaccine booster doses in adults ages ≥50 years and immunocompromised individuals**	Dr. Oliver (CDC)
▪ **CDC guidance for second COVID-19 booster dose**	Dr. Hall (CDC)

Discussion

- **PUBLIC COMMENT**

Agenda (continued): Wednesday April 20, 2022

Break

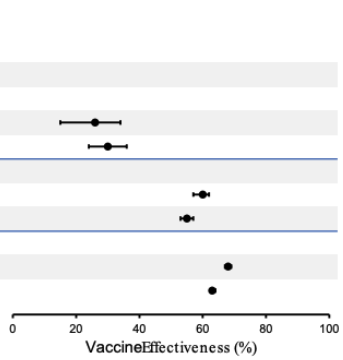
▪ **Summary of FDA advisory committee meeting on future COVID-19 vaccine doses**	Dr. Fink (FDA)
▪ **Framework for Future COVID-19 doses and next steps**	Dr. Oliver (CDC)

Discussion

2. **COVID-19 Vaccine Effectiveness during Omicron (R. Link-Gelles, CDC)**

Increasing Community Access to Testing (ICATT) Partnership, booster VE against symptomatic infection in adults ≥18 years during Omicron, Dec 26, 2021-Mar 23, 2022

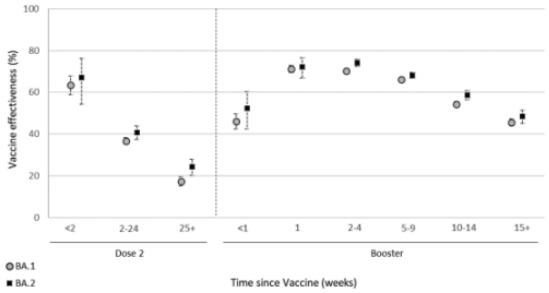
	Tests with vaccine regimen, no.	SARS-CoV-2 positive, (%)	Adjusted VE (95% CI)
Unvaccinated	208,122	50	Ref.
J&J + J&J			
0-1 months since booster	1,023	47	25 (15-34)
2-4 months since booster	2,513	42	30 (24-36)
J&J + mRNA			
0-1 months since booster	3,607	31	60 (57-62)
2-4 months since booster	9,787	30	55 (53-57)
mRNA + mRNA + mRNA			
0-1 months since booster	78,242	27	68 (67-69)
2-4 months since booster	207,276	27	63 (63-64)



Accorsi et al., preliminary unpublished data

Data from the UK: VE vs. symptomatic infection comparing Omicron sublineages (BA.1 vs BA.2) by time since booster

- Pfizer-BioNTech, Moderna, or ChAdOx1-S primary series, Pfizer-BioNTech or Moderna booster
- VE was generally comparable by Omicron sublineage



https://www.medrxiv.org/content/10.1101/2022.03.22.22272691v1.full.pdf

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Overall summary of VE against infection

- VE looks different for recipients of J&J vaccine; lower overall vs. regimens that include at least 1 mRNA
- Evidence of slight waning against infection for 3 mRNA doses by 2-4 months after the last dose
- Early VE data from the UK show similar VE for BA.1 and BA.2 sublineages of Omicron variant

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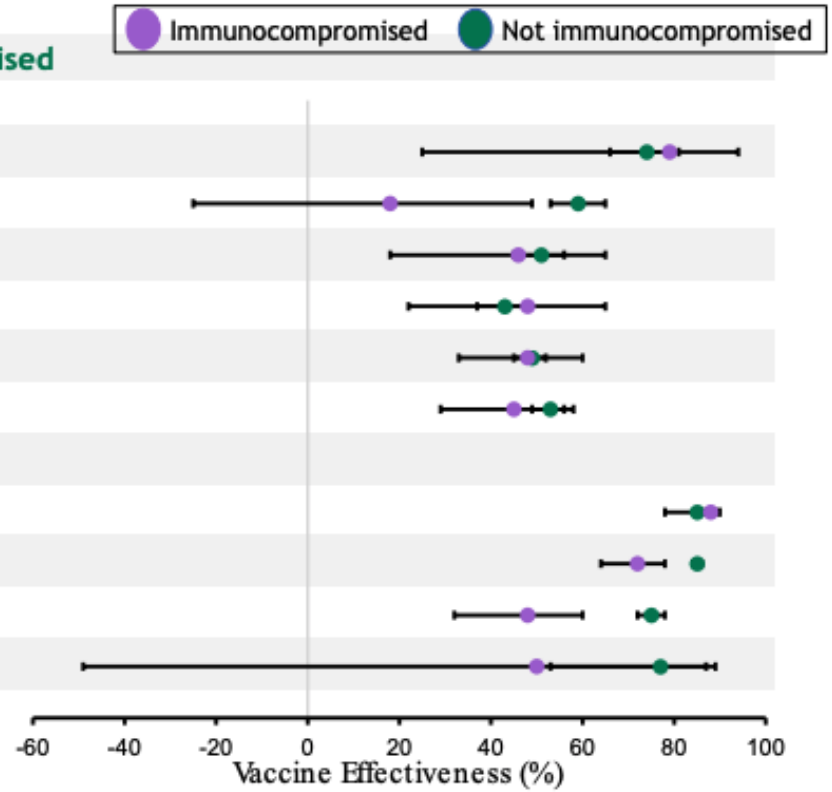
VISION: mRNA VE for ED/UC visits by number of doses and time since last dose receipt for adults ≥50 years, Dec 2021–Mar 2022, by immunocompromised status

	Adjusted VE% (95% CI)	
Status:	Immunocompromised	Not immunocompromised
2 doses		
14-59 days	79 (25-94)	74 (66-81)
60-119 days	18 (-25-49)	59 (66-81)
120-179 days	46 (18-65)	51 (45-56)
180-239 days	48 (22-65)	43 (37-48)
240-299 days	48 (33-60)	49 (45-52)
300+ days	45 (29-58)	53 (49-56)
3 doses		
14-59 days	85 (78-90)	88 (87-89)
60-119 days	72 (64-78)	85 (84-86)
120-179 days	48 (32-60)	75 (72-78)
180-239 days	50 (-49-87)	77 (53-89)



CDC, preliminary unpublished data. Individuals with prior infections excluded. Logistic regression conditioned on calendar week and geographic area, and adjusted for age, sex, race, ethnicity, local virus circulation, respiratory or nonrespiratory underlying medical conditions, and propensity to be vaccinated

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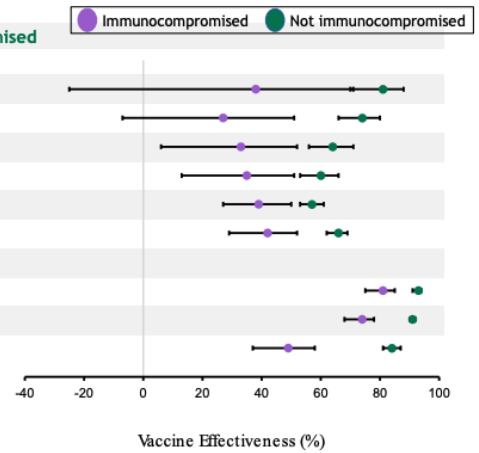
VISION: mRNA VE for hospitalization by number of doses and time since last dose receipt for adults ≥50 years, Dec 2021–Mar 2022, by immunocompromised status

Status:	Adjusted VE% (95% CI) Immunocompromised	Not immunocompromised
2 doses		
14-59 days	38 (-25-71)	81 (70-88)
60-119 days	27 (-7-51)	74 (66-80)
120-179 days	33 (6-52)	64 (56-71)
180-239 days	35 (13-51)	60 (53-61)
240-299 days	39 (27-50)	57 (53-61)
300+ days	42 (29-52)	66 (62-69)
3 doses		
14-59 days	81 (75-85)	93 (91-94)
60-119 days	74 (68-78)	91 (90-92)
120-179 days	49 (37-58)	84 (81-87)



CDC, preliminary unpublished data. Individuals with prior infections excluded. Logistic regression conditioned on calendar week and geographic area, and adjusted for age, sex, race, ethnicity, local virus circulation, respiratory or nonrespiratory underlying medical conditions, and propensity to be vaccinated

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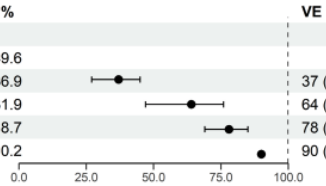
VE against COVID-19-associated hospitalizations during Omicron, Dec 16, 2021-Mar 7, 2022

Medical event/vaccination status	Total	SARS-CoV-2 Positive	Row %	VE % (CI)
Hospitalizations				
Unvaccinated (referent)	12377	6134	49.6	
1 Janssen vaccine dose (14 - 150 + days)	1194	440	36.9	37 (27-45)
2 Janssen vaccine doses (7-120 days)	135	43	31.9	64 (47-76)
1 Janssen/ 1 mRNA vaccine dose (7-120 days)	252	47	18.7	78 (69-85)
3 mRNA vaccine doses (7 - 120 days)	5994	613	10.2	90 (89-91)



- VE of any booster dose is significantly higher than VE for 1 Janssen dose only
- VE of 3 mRNA doses is significantly higher than Janssen plus booster

Natarajan K, Prasad N, Dascomb K, et al. Effectiveness of Homologous and Heterologous COVID-19 Booster Doses Following 1 Ad.26.COV2.S (Janssen [Johnson & Johnson]) Vaccine Dose Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults — VISION Network, 10 States, December 2021-March 2022. MMWR Morb Mortal Wkly Rep. ePub: 29 March 2022. DOI: http://dx.doi.org/10.15585/mmwr.mm7113e2external icon

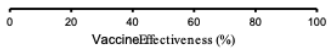
Effectiveness of mRNA COVID-19 vaccines against COVID-19-associated hospitalization, Dec 26, 2021 – Mar 15, 2022

Group	No. of vaccinated case-patients/total case-patients (%)	No. of vaccinated control-patients/ total control-patients (%)	Adjusted* vaccine effectiveness % (95% CI)
3 doses overall	288/909 (32)	508/776 (65)	78 (73–83)
Immunocompromised	153/250 (61)	191/238 (80)	65 (44–78)
7–120 days	89/186 (48)	134/181 (74)	73 (55–84)
>120 days	64/161 (40)	57/104 (55)	54 (16–75)
Not immunocompromised	135/659 (20)	317/538 (59)	85 (80–89)
7–120 days	118/642 (18)	273/494 (55)	86 (81–89)
>120 days	17/541 (3)	44/265 (17)	79 (59–89)

*Adjusted for age (18-64 or ≥65 years), sex, race/ethnicity, admission date (biweekly), and US census region
CDC preliminary unpublished data

IVY: VE against invasive mechanical ventilation or in-hospital death, by variant, Jul 4, 2021-Jan 24, 2022

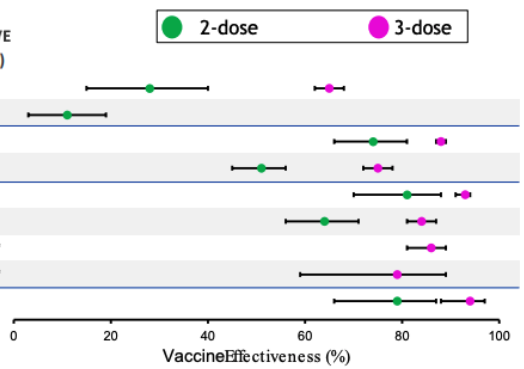
	No. vaccinated cases/ Total no. case (%)	No. vaccinated controls/ Total no. controls (%)	Adjusted VE % (95% CI)
Pre-Delta, 2 doses	13/259 (5.0)	893/1,738 (51.4)	95 (90-97)
Delta	235/1,027 (22.9)	2,741/3,865 (70.9)	89 (87-91)
2 doses, median 159 days after dose 2	218/1,010 (21.6)	2,402/3,526 (68.1)	88 (86-90)
3 doses, median 35 days after dose 3	17/809 (2.1)	339/1,463 (23.2)	95 (91-97)
Omicron	59/154 (38.3)	396/501 (77.0)	86 (79-91)
2 doses, median 256 days after dose 2	46/141 (32.6)	193/308 (62.7)	79 (66-87)
3 doses, median 60 days after dose 3	13/108 (12.0)	193/308 (62.7)	94 (88-97)



Tenforde MW, Self WH, Gaglani M, et al. Effectiveness of mRNA Vaccination in Preventing COVID-19-Associated Invasive Mechanical Ventilation and Death — United States, March 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:459-465. DOI: http://dx.doi.org/10.15585/mmwr.mm7112e1

Summary: VE of 2 doses of mRNA vaccine increases with increasing severity of outcome during Omicron in adults ≥18 years; 3rd dose increases VE

		2-dose Adjusted VE % (95% CI)	3-dose Adjusted VE % (95% CI)
Infection	1mo post-last dose, ICATT	28 (15-40)	65 (62-68)
	3mos post-last dose, ICATT	11 (3-19)	--
Emergency department/ urgent care	Last dose <59 days ago, VISION	74 (66-81)*	88 (87-89)*
	Last dose 120-179 days ago, VISION	51 (45-56)*	75 (72-78)*
Hospitalization	Last dose <59 days ago, VISION	81 (70-88)*	93 (91-94)*
	Last dose 120-179 days ago, VISION	64 (56-71)*	84 (81-87)*
	3rd dose 7-120 days ago, IVY	Not estimated	86 (81-89)**
	3rd dose >120 days ago, IVY	Not estimated	79 (59-89)**
Critical illness/death	2nd dose median 256 days/3rd dose median 60 days ago, IVY	79 (66-87)	94 (88-97)



Booster receipt increases protection across all outcomes.
Booster dose VE remains high among non-immunocompromised individuals 4-6 months after dose.

*Among non-immunocompromised individuals ≥50 years of age. ** Among non-immunocompromised individuals ≥18 years of age.

