Vaccines and Related Biological Products Advisory Committee Meeting Report

Date: April 6, 2022

The Vaccines and Related Biological Products Advisory Committee met on April 6, 2022 to discuss considerations for COVID-19 vaccine booster doses and process for COVID-10 vaccine strain selection to address current and emerging variants. There was no discussion of specific products or votes taken, rather FDA organized summary presentations on the state of the pandemic to stimulate discussion of open scientific and policy questions. These questions included: what is the optimal strain composition for COVID-19 vaccines to address current and emerging SARS-CoV-2 variants; when and how frequently to consider strain composition changes; how to implement a formal process for COVID-19 vaccine strain selection; and what is the optimal timing for use of COVID-19 vaccine booster doses among the general population and among specific sub-populations. The purpose of this VRBPAC meeting was to discuss a framework to address some of the challenges posed by these outstanding questions.

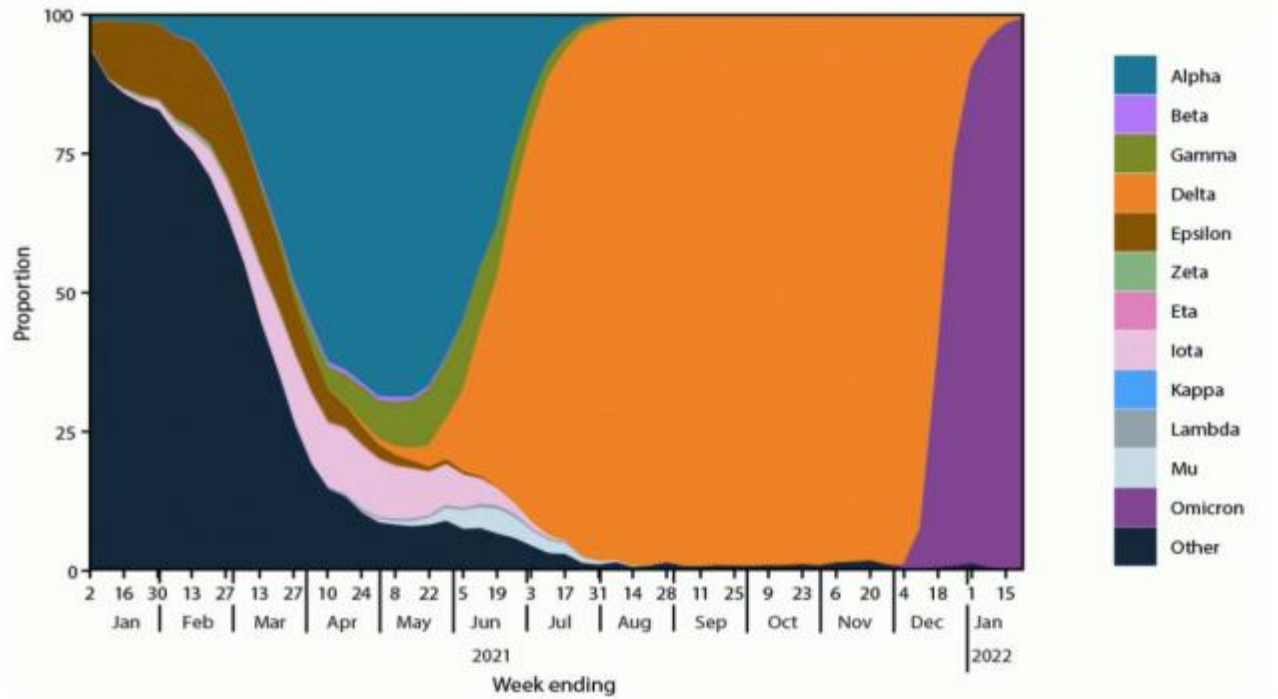
Presentations included Update on the Epidemiology of COVID-19 Variants (CDC), COVID-19 Vaccine Effectiveness in Children and Adults (CDC), Israeli Experience with Fourth Booster Doses in Older Adults (Israeli MOH and Weissman Institute), Predicting Future SARS-CoV-2 Variants (NIAID and Fred Hutch), Modeling of Future US COVID-19 Outbreaks (IHME, Wash U), WHO Perspective on Variants for COVID-19 Vaccine Composition (WHO Melbourne), Perpective on Variant Vaccine Development and Production (BARDA) and Proposed Framework for Addressing Future COVID-19 Outbreaks (CBER). Following this, there was the Public Hearing and 2.5h of committee discussion of how to address FDA questions. Key takeaways (many remained open questions):