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Summary: mRNA VE during Omicron

	Not immunocompromised	Immunocompromised
2-dose VE against:		
Infection (+/- symptoms)	Limited protection, fast waning	Not estimated
ED/UC	Higher protection, some waning	Not estimated
Hospitalization	Highest protection, some waning	Not estimated
3-dose VE against:		
Infection (+/- symptoms)	Some protection, evidence of waning	Not estimated
ED/UC	Some protection, limited waning	Some protection, clear waning
Hospitalization	Highest protection, limited waning	Highest protection, clear waning

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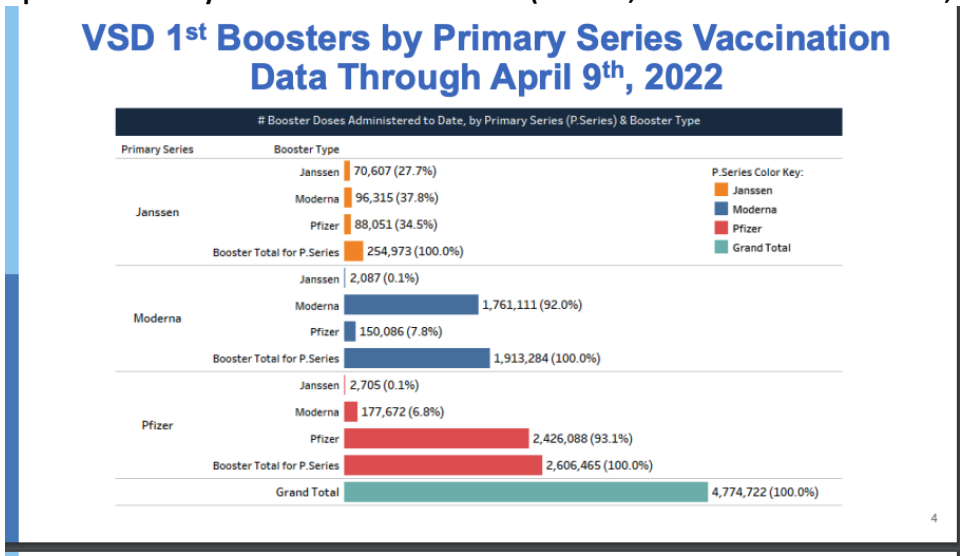
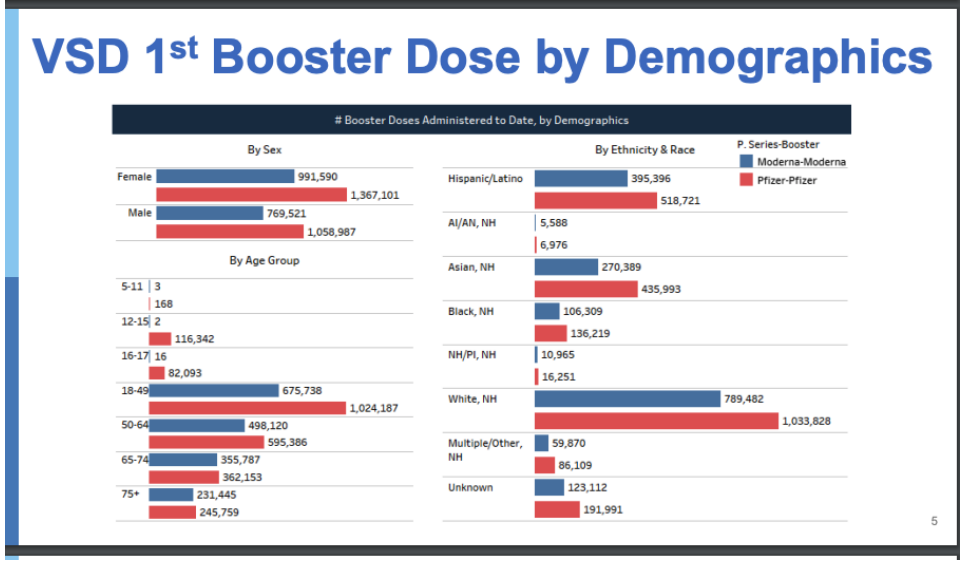
3. Updates on safety of COVID-19 booster dose (N. Klein, NCKP and T. Shimabukuro, CDC)





Signals for Pre-specified Outcomes in 21-day Risk Interval Through 4/12/22

Primary series with	*Pfizer - Pfizer OR Moderna - Moderna*	*Pfizer - Pfizer*	*Moderna - Moderna*	*Janssen*		
Signal after 1st Booster	**Pfizer OR Moderna**	**Pfizer**	**Moderna**	**Pfizer**	**Moderna**	**Janssen**
Outcome Event	**Signal?**					
Acute myocardial infarction	No	No	No	No	No	No
Appendicitis	No	No	No	No	No	No
Bell's palsy	No	No	No	No	No	No
Cerebral venous sinus thrombosis	No	No	No	-	-	No
Disseminated intravascular coagulation	No	No	No	No	-	No
Encephalitis / myelitis / encephalomyelitis	No	No	No	-	-	-
Guillain-Barre syndrome	No	No	No	No	-	No
Stroke, hemorrhagic	No	No	No	No	No	No
Stroke, ischemic	No	No	No	No	No	No
Immune thrombocytopenia	No	No	No	No	No	-
Myocarditis / pericarditis	Yes	No	No	No	No	No
Seizures	No	No	No	No	No	No
Transverse myelitis	No	No	No	-	-	-
Thrombotic thrombocytopenic purpura	No	No	No	-	-	No
Thrombosis with thrombocytopenia syndrome	No	No	No	-	No	-
Venous thromboembolism	No	No	No	No	No	No
Pulmonary embolism	No	No	No	No	No	No

"-" indicates that analyses are not yet possible.

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Chart Review Summary: Myocarditis and Pericarditis after a 1st mRNA COVID-19 Booster Vaccine

- All electronically-identified cases among all ages up to 98 days post vaccination are being chart-reviewed.
- Chart review is completed for 271 cases through March (25 potential cases pending).
- **Adjudicators verified 139/271 (51%) myocarditis/pericarditis cases.**
  - 12–39 years old: 53/68 (78%)
  - 40+ years old: 86/203 (42%)

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Chart Review Summary: Verified Myocarditis and Pericarditis cases after a 1st Booster Vaccine

	12–39 year olds	40+ year olds
Case verification (anytime after vaccination)	**53/68 (78%)**	**86/203 (42%)**
Male sex	38/53 (72%)	51/86 (59%)
History of COVID (>30 days prior to diagnosis)	10/53 (19%)	11/86 (13%)
History of myocarditis/pericarditis	2/53 (4%)	4/86 (5%)
Median age	25 years	68.5 years
Median time from vaccination to symptom onset	**4 days**	**29.5 days**
Adjudication diagnosis		
Myocarditis	12/53 (23%)	12/86 (14%)
Pericarditis	12/53 (23%)	**57/86 (66%)**
Myopericarditis	**29/53 (55%)**	17/86 (20%)

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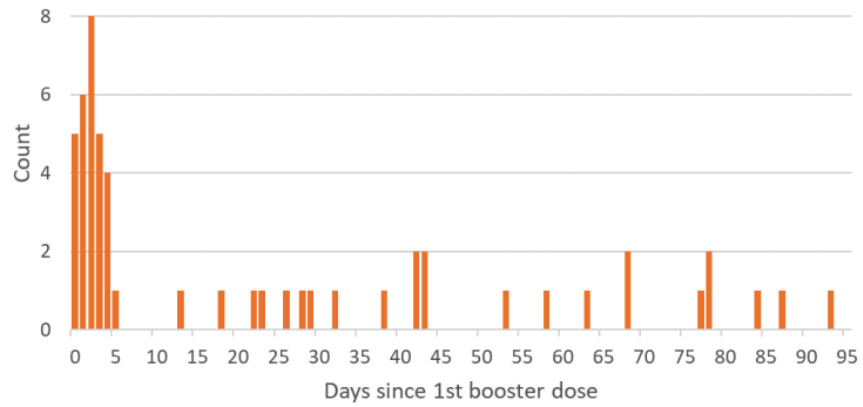
Timing of Symptom Onset after 1st Booster: 53 Verified Myocarditis and Pericarditis Cases in 12–39-Year-Olds



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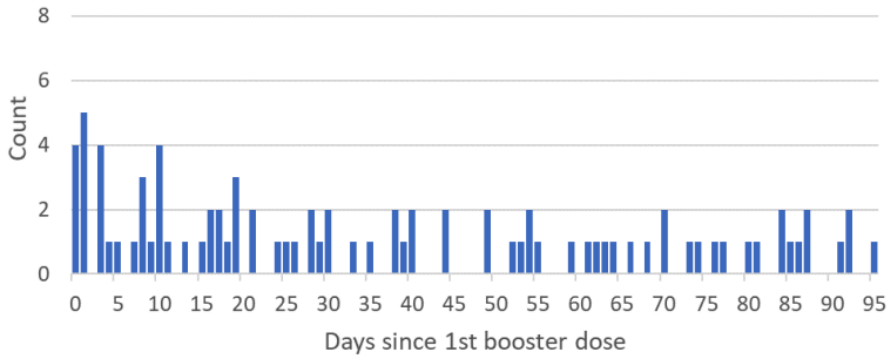
Timing of Symptom Onset after 1st Booster: 86 Verified Myocarditis and Pericarditis Cases in 40+ year-olds



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Verified Myocarditis and Pericarditis in the 0–7 Day Risk Interval

Compared with Events on the Same Calendar Days Among Primary Series and Boosted Comparators

					Analysis			
	Ages	Vaccine	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Events/Million Doses
Primary, Dose 2	12–39	Either	112	14	24.38	14.00 – 44.96	<0.001	38.2 (31.5 – 45.9)
	12–39	Pfizer	83	10	28.07	14.63 – 58.50	<0.001	41.4 (33.1 – 51.1)
	12–39	Moderna	28	3	24.49	7.82 – 105.14	<0.001	30.8 (20.5 – 44.5)
1st Booster[3]	12–39	Either	28	10	4.89	2.24 – 11.31	<0.001	20.3 (13.5 – 29.3)
	12–39	Pfizer	18	6	5.14	1.86 – 15.90	0.001	21.4 (12.7 – 33.8)
	12–39	Moderna[4]	5	3	3.64	0.79 – 19.45	0.097	17.0 (6.8 – 35.0)

[1]Comparison interval is 22–42 days after booster dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, calendar date, and time since primary series.
[3]"Either" includes heterologous and homologous primary -> booster doses. Product specific analyses include only homologous primary-> booster doses.
[4]Two additional cases were in the risk interval but were not included because there were no appropriate comparators. These cases are included in the events/million dose calculation.
[5]One additional case was in the risk interval but not included because there were no appropriate comparators. This case is included in the events/million dose calculation.

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Verified Myocarditis and Pericarditis in the 0–7 Day Risk Interval

Compared with Events on the Same Calendar Days Among Primary Series and Boosted Comparators

					Analysis			
	Ages	Vaccine	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Events/Million Doses
1st Booster[3]	12–39	Either	28	10	4.89	2.24 – 11.31	<0.001	20.3 (13.5 – 29.3)
	12–39	Pfizer	18	6	5.14	1.86 – 15.90	0.001	21.4 (12.7 – 33.8)
	12–39	Moderna[4]	5	3	3.64	0.79 – 19.45	0.097	17.0 (6.8 – 35.0)
	40+	Either[5]	11	15	2.30	0.95 – 5.43	0.063	4.0 (2.1 – 7.0)
	40+	Pfizer[5]	4	5	1.65	0.34 – 7.31	0.509	3.3 (1.1 – 7.6)
	40+	Moderna[4]	4	8	1.85	0.43 – 6.85	0.373	4.6 (1.7 – 10.1)

[1]Comparison interval is 22–42 days after booster dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, calendar date, and time since primary series.
[3]"Either" includes heterologous and homologous primary -> booster doses. Product specific analyses include only homologous primary->booster doses.
[4]Two additional cases were in the risk interval but were not included because there were no appropriate comparators. These cases are included in the events/million dose calculation.
[5]One additional case was in the risk interval but not included because there were no appropriate comparators. This case is included in the events/million dose calculation.

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Verified Myocarditis and Pericarditis in the 0–21 Day Risk Interval

Compared with Events on the Same Calendar Days Among Primary Series and Boosted Comparators

					Analysis			
	Ages	Vaccine	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Events/Million Doses
1st Booster[3]	12–39	Either	30	10	1.90	0.91 – 4.25	0.092	21.9 (14.8 – 31.2)
	12–39	Pfizer	19	6	2.07	0.79 – 6.05	0.146	22.8 (13.7 – 35.6)
	12–39	Moderna[4]	6	3	1.36	0.33 – 6.87	0.697	19.5 (8.4 – 38.5)
	40+	Either[5]	29	15	1.96	1.02 – 3.88	0.044	11.0 (7.5 – 15.4)
	40+	Pfizer[5]	15	5	3.01	1.06 – 9.68	0.038	12.5 (7.5 – 19.5)
	40+	Moderna[6]	9	8	1.28	0.42 – 3.80	0.650	9.3 (4.8 – 16.3)

[1]Comparison interval is 22–42 days after booster dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, calendar date, and time since primary series.
[3]"Either" includes heterologous and homologous primary -> booster doses. Product specific analyses include only homologous primary-> booster doses.
[4]Two additional cases were in the risk interval but were not included because there were no appropriate comparators. These cases are included in the events/million dose calculation.
[5]Four additional cases were in the risk interval but not included because there were no appropriate comparators. These cases are included in the events/million dose calculation.
[6]Three additional cases were in the risk interval but not included because there were no appropriate comparators. These cases are included in the events/million dose calculation.

19

Summary: Preliminary Findings of RCA Monitoring for 1st Boosters

- In weekly surveillance, the only safety signal has been for myocarditis/pericarditis in the 21 days after a 1st booster dose.
  - No other safety signals in weekly monitoring of pre-specified outcomes.
- Myocarditis/pericarditis differed between persons ages 12–39 and 40+ years.
  - 12–39 years: mostly myocarditis and myopericarditis with onset <7 days after 1st booster.
  - 40+ years: mostly pericarditis; cases more spread out in the 3 weeks after 1st booster.
- For persons ages 12–39 years, rate ratios for myocarditis/pericarditis 0–7 days after 1st booster dose were elevated.
  - Rate per million 1st booster doses administered was not higher than after primary series dose 2 mRNA COVID-19 vaccination.
- For persons ages 40 years and older, rate ratios for myocarditis/pericarditis were elevated, but less so, in the 0–7 and 0–21 days after the 1st booster dose compared with persons ages 12–39 years.
- Surveillance is ongoing.

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U.S. reports to VAERS following 1st booster mRNA COVID-19 vaccination* (as of April 11, 2022)

Doses admin†	Total reports	Median age	Male‡ n (%)	Female‡ n (%)	Non-serious n (%)	Serious n (%)
93,118,318	52,063	53 years	17,281 (33)	33,692 (65)	47,014 (90)	5,049 (10)

- Proportions by seriousness and sex were comparable to primary series
  - Most reports (90%) were non-serious
  - Most reports (65%) were among females

* Among persons receiving Pfizer-BioNTech dose 3: children and adolescents ages 12–15 years vaccinated during Jan 3 – April 11, 2022, and ages 16–17 years vaccinated during Dec 9, 2021 – April 11, 2022; adults ages ≥18 years vaccinated during September 22, 2021 – April 11, 2022. Among persons receiving Moderna booster doses, adults ages ≥18 years vaccinated during October 20, 2021 – April 11, 2022. All reports received and processed as of April 11, 2022.

† Doses of Pfizer-BioNTech dose 3 administered among children and adolescents ages 12–15 years during January 6 – Apr 14, 2022; adolescents ages 16–17 years during Dec 9, 2021 – April 14, 2022; adults ages ≥18 years during September 22, 2021 – April 14, 2022. Doses of Moderna dose 3 administered among adults ages ≥18 years during October 28, 2021 – April 14, 2022

‡ Sex was not reported in approximately 2% of reports.

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U.S. reports to VAERS following 1st booster mRNA COVID-19 vaccination, by race and ethnicity* (as of April 11, 2021)

Race and ethnicity	n (%)
Non-Hispanic White	25,508 (49)
Unknown or not reported	14,787 (28)
Hispanic†	3,616 (7)
Non-Hispanic Other	2,987 (6)
Non-Hispanic Black	2,264 (4)
Non-Hispanic Asian	1,764 (3)
Non-Hispanic multiracial	561 (1)
Non-Hispanic American Indian/Alaskan Native	520 (<1)
Non-Hispanic Native Hawaiian or Other Pacific Islander	56 (<1)
Total	**52,063**

* Among persons receiving Pfizer-BioNTech dose 3: children and adolescents ages 12–15 years vaccinated during Jan 3 – April 11, 2022, and ages 16–17 years vaccinated during Dec 9, 2021 – April 11, 2022; adults ages ≥18 years vaccinated during September 22, 2021 – April 11, 2022. Among persons receiving Moderna booster doses, adults ages ≥18 years vaccinated during October 20, 2021 – April 11, 2022. All reports received and processed as of April 11, 2022.

† Includes persons reported as of Hispanic ethnicity, but of unreported or unknown race.

25

Most frequently reported non-serious adverse events to VAERS following 1st booster mRNA COVID-19 vaccination (47,014 total non-serious reports)* (as of April 11, 2022)

Non-serious reports (all reports)

Rank	Adverse event (not mutually exclusive)	n (%)
1	Headache	6,119 (13)
2	Pyrexia	5,840 (12)
3	Pain	5,783 (12)
4	Fatigue	5,420 (12)
5	Expired Product Administered	5,082 (11)
6	Chills	4,836 (10)
7	Product Storage Error	4,030 (9)
8	Pain In Extremity	3,813 (8)
9	Nausea	3,209 (7)
10	Dizziness	2,982 (6)

Non-serious reports (clinical outcomes)†

Rank	Adverse event (not mutually exclusive)	n (%)
1	Headache	6,119 (13)
2	Pyrexia	5,840 (12)
3	Pain	5,783 (12)
4	Fatigue	5,420 (12)
5	Chills	4,836 (10)
6	Pain In Extremity	3,813 (8)
7	Nausea	3,209 (7)
8	Dizziness	2,982 (6)
9	Urticaria	2,966 (6)
10	Lymphadenopathy	2,896 (6)

* Among persons receiving Pfizer-BioNTech dose 3: children and adolescents ages 12–15 years vaccinated during Jan 3 – April 11, 2022, and ages 16–17 years vaccinated during Dec 9, 2021 – April 11, 2022; adults ages ≥18 years vaccinated during September 22, 2021 – April 11, 2022. Among persons receiving Moderna booster doses, adults ages ≥18 years vaccinated during October 20, 2021 – April 11, 2022. All reports received and processed as of April 11, 2022.

† Determined by subject matter expert consensus

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Most frequently reported serious adverse events to VAERS following 1st booster mRNA COVID-19 vaccination (5,049 total serious reports) (as of April 11, 2022)

Serious reports (all reports)

Rank	Adverse event (not mutually exclusive)	n (%)
1	Covid-19	1,196 (24)
2	Sars-Cov-2 Test Positive	997 (20)
3	Dyspnoea	817 (16)
4	Death	549 (11)
5	Chest Pain	440 (9)
6	Pyrexia	436 (9)
7	Asthenia	435 (9)
8	Condition Aggravated	396 (8)
9	Fatigue	386 (8)
10	Pain	369 (7)

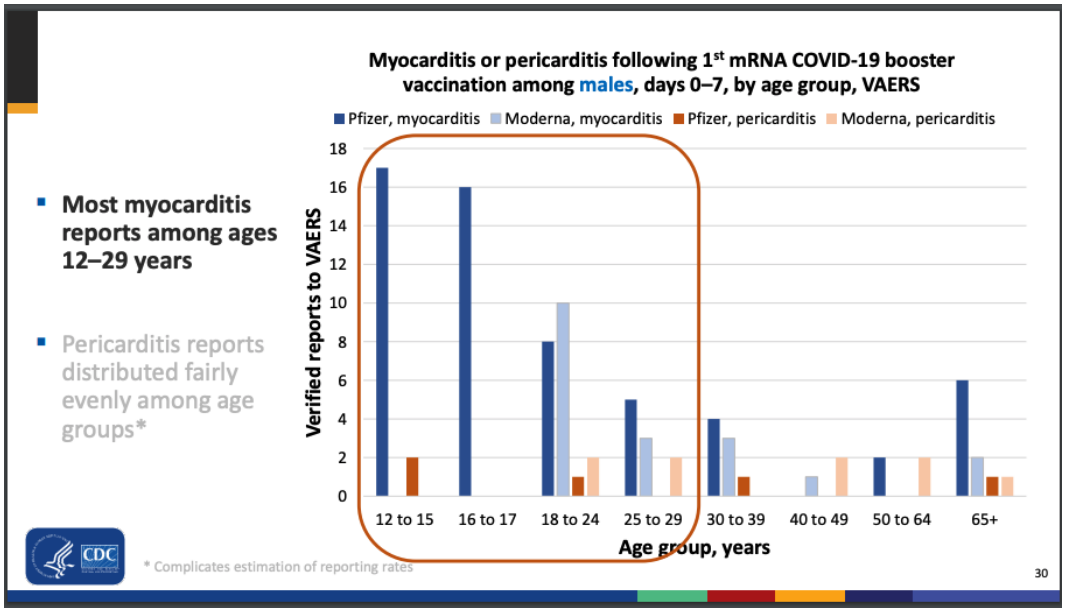
Serious reports (clinical outcomes)†

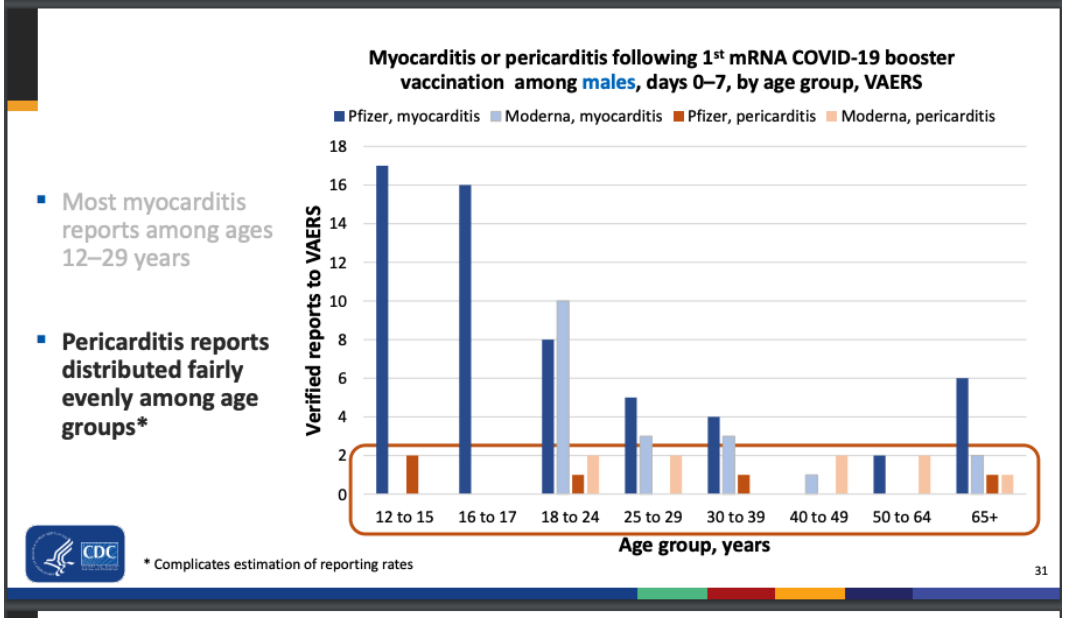
Rank	Adverse event (not mutually exclusive)	n (%)
1	Covid-19	1,196 (24)
2	Sars-Cov-2 Test Positive	997 (20)
3	Dyspnoea	817 (16)
4	Death	549 (11)
5	Chest Pain	440 (9)
6	Pyrexia	436 (9)
7	Asthenia	435 (9)
8	Fatigue	386 (8)
9	Pain	369 (7)
10	Cough	328 (7)

* Among persons receiving Pfizer-BioNTech dose 3: children and adolescents ages 12–15 years vaccinated during Jan 3 – April 11, 2022, and ages 16–17 years vaccinated during Dec 9, 2021 – April 11, 2022; adults ages ≥18 years vaccinated during September 22, 2021 – April 11, 2022. Among persons receiving Moderna booster doses, adults ages ≥18 years vaccinated during October 20, 2021 – April 11, 2022. All reports received and processed as of April 11, 2022.

† Determined by subject matter expert consensus

27


Myocarditis or pericarditis following 1st mRNA COVID-19 booster vaccination among males, days 0–7, by age group, VAERS
Pfizer, myocarditis
Moderna, myocarditis
Pfizer, pericarditis
Moderna, pericarditis
Most myocarditis reports among ages 12–29 years
Pericarditis reports distributed fairly evenly among age groups*
Verified reports to VAERS
0
2
4
6
8
10
12
14
16
18
12 to 15
16 to 17
18 to 24
25 to 29
30 to 39
40 to 49
50 to 64
65+
Age group, years
* Complicates estimation of reporting rates
30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30 to 39
40 to 49
50 to 64
65+
Age group, years
* Complicates estimation of reporting rates
31

Reporting rates of myocarditis (per 1 million doses administered) among males following 1st mRNA COVID-19 booster vaccination, by risk interval*

- **41,670,922** 1st mRNA COVID-19 booster vaccinations administered in males*
- Reporting rates exceed background incidence in ages 12–29 years
- Reporting rates highest in males ages 16–17 years, followed by 12–15 years

	Pfizer-BioNTech	Moderna
age group	Days 0–7	Days 0–7
12 to 15	17.2	N/A
16 to 17	23.2	N/A
18 to 24	5.4	12.1
25 to 29	4.8	4.0
30 to 39	1.5	1.5
40 to 49	0.0	<1.0
50 to 64	<1.0	0.0
65+	<1.0	<1.0

* Among persons receiving Pfizer-BioNTech dose 3: children and adolescents ages 12–15 years vaccinated during Jan 3 – April 11, 2022, and ages 16–17 years vaccinated during Dec 9, 2021 – April 11, 2022; adults ages ≥18 years vaccinated during September 22, 2021 – April 11, 2022. Among persons receiving Moderna booster doses, adults ages ≥18 years vaccinated during October 20, 2021 – April 11, 2022. All reports received and processed as of April 11, 2022. Doses administered as of April 14, 2022. An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for day 0–7 and 0–21 risk periods, this estimated background is 0.2 to 2.2 per 1 million person risk period.