- Covid is constantly changing and although less severe, Omicron still has resulted in a lot of hospitalizations
- CDC presented data showing that a second booster dose does benefit but perhaps for only a short time
- mRNA #3 receipt increases protection across all severity outcomes and remains high among immunocompetents for 4-6 mo
- Israeli data on mRNA #4 in 60+ results in 2-4-fold further protection against death compared with mRNA #3 precipients (NEJM today)
- New strains most likely will come from Omicron variants but it's possible that another variant will emerge out of nowhere that evades vaccine
- WHO presented how they choose new influenza strains but also highlighted differences for COVID, especially that there is not clear seasonality
- BARDA presentation outlined timeline of manufacturing; should we make multivalent vaccines or stick with monovalent? For new vaccine for fall, clinical trials have to start in early May to meet demand
- What lab results will tell us we need an updated vaccine? Real-world effectiveness needs to be part of the decision as no CoP as yet
- FDA stated if vaccine is changed, this will be applied to all vaccines to minimize confusion in the field with differing regimens
- Consensus that we can't keep boosting every few months; what level of protection will be enough?
- Another meeting is planned on this topic, likely early summer
- A selection of slides from the various presentations can be found in the following pages, the full set of slide presentations can be found HERE.

1. **Update on Epidemiology of SARS-KCoV-2 Strains (H. Scobie, CDC)**

Changing Landscape of Circulating Variants

FIGURE 1. National weekly proportion estimates* of SARS-CoV-2 variants' — United States, January 2, 2021–January 22, 2022

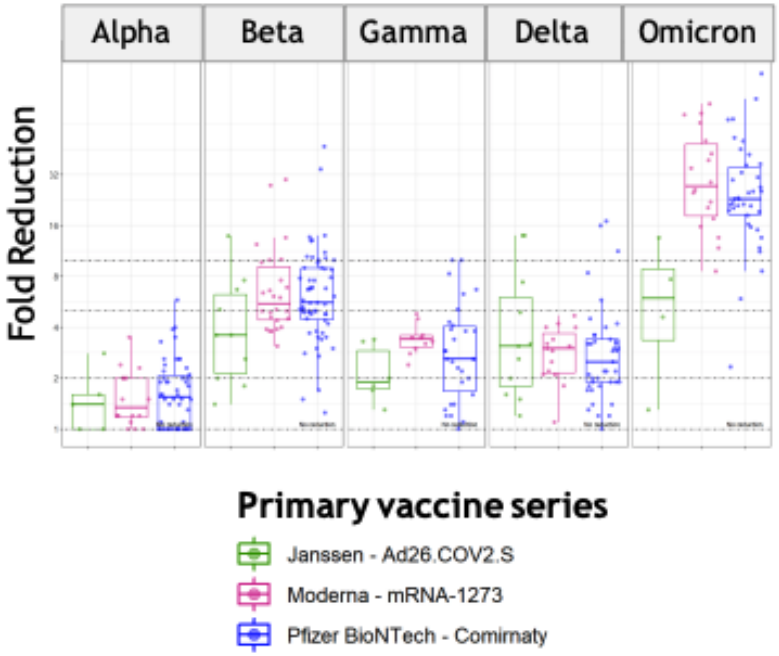


Lambrou et al. Genomic Surveillance for SARS-CoV-2 Variants: Predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) Variants — United States, June 2021-January 2022 https://www.cdc.gov/mmwr/volumes/71/wr/mm7106a4.htm

Neutralization of Omicron Variant by Sera from Vaccinees

Studies (n=42) of U.S. vaccines using both pseudoviruses & live viruses

- Reduction compared with wild-type:
  - 25-fold for mRNA vaccine without booster dose
  - 6-fold for mRNA vaccine with booster dose
- Neutralization of Omicron below limit of detection for many individuals receiving two mRNA doses or one Janssen dose
  - Above limit of detection in many vaccinated people receiving booster or who were also previously infected
- Given detection limits of assays, difficult to evaluate whether people have levels of antibodies needed to protect against severe disease



Source: Data Summary and Neutralization Plots at ViewHub by IVAC https://view-hub.org/resources, Accessed March 28, 2022
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-12-16/06-covid-scobie-508.pdf

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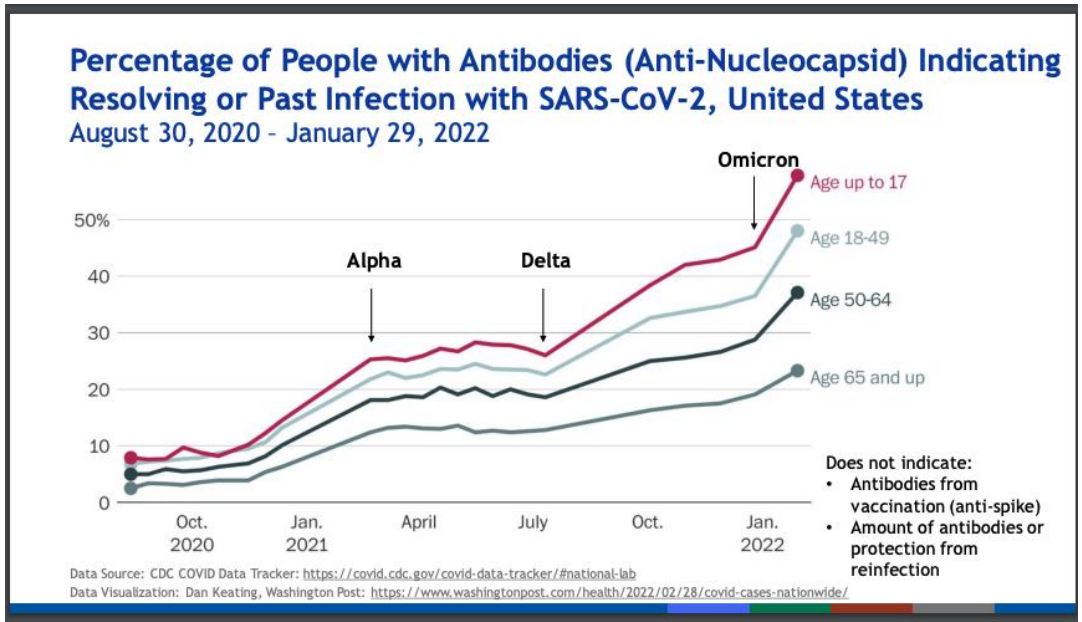
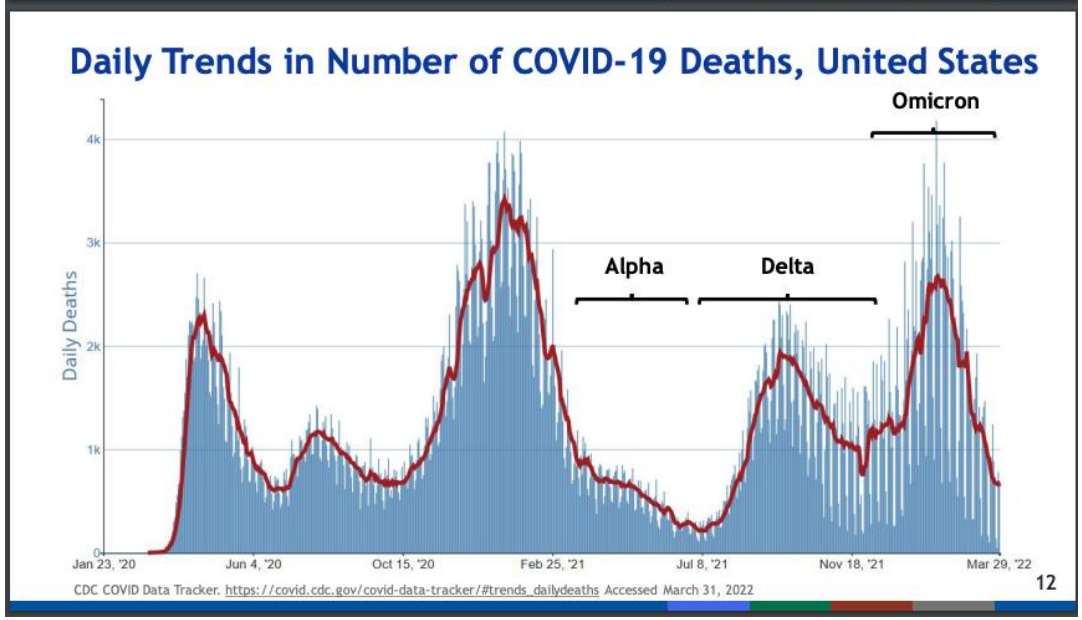