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Clinical outcomes of myocarditis and pericarditis following 1st mRNA COVID-19 booster vaccination*

- **93,118,318** total booster doses administered*
- Patients not hospitalized received outpatient care
- Patients still recovering are stable or improving

	Myocarditis (N=110)	Pericarditis (N=38)
Hospitalized	90/110 (82%)	15/38 (39%)
Discharged	90/90 (100%)	15/15 (100%)
Known outcomes	86/90 (96%)	14/15 (93%)
Recovered from symptoms at last follow up	51/86 (59%)	10/14 (71%)

* Doses of Pfizer-BioNTech dose 3 administered among children and adolescents ages 12–15 years during January 6 – Apr 14, 2022; adolescents ages 16–17 years during Dec 9, 2021 – April 14, 2022; adults ages ≥18 years during September 22, 2021 – April 14, 2022. Doses of Moderna dose 3 administered among adults ages ≥18 years during October 28, 2021 – April 14, 2022

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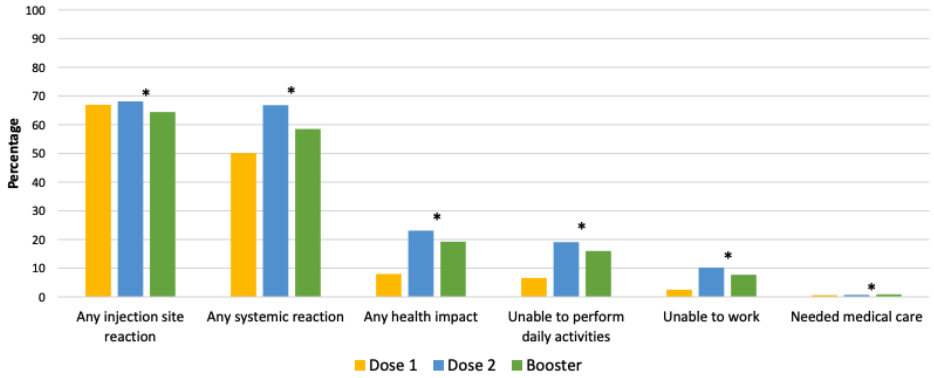
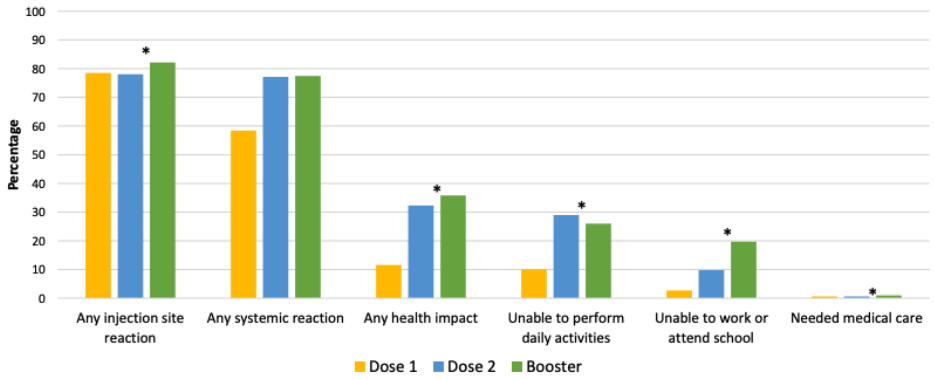
Reactions and health impact events reported by v-safe participants aged ≥18 years at least once in days 0–7 after homologous Pfizer-BioNTech vaccination, by dose



Includes 336,618 participants who completed at least one survey in the first week after each dose, data collected during September 22–April 10, 2022
* Dose 2 compared to dose 3: statistically significant difference (p-value <0.05) using multivariable generalized estimating equations model that accounted for the correlation between registrants and adjusted for demographic variables.

39

Reactions and health impact events reported by v-safe participants aged 12–17 years at least once in days 0–7 after homologous Pfizer-BioNTech vaccination, by dose



Includes 3,694 participants who completed at least one survey in the first week after each dose, data collected during December 9, 2021–April 10, 2022
* Dose 2 compared to dose 3: statistically significant difference (p-value <0.05) using multivariable generalized estimating equations model that accounted for the correlation between registrants and adjusted for demographic variables.

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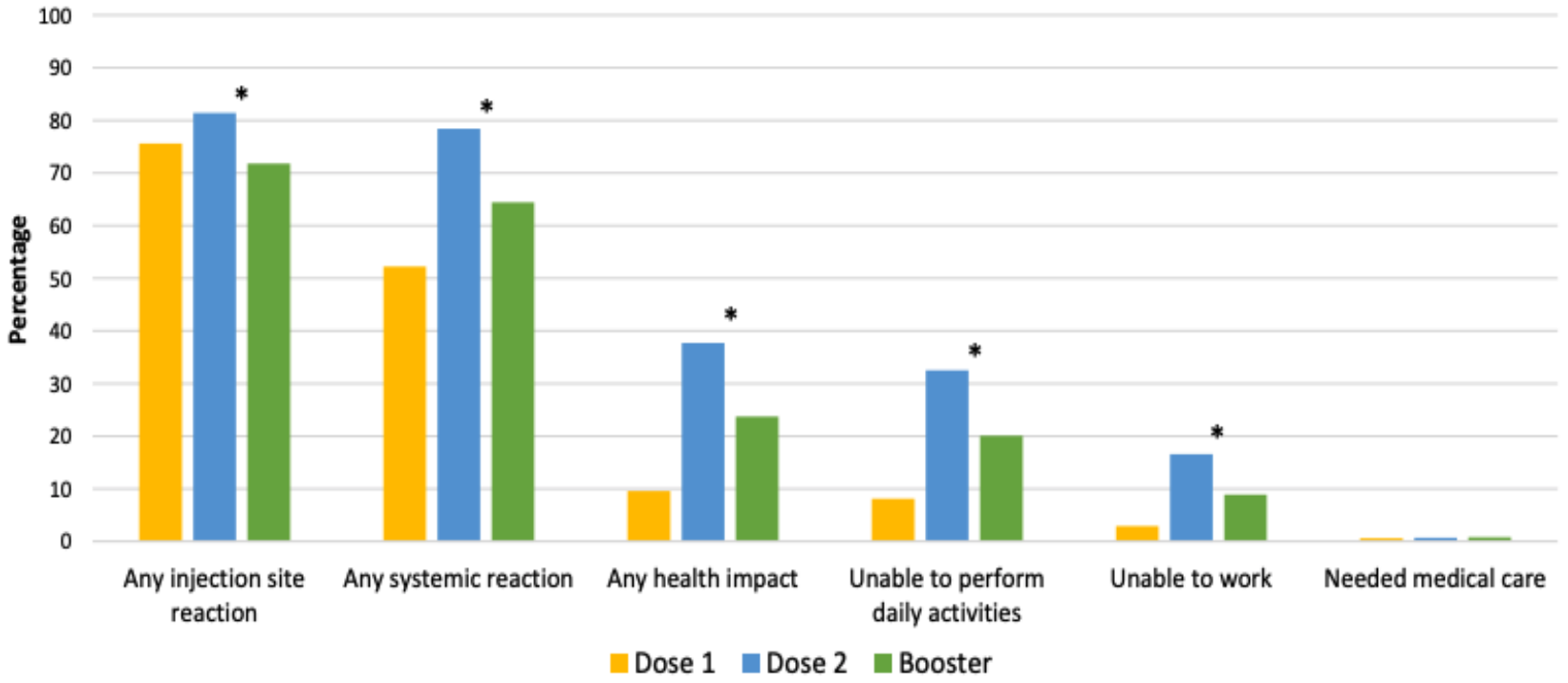
Reactions and health impact events reported by v-safe participants aged ≥18 years at least once in days 0–7 after homologous Moderna vaccination, by dose



Includes 311,374 participants who completed at least one survey in the first week after each dose, data collected during October 20–April 10, 2022
* Dose 2 compared to dose 3: statistically significant difference (p-value <0.05) using multivariable generalized estimating equations model that accounted for the correlation between registrants and adjusted for demographic variables.

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Summary

VSD Rapid Cycle Analysis (RCA) monitoring

- The only safety signal detected for any pre-specified outcome following 1st booster dose has been for myocarditis/pericarditis in the 21 days after mRNA COVID-19 vaccination
- Myocarditis/pericarditis differed between persons ages 12–39 and 40+ years
  - 12–39 years: mostly myocarditis and myopericarditis with onset <7 days after vaccination
  - 40+ years: mostly pericarditis; cases more spread out in the 3 weeks after vaccination
- For persons ages 12–39 years, rate ratios for myocarditis/pericarditis 0–7 days after 1st booster dose were elevated
  - Rate per million 1st booster doses administered was not higher than after dose 2 mRNA COVID-19 vaccination
- For persons ages 40 years and older, rate ratios for myocarditis/pericarditis were elevated, but less so in the 0–7 and 0–21 days after the 1st booster dose compared to persons ages 12–39 years

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Summary (cont.)

VAERS monitoring (after 93 million 1st mRNA COVID-19 booster vaccinations in the United Sates)

- Local and systemic reactions are most commonly reported following 1st booster dose
- 110 verified reports of myocarditis and 38 of pericarditis
  - Myocarditis reporting rates were highest among young males (ages 12–29 years)
    - Reporting rates for persons ages 12–29 years following 1st booster exceeded background, but were lower compared to post-dose 2 rates with primary series
  - Pericarditis reports were relatively rare, and distributed evenly among males and females and among the varied age groups
  - More myocarditis (82%) than pericarditis (39%) case patients were hospitalized
    - Most hospitalized patients recovered from symptoms at time of follow up*

V-safe monitoring

- No unusual or unexpected findings or new safety concerns identified

*Follow up varies based on timing of the report and healthcare records availability

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Summary (cont.)

- Active surveillance in VSD and passive surveillance in VAERS suggests an increased risk of myocarditis/pericarditis following the 1st mRNA COVID-19 booster vaccination
  - For myocarditis, the findings are consistent with those observed with primary series vaccination, but the risk appears to be lower following the 1st booster dose compared to dose 2 of primary series
    - Risk of myocarditis is highest in younger males with onset clustering within 0–7 days of 1st booster vaccination
    - Pericarditis is less common, more evenly distributed between males and females, and more evenly distributed across age groups
- Local and systemic reactogenicity and health impacts appear similar or attenuated for 1st mRNA COVID-19 booster vaccination compared to dose 2 of primary series
- Monitoring is ongoing

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4. **VaST assessment (K. Talbot, Wake Forest)**

Safety of first mRNA COVID-19 booster dose

- **v-safe**
  - Age ≥18 years: injection site, systemic reactions less frequent following booster than following primary dose 2
  - Age 12–17 years: frequency of reactions equal or slightly higher following booster than following primary dose 2
- **Vaccine Adverse Event Reporting System (VAERS)**
  - Myocarditis rates highest among males ages 12–29 years
    - Rates higher than background, lower than after primary dose 2
  - Pericarditis reported similarly by sex and age group
    - Low case counts complicate estimation of rates

5

Safety of first mRNA COVID-19 booster dose (continued)

- **Vaccine Safety Datalink (VSD) rapid cycle analysis**
  - Only safety signal: myocarditis/pericarditis in the 21 days after a 1st booster dose
  - Myocarditis/pericarditis differed by age group
    - 12–39 years: mostly myocarditis/myopericarditis, onset < 7 days after vaccination; rate per million 1st booster doses not higher than after primary series dose 2
    - ≥ 40 years: mostly pericarditis, onset up to 3 weeks after vaccination
- **Department of Veteran's Affairs (VA) rapid cycle analysis**
  - No safety signals observed for mRNA booster dose in a 21-day window.
  - Chart review confirmed 15 of 40 myocarditis/pericarditis reports after booster dose
    - 10 pericarditis, 5 myocarditis
    - 14 of 15 in persons age ≥ 40 years

6

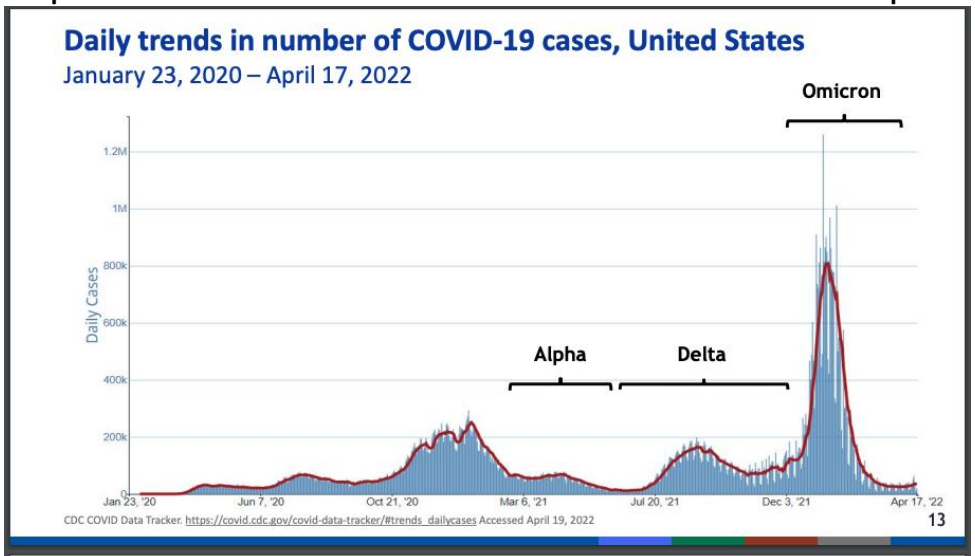
VaST assessment

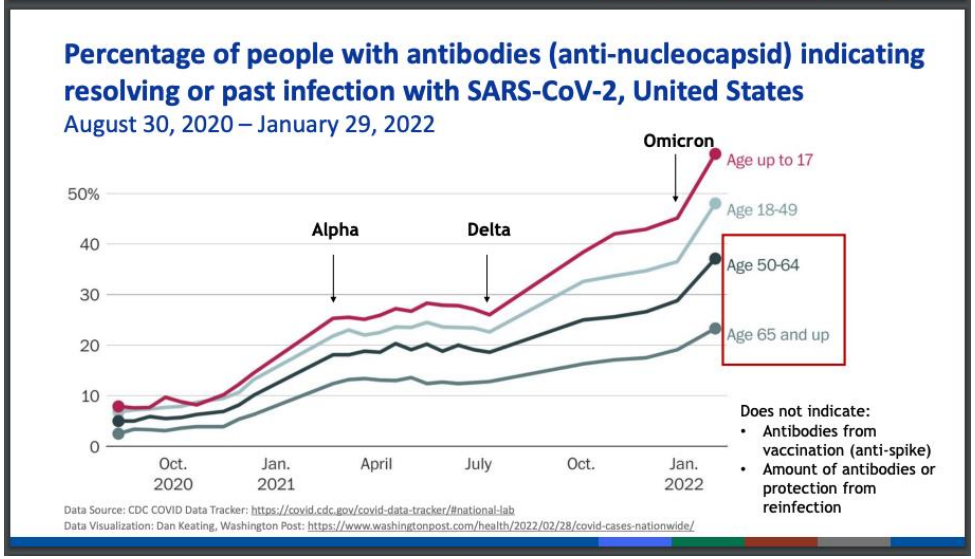
COVID-19 vaccine first booster dose safety data to inform second dose booster vaccination