Percentage of People with Antibodies (Anti-Nucleocapsid) Indicating Resolving or Past Infection with SARS-CoV-2, United States
August 30, 2020 – January 29, 2022
Omicron
Age up to 17
Age 18-49
Age 50-64
Age 65 and up
Alpha
Delta
50%
40
30
20
10
0
Oct. 2020
Jan. 2021
April
July
Oct.
Jan. 2022
Does not indicate:
• Antibodies from vaccination (anti-spike)
• Amount of antibodies or protection from reinfection
Data Source: CDC COVID Data Tracker: https://covid.cdc.gov/covid-data-tracker/#national-lab
Data Visualization: Dan Keating, Washington Post: https://www.washingtonpost.com/health/2022/02/28/covid-cases-nationwide/


Daily Trends in Number of COVID-19 Deaths, United States
Omicron
Alpha
Delta
Daily Deaths
4k
3k
2k
1k
0
Jan 23, '20
Jun 4, '20
Oct 15, '20
Feb 25, '21
Jul 8, '21
Nov 18, '21
Mar 29, '22
CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths Accessed March 31, 2022
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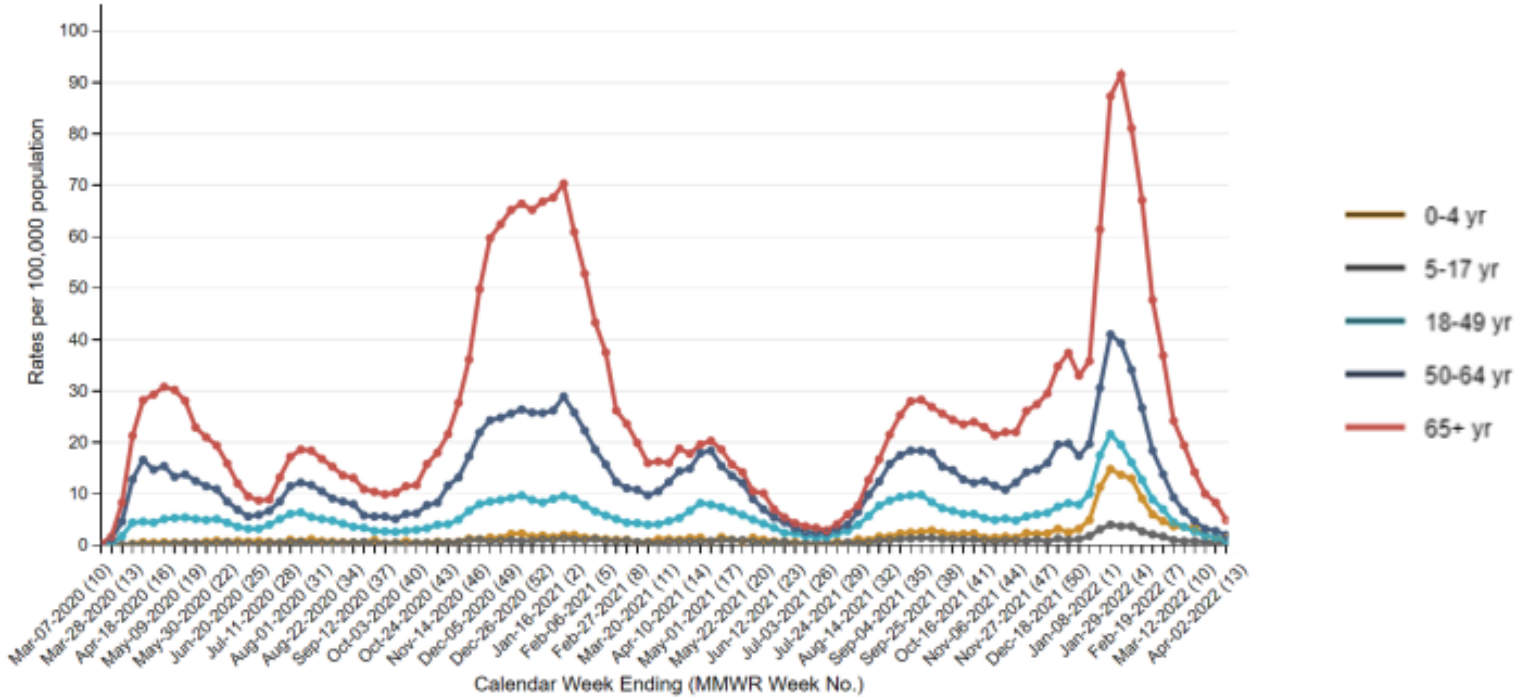
Weekly Trends in COVID-19-Associated Hospitalization Rates by Age Group, United States, March 7, 2020 - March 26, 2022



A population-based surveillance system (COVID-NET) collected data on laboratory-confirmed COVID-19-associated hospitalizations among adults through a network of over 250 acute-care hospitals in 14 states.

CDC COVID-NET. https://gis.cdc.gov/grasp/covidnet/covid19_3.html Accessed March 31, 2022

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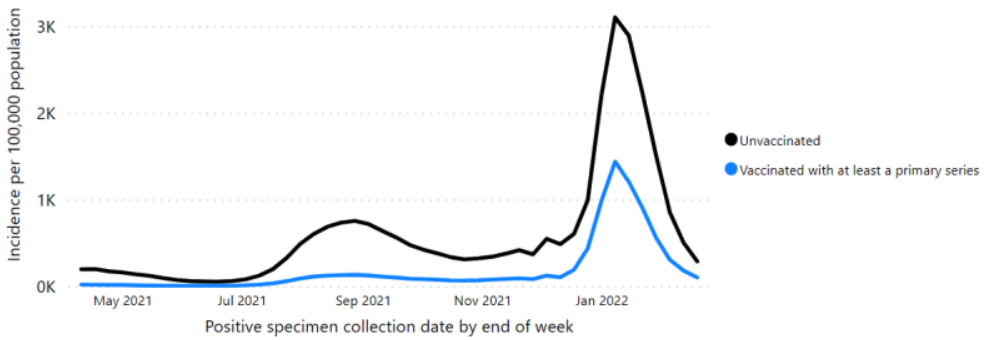
Age-Adjusted Rates of COVID-19 Cases by Vaccination Status
April 04 - February 19, 2022 (29 U.S. Jurisdictions)



Unvaccinated people aged 5 years and older had:

2.8X
Risk of Testing Positive for COVID-19

in February, compared to people vaccinated with at least a primary series.

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed March 17, 2022

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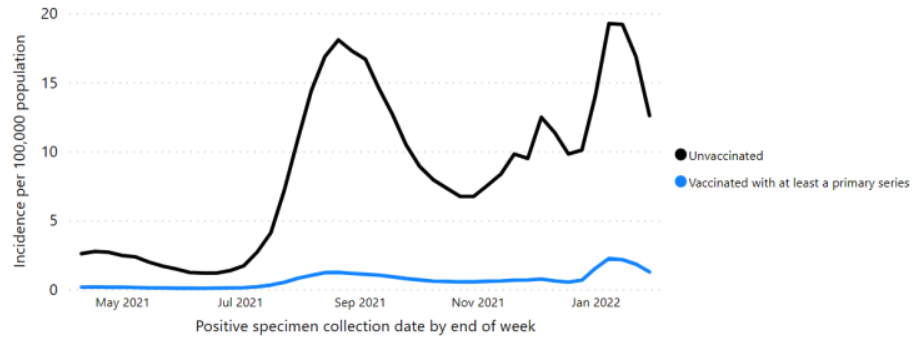
Age-Adjusted Rates of COVID-19 Deaths by Vaccination Status
April 04 - February 19, 2022 (29 U.S. Jurisdictions)



Unvaccinated people aged 5 years and older had:

9X
Risk of Dying from COVID-19

in January, compared to people vaccinated with at least a primary series.