- VaST has provided assessments on booster dose safety at 4 ACIP meetings
- Today's assessment included data from VSD as well as v-safe, VAERS, VA
- Reactogenicity is similar to or lower than that seen after the primary series
- Myocarditis risk appears lower than after a primary series dose 2
- Further work and analyses are needed to understand pericarditis risk
- While data do not suggest safety concerns beyond those previously identified, VaST will carefully monitor data on myocarditis and pericarditis after booster doses

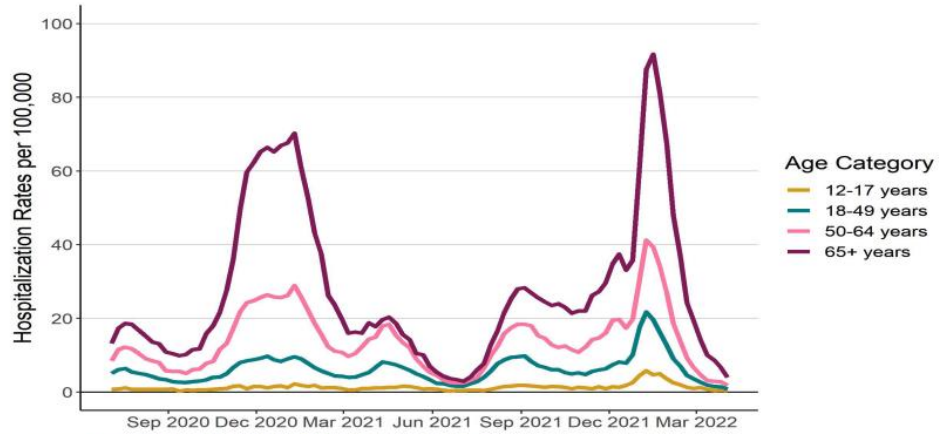
7

5. Updates on EtR Framework for booster doses adults 50+ and immunocompromised (S. Oliver, CDC)





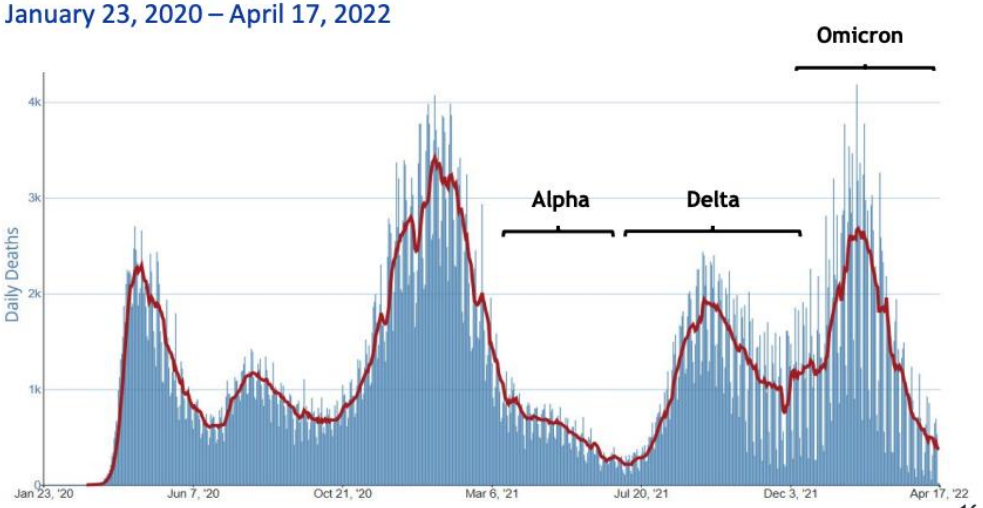
Weekly trends in COVID-19-associated hospitalization rates by age group, United States, July 4, 2020 – April 9, 2022



Source: CDC's COVID-NET, https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network, Accessed April 19, 2022

Daily trends in number of COVID-19 deaths, United States

January 23, 2020 – April 17, 2022



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths Accessed April 13, 2022

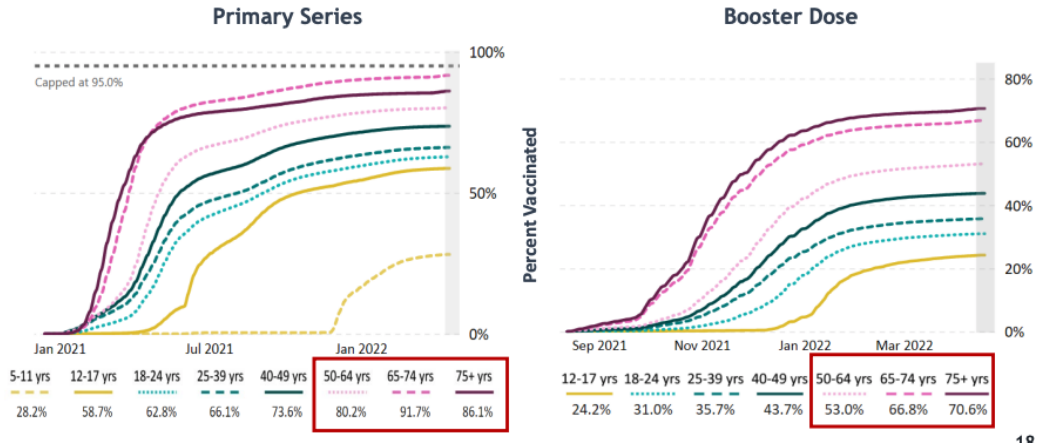
16

COVID-19 vaccinations in the United States,
As of April 18, 2022

218.9M **People fully vaccinated**	70.1% Population ≥5 Years of Age
99.5M **People received a booster dose***	47.2% Population ≥12 Years of Age

*This includes people who received booster doses and people who received additional doses.
https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed April 19, 2022

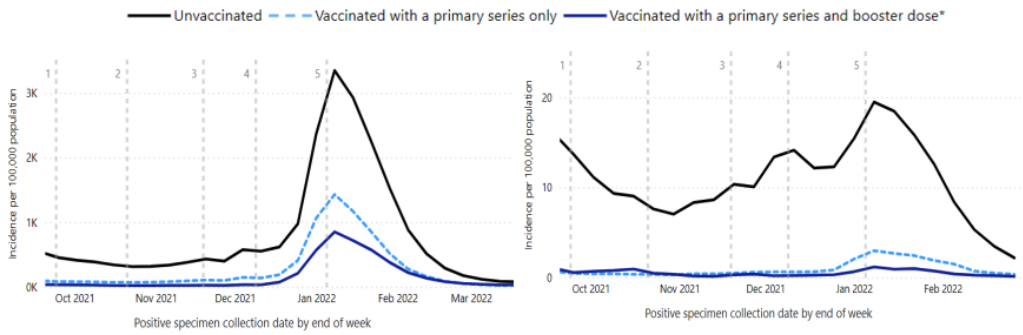
Percentage of people vaccinated with at least a primary series or booster dose by age group and date administered, United States



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed April 19, 2022

18

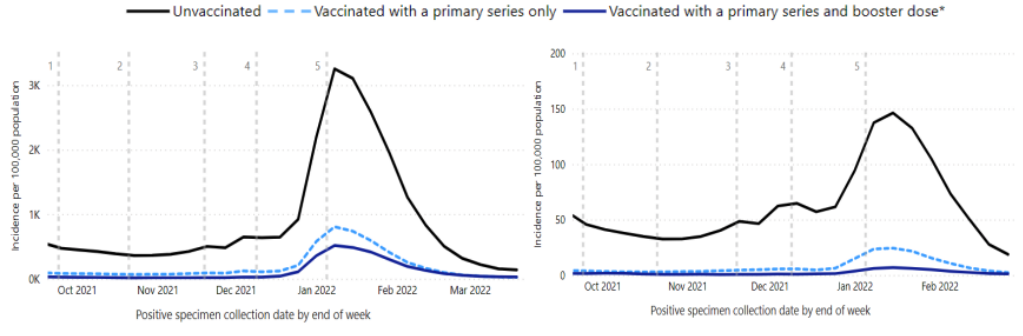
Age-adjusted rates of COVID-19 cases & deaths by vaccination status and receipt of booster dose among adults 50-64 years,*



*This includes people who received booster doses and people who received additional doses.
** Data from September 19, 2021 – March 19, 2022 (24 U.S. jurisdictions)
+ Data from September 19, 2021 – February 26, 2022 (23 U.S. jurisdictions)
CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed April 19, 2022

21

Age-adjusted rates of COVID-19 cases & deaths by vaccination status and receipt of booster dose among adults ≥65 years,*



*This includes people who received booster doses and people who received additional doses.
** Data from September 19, 2021 – March 19, 2022 (24 U.S. jurisdictions)
+ Data from September 19, 2021 – February 26, 2022 (23 U.S. jurisdictions)
CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed April 19, 2022

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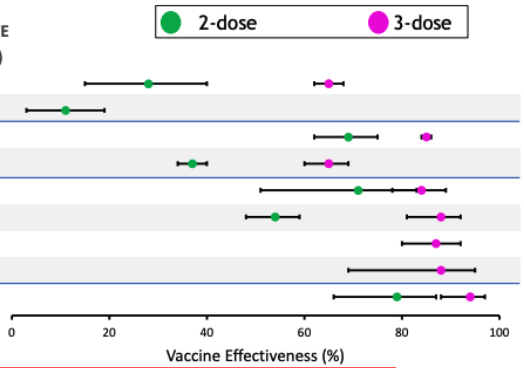
Summary: VE of 2 doses of mRNA vaccine increases with increasing severity of outcome during Omicron in adults ≥18 years; 3rd dose increases VE

		2-dose Adjusted VE % (95% CI)	3-dose Adjusted VE % (95% CI)
Infection	1mo post-last dose, ICATT	28 (15-40)	65 (62-68)
	3mos post-last dose, ICATT	11 (3-19)	--
Emergency department/ urgent care	Last dose <2m ago, VISION	69 (62-75)	85 (84-86)
	Last dose 4-<6m ago, VISION	37 (34-40)	65 (60-69)
Hospitalization	Last dose <2m ago, VISION	71 (51-83)	84 (78-89)*
	Last dose 4-<6m ago, VISION	54 (48-59)	88 (81-92)*
	3rd dose 7-120 days ago, IVY	Not estimated	87 (80-92)*
	3rd dose >120 days ago, IVY	Not estimated	88 (69-95)*
Critical illness/death	2nd dose median 256 days/3rd dose median 60 days ago, IVY	79 (66-87)	94 (88-97)



Booster receipt increases protection across all outcomes.
Booster dose VE remains high among immunocompetent individuals 4-6 months after dose.

*Among immunocompetent individuals ≥65 years of age.

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Summary: mRNA VE during Omicron

Persons with moderate to severe immunocompromise

	Immunocompetent	Immunocompromised
2-dose VE against:		
Infection (+/- symptoms)	Limited protection, fast waning	Not estimated
ED/UC	Higher protection, some waning	Not estimated
Hospitalization	Highest protection, some waning	Not estimated
3-dose VE against:		
Infection (+/- symptoms)	Some protection, evidence of waning	Not estimated
ED/UC	Some protection, limited waning	Some protection, clear waning
Hospitalization	Highest protection, limited waning	Highest protection, clear waning
	2-dose primary series + 1st booster	3-dose primary series

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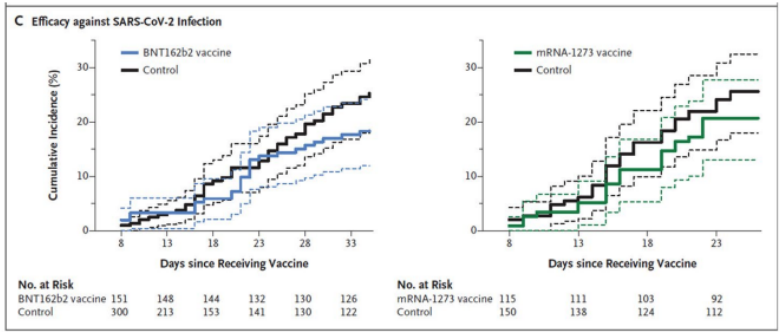
Summary

Public Health Problem

- Current 7-day average of COVID-19 cases ~**4%** of peak seen during Omicron surge
- COVID-19 related hospitalization admissions and deaths also continuing to decline from recent winter Omicron surge
- COVID-19 cases, hospitalizations, and deaths **2–20 times higher** in unvaccinated individuals in recent months, compared to vaccinated individuals
- Vaccine effectiveness for 3 doses (primary series + booster) in immunocompetent older adults remains **high**, especially for more severe outcomes

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among healthcare workers – Israel

- Vaccine efficacy against infection of 4 vs. 3 doses
  - Pfizer-BioNTech: 30% (-9%, 55%); Moderna: 11% (-43%, 44%)



https://www.nejm.org/doi/full/10.1056/NEJMc2202542

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among persons ages ≥60 years – Israel

- On January 2, 2022, began administering a 4th dose of Pfizer-BioNTech COVID-19 vaccine to people ages ≥60 years, who had received a 3rd dose of vaccine at least 4 months earlier
- Follow-up from January 10-March 2 for confirmed infection and February 18 for severe illness

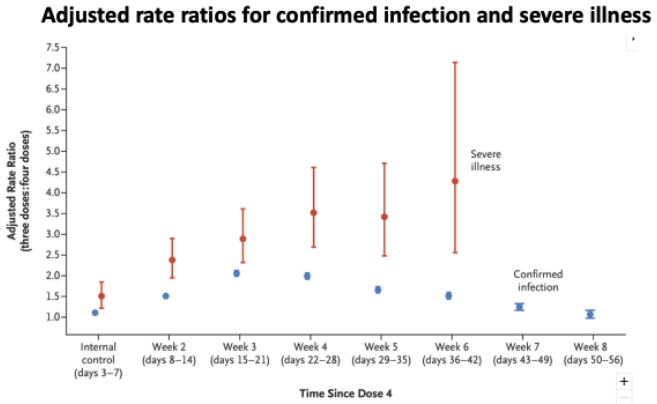
	Cases (person-days at risk)		Rate Ratio (95% CI)	Adjusted rate difference per 100,000 person-days at risk (95% CI)
	3rd dose only	Week 4 after 4th dose	3rd dose only vs week 4 after 4th dose	3rd dose only vs. week 4 after 4th dose
Confirmed infections	111,780 (31,000,299)	7,225 (3,883,824)	2.0 (1.9, 2.1)	170 (162, 176)
Severe illness	1210 (24,857,976)	66 (3,639,393)	3.5 (2.7, 4.6)	3.9 (3.4, 4.5)

4th dose estimated to prevent additional **3-4 cases** of severe disease per 100,000 person-days compared to 3 doses

https://www.nejm.org/doi/full/10.1056/NEJMoa2201570

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among persons ages ≥60 years – Israel

- Rapid waning of additional protection against infection



https://www.nejm.org/doi/full/10.1056/NEJMoa2201570

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among persons ages ≥60 in a large healthcare organization – Israel

- Included healthcare organization members ages ≥60 years, eligible to receive the fourth vaccine dose, with no previous PCR confirmed SARS-CoV-2 infection
- Matched to eligible persons who had not yet received a fourth dose according to a set of potential confounders
- 182,122 were recruited and matched to controls after receiving dose 4 and were followed for a median of 26 days (interquartile range: 7 to 30)

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2201688?articleTools=true

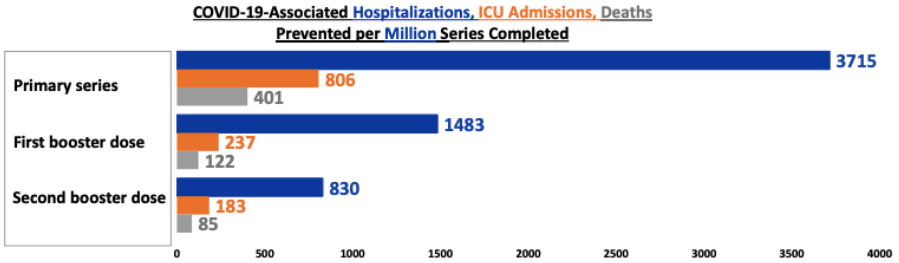
Benefits after mRNA COVID-19 booster dose among persons ages ≥50 years

Scenario:

- 55% VE for primary series[1]
- Boost to 88% VE for single booster[1]
- Assumed boost to 95% VE for second booster[2]

For every million series completed

Vaccine series	VE for hospitalization
Primary series	55%
Primary series + booster dose	88%
Primary series + second booster dose	95%



VE: Vaccine Effectiveness; [1] VE estimate from IVY and VISION: https://covid.cdc.gov/covid-data-tracker/#vaccine-effectiveness; [2] Relative VE estimate for 4th dose: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2201688?articleTools=true; COVID-NET hospitalization rates from the week of February 26, 2022

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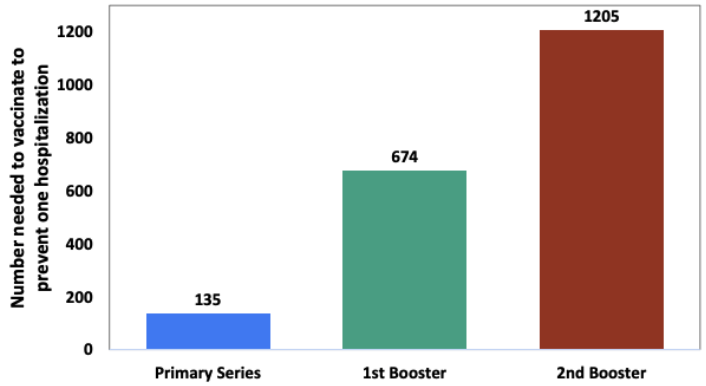
Number needed to vaccinate to prevent one hospitalization over 4 months in persons aged ≥50 years, primary series versus 1st booster versus 2nd booster



To prevent one hospitalization:
Need to vaccinate **5 – 9 times** as many persons with booster doses compared to primary series

Note: Number needed to vaccinate was calculated using the marginal benefit of each additional dose, therefore the number needed to vaccinate for each booster dose considers only the added benefit received from that booster dose

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Limitations

- The model assumes static hospitalization rate over 120 days
  - As rates increase, anticipated benefits also increase. Hospitalization rates among unvaccinated persons tend to have larger increases during times of increased transmission than those seen among vaccinated persons. Therefore, relative benefits of primary series compared to boosters will likely be larger during times of higher transmission.
- Model does not account for prior infection
- Unable to calculate benefits for persons with immunocompromise, however we anticipate that benefits would be greater and risks would be smaller in this population

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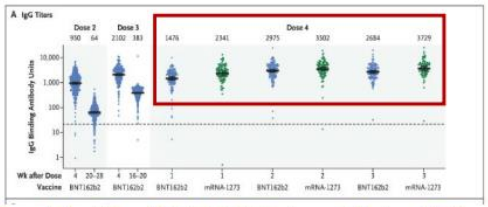
Other considerations:
Myocarditis and pericarditis

- Risk of myocarditis/pericarditis identified after COVID-19 vaccine booster doses in individuals ages ≥12 years
  - Among those ages **12–39 years**: mostly myocarditis and myopericarditis with onset <7 days after 1st booster; the risk is not as high as after the 2nd dose in primary series
  - Among those ages **≥40 years**: mostly pericarditis, and the small elevated risk is more spread out in the 3 weeks after 1st booster
- Next steps:
  - Evaluate severity and clinical course for pericarditis cases in individuals ages ≥40 years
- Continue to review COVID-19 vaccine booster dose safety data with VaST

Other considerations:
Immune tolerance

- Concern that giving additional doses of COVID-19 vaccine would lead to lower antibody levels (failure to restore antibody levels to what was seen after a previous dose) or T-cell exhaustion
- Data do not suggest this is a concern with COVID-19 vaccines currently
  - Antibody levels (IgG binding antibodies) after a 4th dose in Israel returned to similar levels seen shortly after a 3rd dose
- **Timing** between doses likely an important factor as well
  - When attempting to induce immune tolerance (e.g. allergy shots), must have very frequent (weekly/monthly) exposure
- Continue to closely monitor

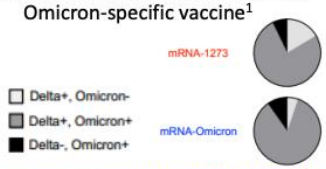


Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron | NEJM

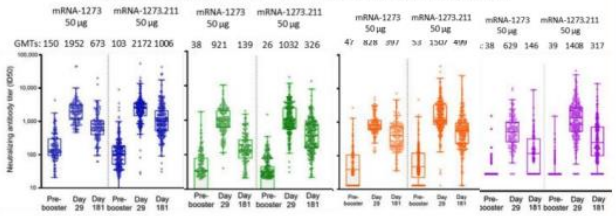
Other considerations:
Imprinting

- Concern that initial exposure to one virus strain primes B-cell memory and limits the development of memory B cells and neutralizing antibodies against new strains
- Data suggest a diverse response obtained after priming with current vaccines

In animal study, majority of memory B-cell responses after a booster were cross-reactive to multiple variants (dark grey) after both ancestral vaccine and Omicron-specific vaccine[1]



After being primed with ancestral SARS-CoV-2 containing vaccine, boost with ancestral or Beta-variant vaccine elicited neutralizing antibody titers to variety of variants[2]



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

Summary
Benefits and Harms

- Data from Israel demonstrate increased immune response after fourth dose
  - Higher rates of infection and severe illness seen in 3-dose recipients compared to 4-dose recipients
- Greatest benefit from vaccination is achieved from receipt of **primary series** and **first booster dose**
  - Additional benefits may be achieved through receipt of a second booster dose
- Known and possible **benefits outweigh risks** (including theoretical risks)
  - Individual factors that influence magnitude of benefits for second booster
  - Monitor additional data to inform theoretical risks

Summary

Values and Acceptability

- Majority of adults (60-80%) state they may get a second booster dose
  - Varies by age and race/ethnicity
- ~20% of boosted adults ages 50 and over would prefer a vaccine focused on new variants, and 10% state they would either get a vaccine now + fall, but not both
- Strong healthcare provider recommendation influential in decision to receive additional COVID-19 vaccine doses

Eligible population for second COVID-19 vaccine booster doses

- Among people who are fully vaccinated, approximately **52%** of people ages 50-64 years and **67%** of people ages ≥65 years have received a COVID-19 vaccine booster dose
- At the time of authorization, **~30** million people eligible (at least 4 months after their previous dose)
  - ~10 million eligible individuals ages 50-64 years
  - ~20 million eligible individuals ages ≥65 years
- Based on the timing of recommendations, people with immunocompromised conditions would not be eligible for second booster (5th total dose) until May 13th at the earliest

Uptake of second COVID-19 vaccine booster doses

- The number of people reportedly getting vaccinated has nearly tripled since authorization of second booster doses, to an average of 447,000 per day in the week ending April 8th, compared with 160,000 per day in the week ending March 29th.[1,2]
- As of April 19, 2022, approximately **1.1 million** second COVID-19 vaccine booster doses given in adults ages 50–64 years and **3.2 million** second booster doses given in adults ages ≥65 years since authorization

1. SEAN COVID-19 Survey Summary: April 15, 2022. https://www.langerresearch.com/wp-content/uploads/SEAN-COVID-19-Survey-Summary_4-15-22.pdf. Accessed April 15, 2022
2. CDC COVID Data Tracker. Trends in Number of COVID-19 Vaccinations in the US. https://covid.cdc.gov/covid-data-tracker/#vaccination-trends_vacctrends-total-daily. Accessed April 15, 2022
3. Data Source: IZDL All Admin

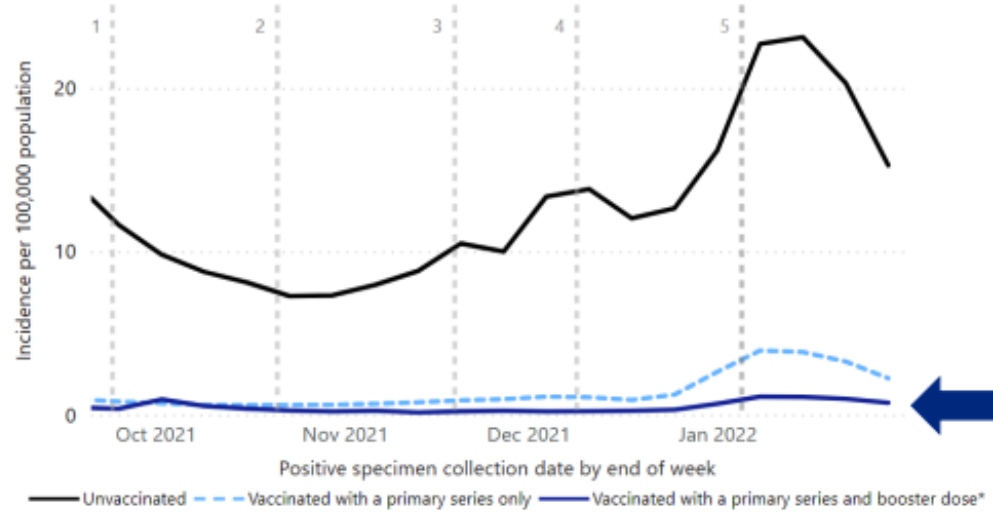
Summary

Equity

- Racial and ethnic minority groups are under-represented in the population ages ≥65 years, both overall and among COVID-19-associated hospitalizations
  - COVID-19-associated hospitalizations among adults ages 50-64 years are more consistent with underlying population
- Underlying medical conditions more prevalent in racial and ethnic minority groups
- A second booster recommendation for adults ages ≥50 years may prevent COVID-19 among persons from racial and ethnic minority groups and persons with underlying medical conditions

Summary

- Top priority remains **vaccination** of **unvaccinated individuals**
  - **Benefits** of COVID-19 vaccine primary series **largest** across all sex and age groups
  - Additional benefits to receiving first COVID-19 booster dose



Current policy question focused on the population with COVID-19 vaccine primary series and booster, with lowest rates of severe disease currently

Age-Adjusted Rates of COVID-19 Deaths by Vaccination Status and Receipt of Booster Dose, September 19 – January 29, 2022 (26 U.S. Jurisdictions) CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status

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Work Group Interpretation

Goals of COVID-19 vaccines:

- Primary goal: Prevention of **severe disease**
- Secondary goals:
  - Maintaining workforce and healthcare capacity
  - Reduce infection rates and risk of transmission
  - Improved mental health with more social interactions
  - Prevention of post-COVID conditions
- COVID-19 vaccines continue to offer **high levels** of protection against severe disease- especially for individuals who have received a booster dose
- Vaccines are a critical aspect of protection against severe COVID-19; monoclonal antibodies and antivirals are also essential
- Continued research into vaccines that may also have prolonged protection against SARS-CoV-2 infection (e.g. mucosal vaccines) important

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Work Group Interpretation

Adults ages 50 years and older

- The risk of COVID-19 increase with age; a 2nd booster (4th total dose) for older adults can help ensure those at risk are protected from severe disease
- Current VE data shows limited waning for immunocompetent adults after a 3rd dose
- Lower COVID-19 case counts and hospitalization rates currently
- May have recommendations for additional COVID-19 vaccines in the future
- Work Group supported recommendation that adults ages 50 and over may receive a 2nd COVID-19 vaccine booster dose

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Work Group Interpretation

Immunocompromised individuals ages 12 years and older

- Earliest eligibility for this 2nd booster (5th dose) would be mid-May, based on timing of previous recommendations
- Currently available VE data from 3rd dose in primary series; no VE data from the currently recommended 1st booster (4th dose)
- Lower COVID-19 case counts and hospitalization rates currently; however, immunocompromised individuals likely remain at higher risk for severe outcomes
- Important that immunocompromised individuals receive **all** doses of primary series (including additional doses) and 1st booster dose
- Work Group supported recommendation that immunocompromised individuals ages 12 and over may receive a 2nd COVID-19 vaccine booster dose

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Work Group Interpretation

- Recommendations that individuals **may receive** a COVID-19 vaccine 2nd booster reflect **current conditions** in the pandemic:
  - Wide availability of COVID-19 vaccines
  - High protection against severe disease from primary series and first booster dose
  - Low rates of COVID-19 cases and hospitalizations
  - Use of antivirals and monoclonal antibodies for SARS-CoV-2
- As the 2nd booster is already authorized and available, can rapidly adjust recommendations if COVID-19 epi changes in the future
- Current recommendation allows for **flexibility**, giving patients and providers **access** to this vaccine dose and the ability to decide based on individual factors and timing

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Summary

- Additional booster doses of COVID-19 vaccines likely be needed in the future
- Important to **optimize** vaccine recommendations based on current conditions, while maintaining **flexibility** to update recommendations as needed if epidemiology changes

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Question to ACIP

- What are the factors that would influence the benefit/risk discussion for patients and providers regarding second booster doses of COVID-19 vaccines?