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed March 17, 2022

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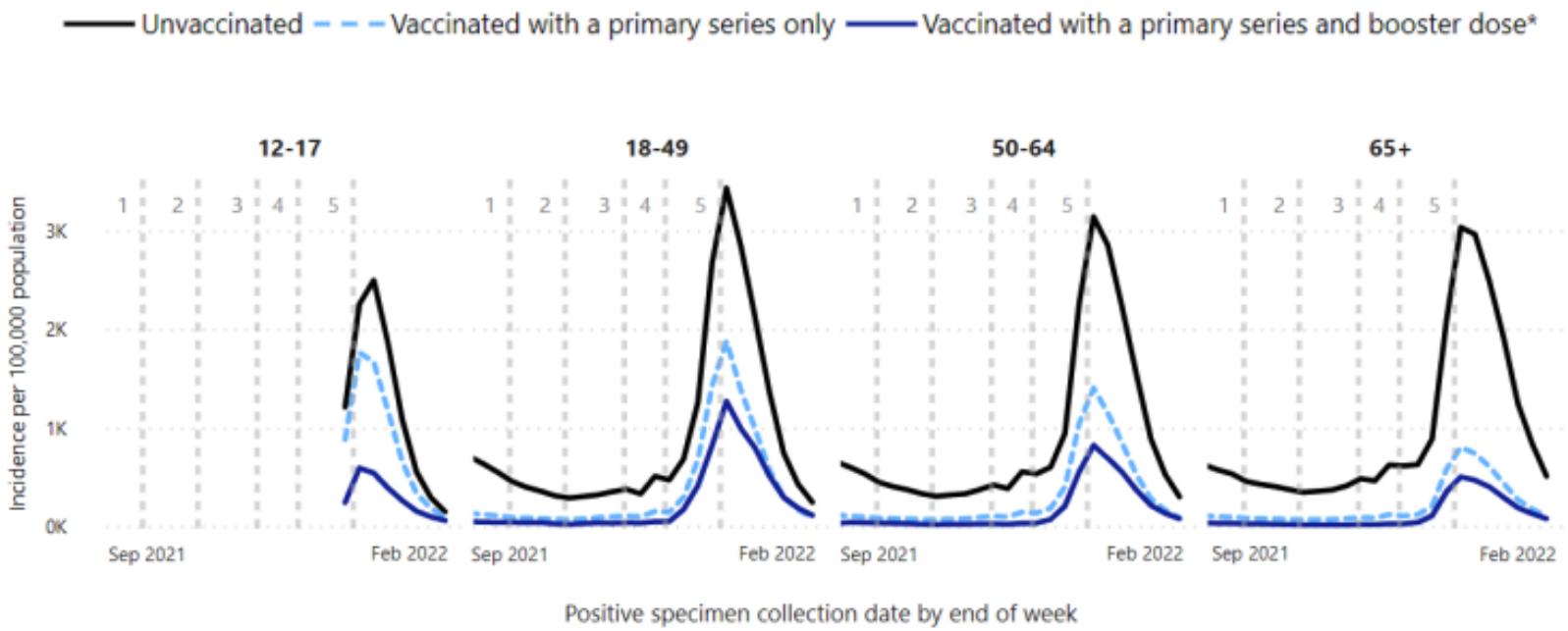
Rates of COVID-19 Cases by Vaccination Status, Receipt of Booster Dose,* and Age Group, September 19 - January 29, 2022 (26 U.S. Jurisdictions)