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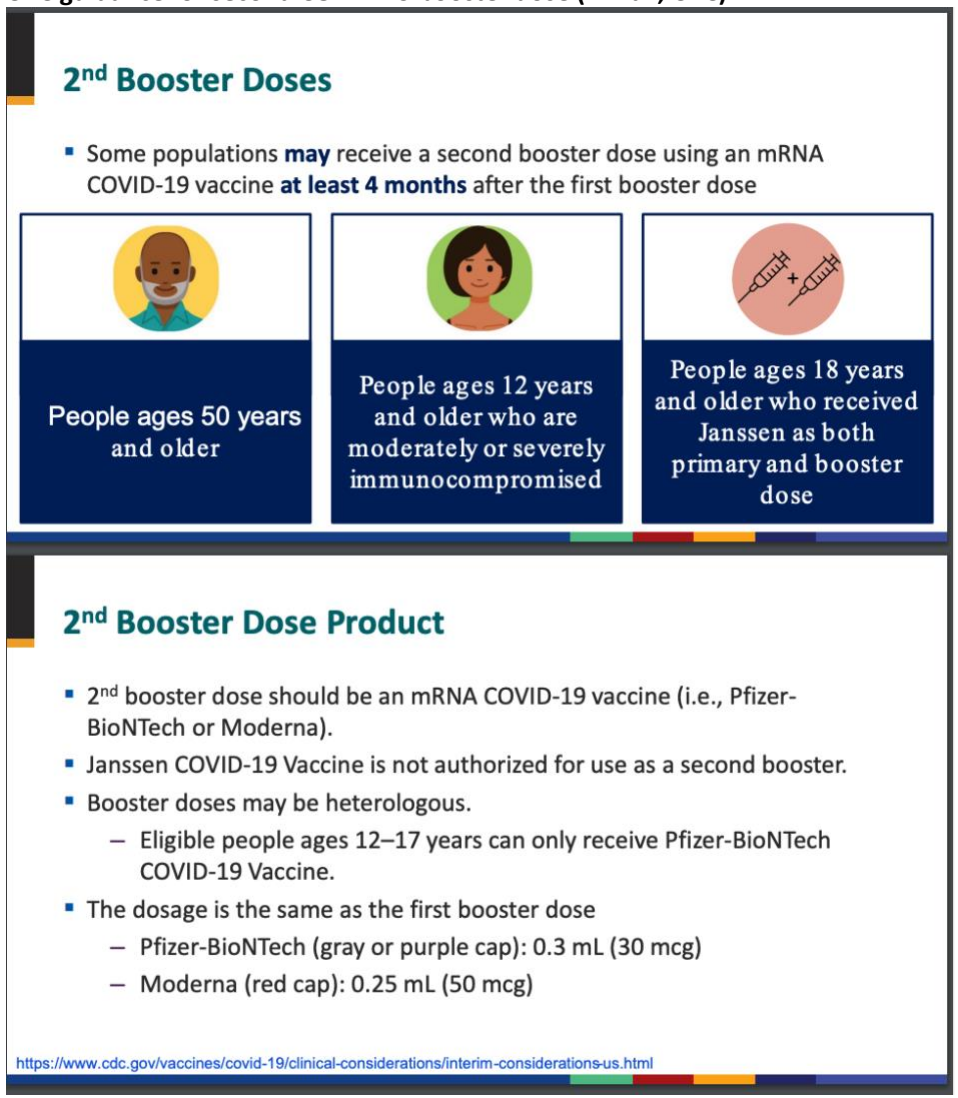
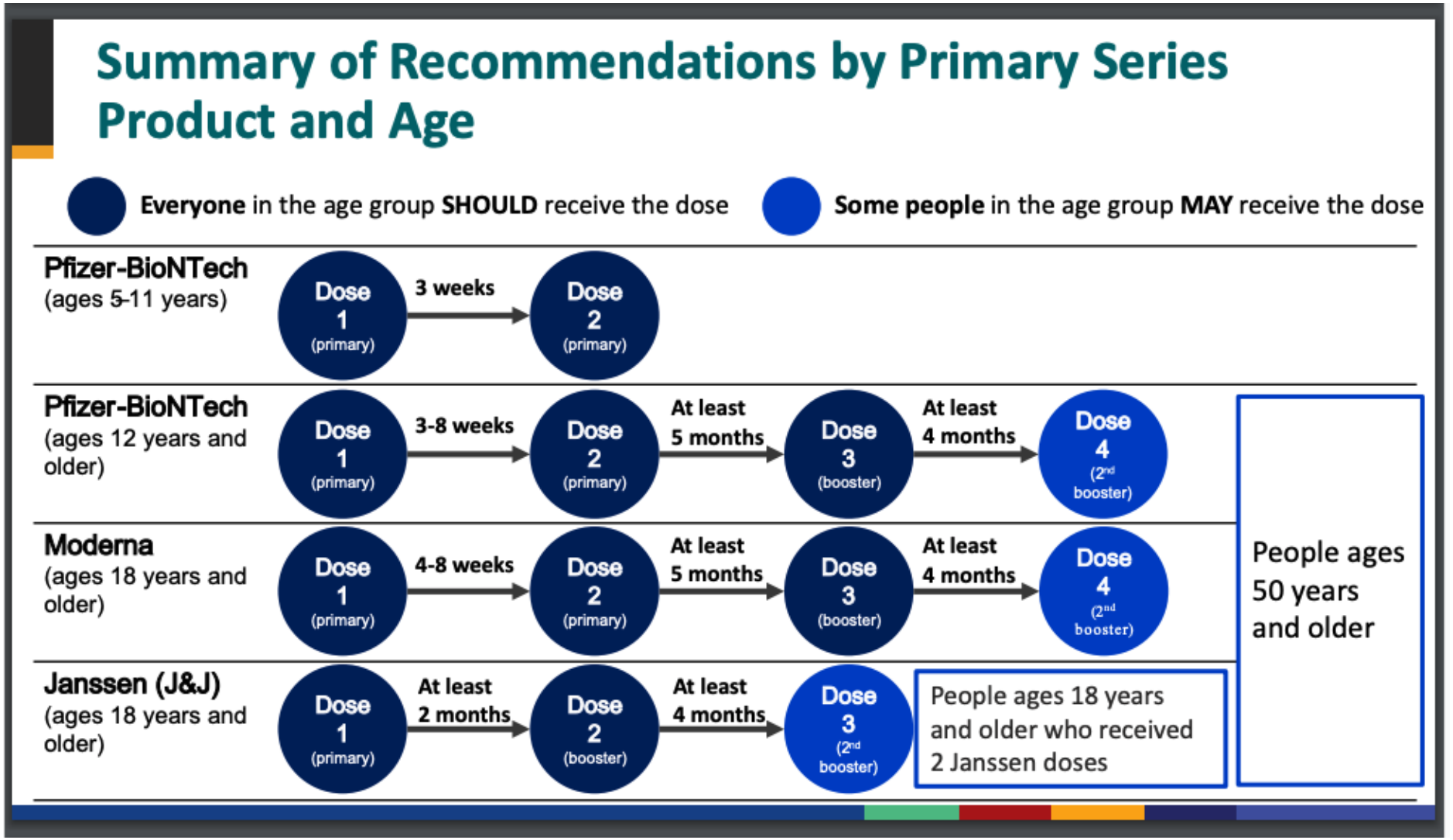
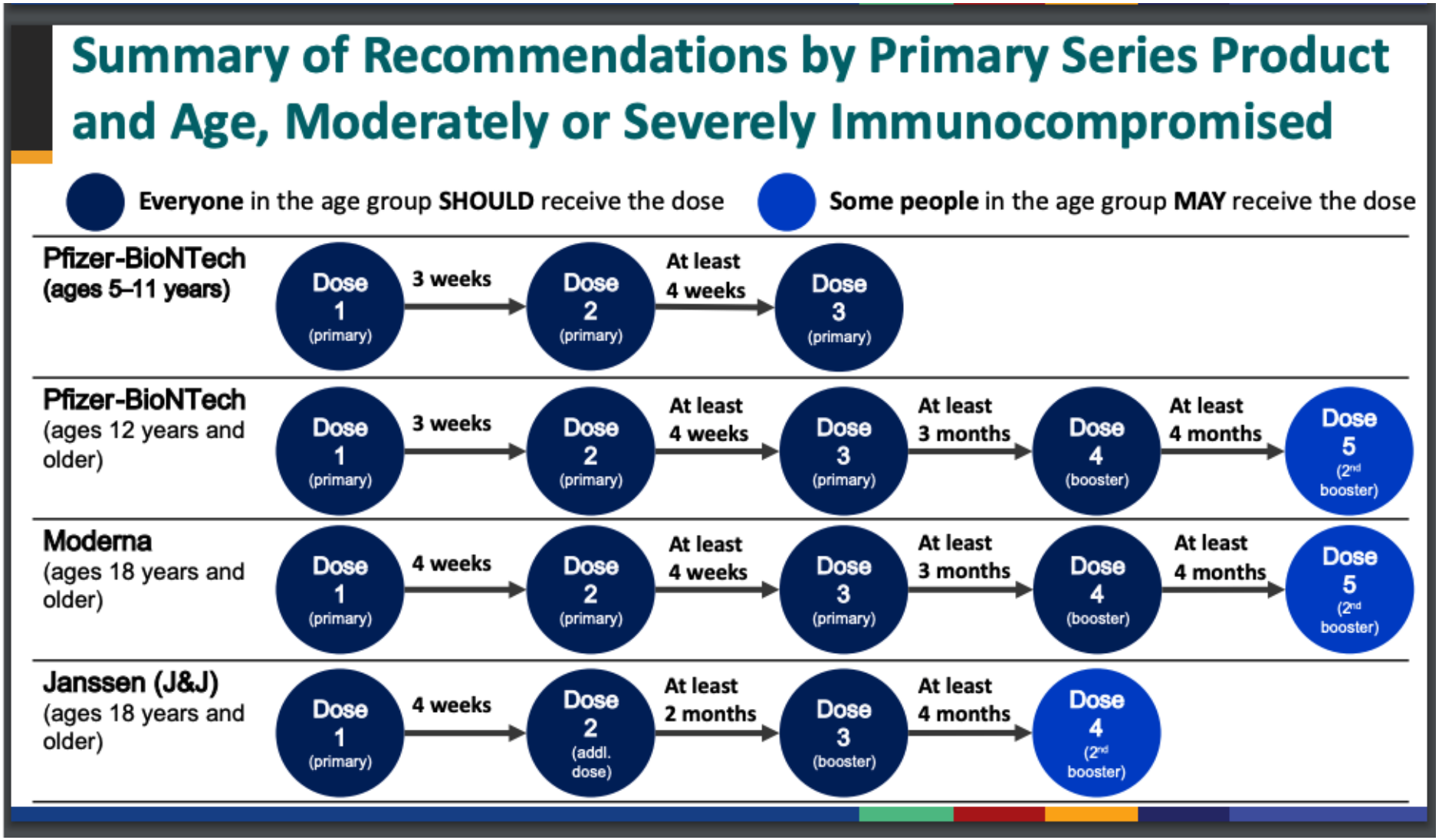
6. CDC guidance for second COVID-19 booster dose (E. Hall, CDC)




Summary of Recommendations by Primary Series Product and Age
Everyone in the age group SHOULD receive the dose
Some people in the age group MAY receive the dose
Pfizer-BioNTech (ages 5-11 years)
Dose 1 (primary)
3 weeks
Dose 2 (primary)
Pfizer-BioNTech (ages 12 years and older)
Dose 1 (primary)
3-8 weeks
Dose 2 (primary)
At least 5 months
Dose 3 (booster)
At least 4 months
Dose 4 (2nd booster)
Moderna (ages 18 years and older)
Dose 1 (primary)
4-8 weeks
Dose 2 (primary)
At least 5 months
Dose 3 (booster)
At least 4 months
Dose 4 (2nd booster)
Janssen (J&J) (ages 18 years and older)
Dose 1 (primary)
At least 2 months
Dose 2 (booster)
At least 4 months
Dose 3 (2nd booster)
People ages 18 years and older who received 2 Janssen doses
People ages 50 years and older