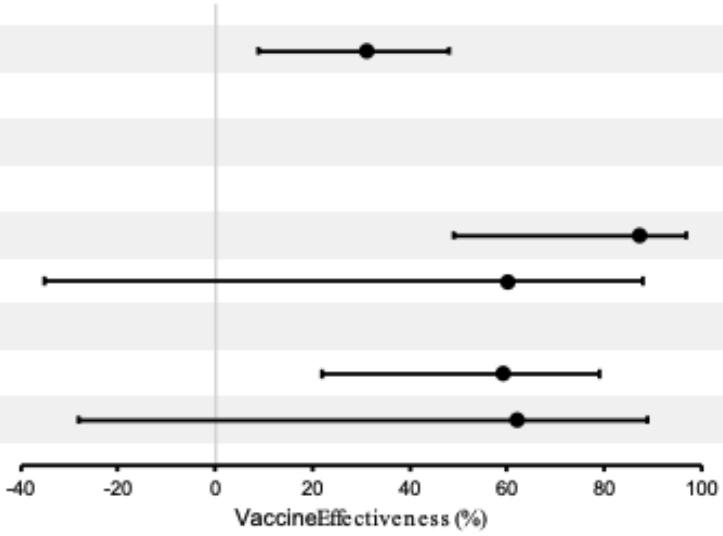
*This includes people who received booster doses and people who received additional doses.
CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed March 28, 2022

2. COVID Vaccine Effectiveness in Children and Adults (R. Link-Gelles, CDC)

Endpoint: infection Population: children

PROTECT: VE against SARS-CoV-2 infection by age group during Delta and Omicron variant predominance, Jul 2021-Feb 2022

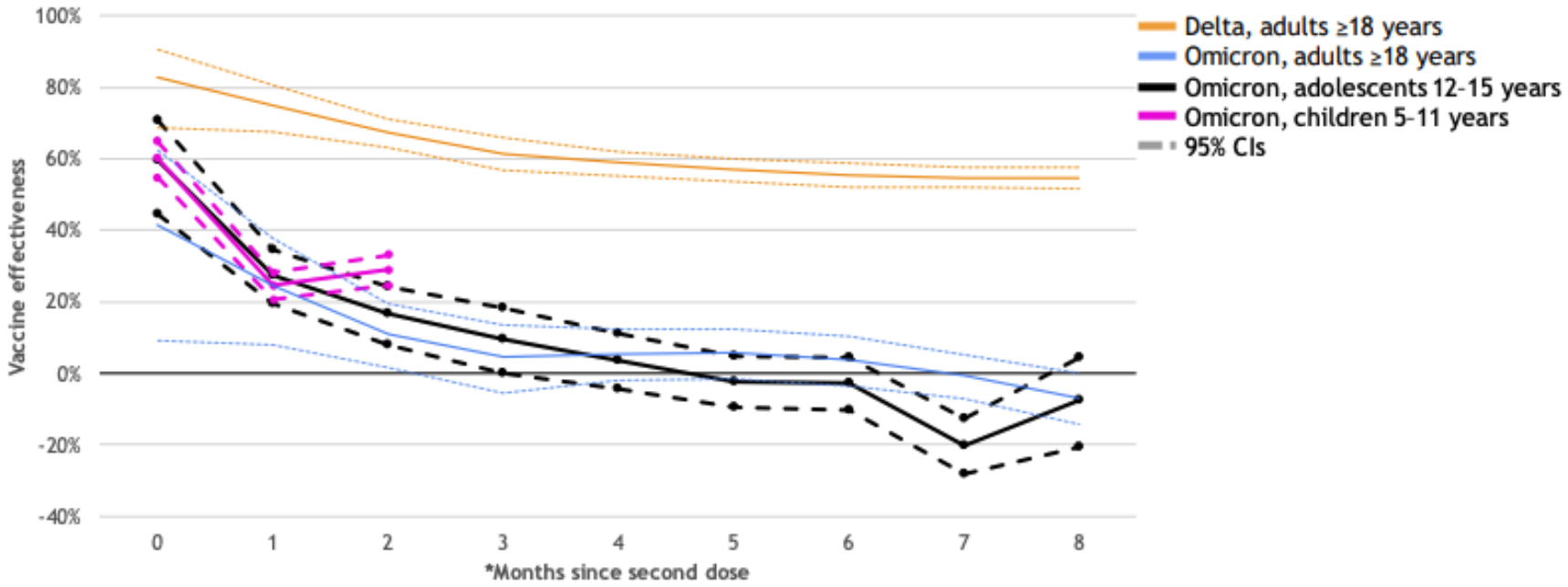
	Person-days	SARS-CoV-2 positive	Adjusted VE % (95% CI)
5 - 11 years old			
Omicron variant			
2-dose (14-82 days)	29,996	184	31 (9-48)
12 - 15 years old			
Delta variant			
2-dose (14-149 days)	16,517	3	87 (49-97)
2-dose (≥150 days)	7,058	4	60 (-35-88)
Omicron variant			
2-dose (14-149 days)	2,623	14	59 (22-79)
2-dose (≥150 days)	2,809	4	62 (-28-89)