Summary of Recommendations by Primary Series Product and Age, Moderately or Severely Immunocompromised



Eligible People Who May Consider Getting the 2nd Booster Dose As Soon As Possible

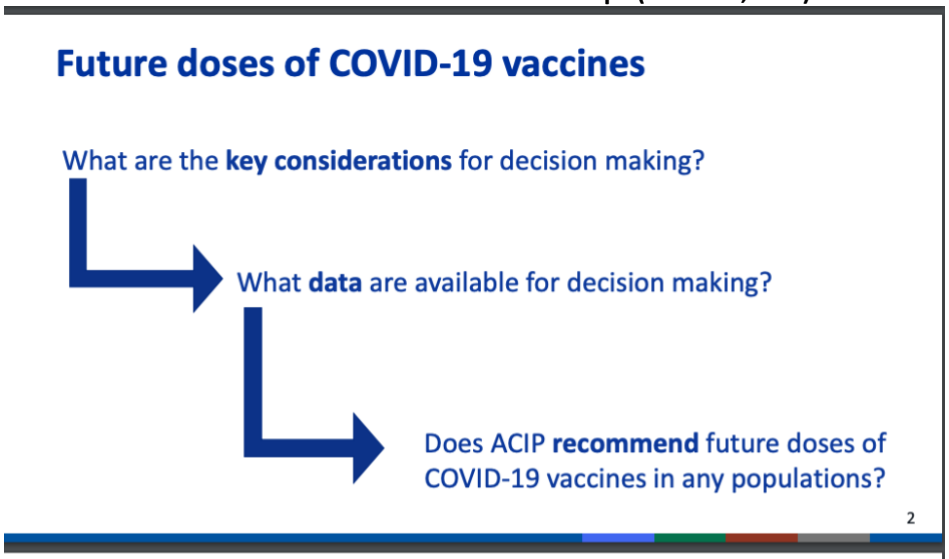
- People with certain underlying medical conditions that increase the risk of severe COVID-19 illness
- People who are moderately or severely immunocompromised
- People who live with someone who is immunocompromised, at increased risk for severe disease, or who cannot be vaccinated due to age or contraindication
- People at increased risk of exposure to SARS-CoV-2, such as through occupational, institutional, or other activities (e.g., travel or large gatherings)
- People living or working in an area where the COVID-19 community level is medium or high

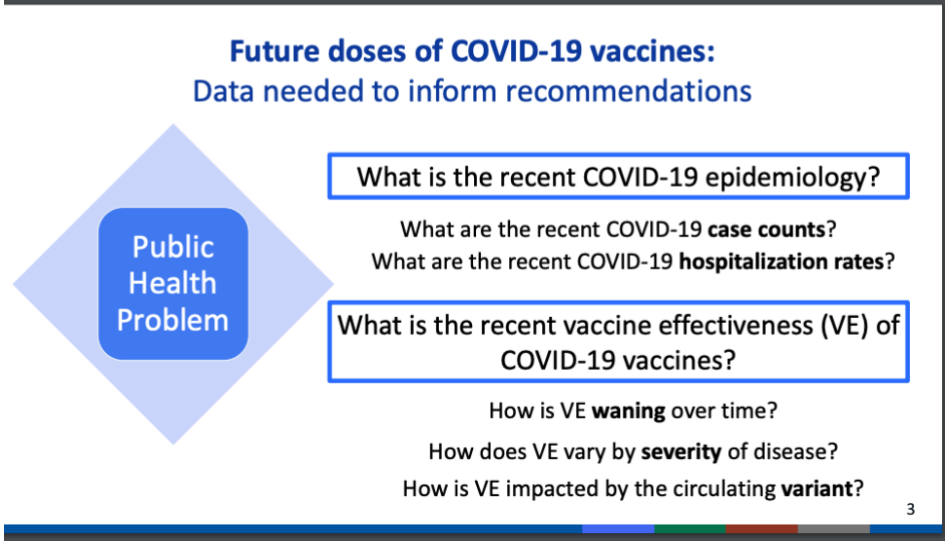
Eligible People Who May Consider Waiting to Receive a 2nd Booster Dose

- People with recent SARS-CoV-2 infection within the past 3 months
- People who may be hesitant about getting another recommended booster dose in the future, as a booster dose may be more important in the fall and/or if a variant-specific vaccine is needed.

N

7. Framework for future COVID-19 doses and next steps (S. Oliver, CDC)





Future doses of COVID-19 vaccines:
Data needed to inform recommendations

Public Health Problem

Does the need vary by **population**?

- Older adults
- Immunocompromised individuals
- Other vulnerable populations

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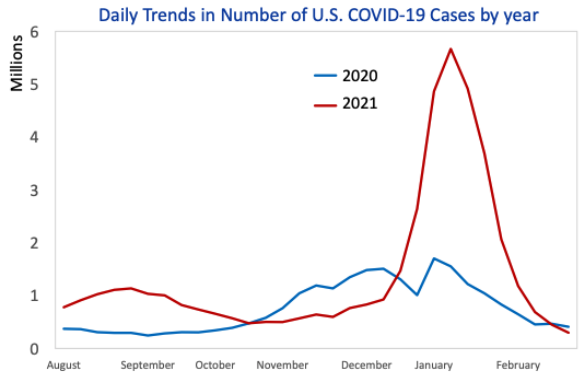
Future doses of COVID-19 vaccines

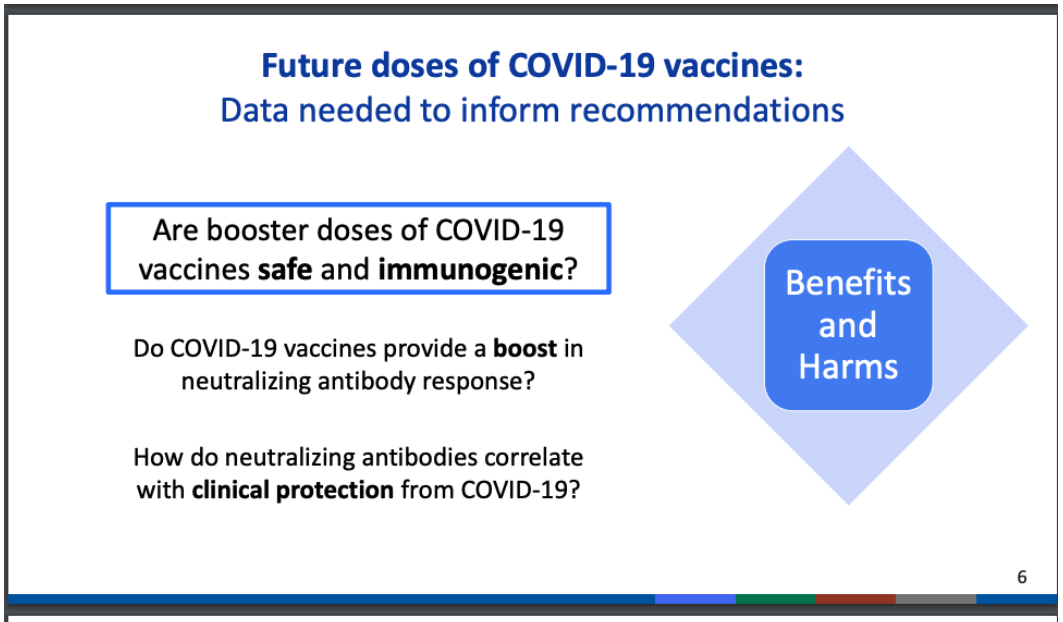
Public Health Problem

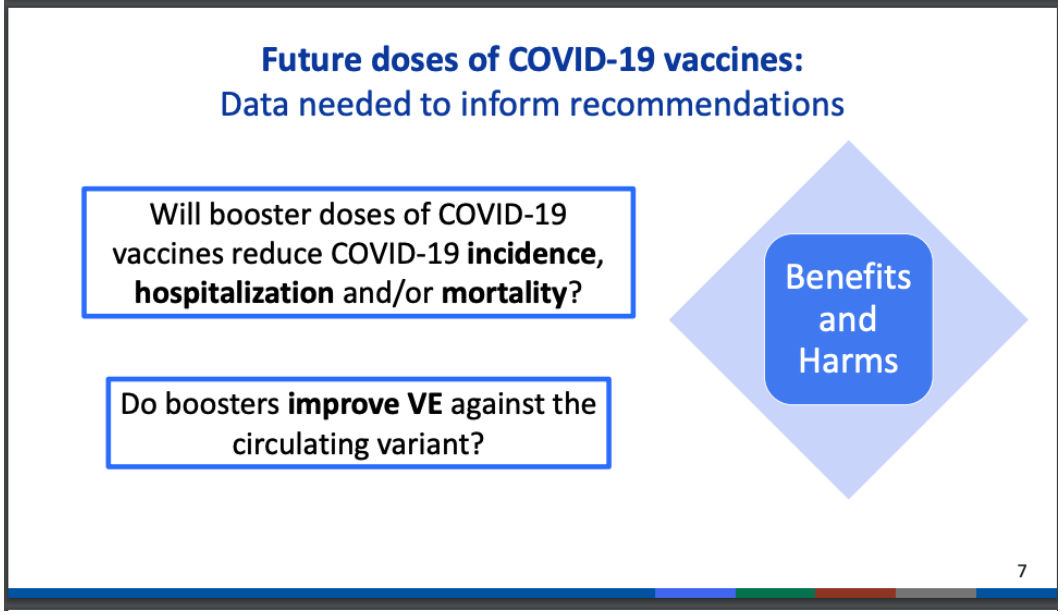
- COVID-19 epidemiology unpredictable to date, without defined seasonality
- Winter surges noted in the two prior years
  - 2020 surge began in October/November
  - 2021 surge began in December/January
- Likely difficult to predict timing of future surges



https://covid.cdc.gov/covid-data-tracker/#trends_dailycases

5


Future doses of COVID-19 vaccines:
Data needed to inform recommendations
Are booster doses of COVID-19 vaccines safe and immunogenic?
Do COVID-19 vaccines provide a boost in neutralizing antibody response?
How do neutralizing antibodies correlate with clinical protection from COVID-19?
Benefits and Harms
6


Future doses of COVID-19 vaccines:
Data needed to inform recommendations
Will booster doses of COVID-19 vaccines reduce COVID-19 incidence, hospitalization and/or mortality?
Do boosters improve VE against the circulating variant?
Benefits and Harms
7

Future doses of COVID-19 vaccines

Benefits and Harms

- Important to define **goal** of future doses of COVID-19 vaccines: prevention of infection/transmission or prevention of severe disease
  - Prevention of infection/transmission **time-limited**: would require timing of vaccine roll-out just prior to any increase in COVID-19 cases
  - Prevention of severe disease more **durable**: would allow more flexibility in timing of future vaccine roll-out
  - Preserving capacity of **healthcare infrastructure** in winter likely important
- Data may support different recommendations for general population and vulnerable populations

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Future doses of COVID-19 vaccines

Benefits and Harms

- Vaccines that prompt a **diverse immune response** likely provide better protection against current (and possibly future) SARS-CoV-2 variants
- Considerations for diverse immune response from COVID-19 vaccines:
  - **Time** between recommended doses of COVID-19 vaccines
  - Possibly expanding vaccines to include additional SARS-CoV-2 **variants**
  - Possibly expanding to include different COVID-19 vaccine **platforms** (e.g. protein subunit vaccines)

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Future doses of COVID-19 vaccines:
Data needed to inform recommendations

What are the **implementation considerations** for future doses of COVID-19 vaccines?

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Future doses of COVID-19 vaccines

- Important to have COVID-19 vaccine policy that is **simple**
  - Policies that differ by type of vaccine (current and previous doses) are difficult
  - For many vaccines, recommendations are not dependent on type of vaccine received previously
  - Vaccines based on timing (e.g. annual booster) may be easier to communicate than number (e.g. second booster, fourth dose, etc)

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Future doses of COVID-19 vaccines:
Summary

- Policy around future doses require **continued evaluation** of COVID-19 epidemiology and vaccine effectiveness, including the impact of both **time** and **variants**, and the ability of doses to **improve** protection
- Evolution of COVID-19 vaccines will be important as SARS-CoV-2 virus evolves
  - May include evolution of strains included in the vaccines as well as vaccine platform
- Vaccine policy that is **simple** and **easy to communicate** and implement will be important to optimize uptake
  - Balance simplicity with need to provide optimal protection to vulnerable populations

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Future doses of COVID-19 vaccines:
Summary

- Consider the impact of each COVID-19 vaccine recommendation:
  - Time and resources of pharmacies, providers and public health staff
  - Effect on vaccine confidence and uptake
  - Incremental balance of benefits and risks
  - Monitor for any negative impact of repeated boosting on antibody titers

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Future doses of COVID-19 vaccines:
Next Steps

- FDA and CDC will continue to partner for future discussions
- ACIP will continue to review additional data:
  - COVID-19 epidemiology, genomic surveillance and vaccine effectiveness
  - Manufacturer data on safety, immunogenicity and possible efficacy of variant-specific vaccines
- Further discussions around feasibility, implementation, and balance of benefit and risks by age group and population to inform the timing and populations for future doses of COVID-19 vaccines

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Questions for ACIP

1. What does ACIP think should be the primary **goal** for future doses of COVID-19 vaccines?
2. What other **data** would be important for ACIP to review?
3. What are other **considerations** for future doses of COVID-19 vaccines?

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Safety Platforms for Emergency vACcines (SPEAC)
Brighton Collaboration
The Task Force for Global Health
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Email: bc-coordinator@taskforce.org

www.brightoncollaboration.us