Fowlkes AL, Yoon SK, Lutrick K, et al. Effectiveness of 2-Dose BNT162b2 (Pfizer BioNTech) mRNA Vaccine in Preventing SARS-CoV-2 Infection Among Children Aged 5-11 Years and Adolescents Aged 12-15 Years — PROTECT Cohort, July 2021-February 2022. MMWR Morb Mortal Wkly Rep 2022;71:422-428. DOI: http://dx.doi.org/10.15585/mmwr.mm7111e1external icon

Endpoint: infection | Population: adults & children

ICATT: Pfizer-BioNTech 2-dose VE against symptomatic infection, by age group and variant



*Vaccination dose dates are collected as month and year. Month 0 represents tests in the same month as 2nd dose (at least 2 weeks after 2nd dose). For all months greater than or equal to 1 the value represents the difference between calendar month of test and calendar month of 2nd dose receipt (at least 2 weeks after 2nd dose).

Britton et al., preliminary unpublished data

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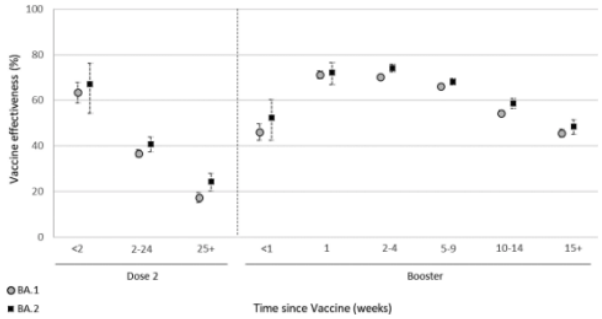
Endpoint: infection | Population: adults

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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Endpoint: infection | Population: all

Overall summary of VE against infection

- mRNA VE against infection during Omicron starts lower than during Delta and wanes faster.
- Patterns of mRNA VE and waning by time since last dose look similar across age groups.
- Waning looks different for recipients of J&J vaccine; lower overall
- Early VE data from the UK show similar VE for BA.1 and BA.2 sublineages of Omicron variant

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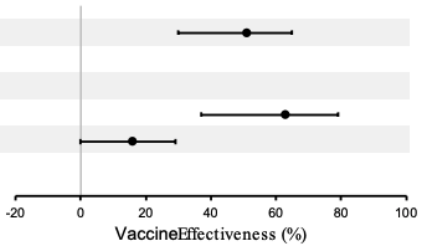
Endpoint: emergency department/urgent care | Population: children

VISION: mRNA VE for ED/UC by age during Omicron predominance, mid-Dec, 2021-Jan 29, 2022

	Total	SARS-CoV-2 positive, no. (%)	Adjusted VE % (95% CI)
5-11 years			
Unvaccinated	5,938	2,409 (40.6)	Ref
2 doses, 14-66 days earlier	486	118 (24.3)	51 (30-65)
12-15 years			
Unvaccinated	2,336	1,254 (53.7)	Ref
2 doses, 14-66 days earlier	86	24 (27.9)	63 (37-79)
2 doses, ≥67 days earlier	1,105	496 (44.9)	16 (0-29)
3 doses, ≥7 days earlier	10	3 (30)	Not calculated



CDC preliminary unpublished data, 2022

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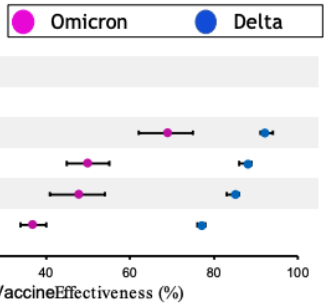
Endpoint: emergency department/urgent care | Population: adults

VISION: mRNA VE for ED/UC visits by number of doses and time since last dose receipt for adults ≥18 years, Aug 2021-Jan 2022

Predominant variant:	Adjusted VE % (95% CI) Delta	Omicron
2 doses		
<2 months	92 (91-94)	69 (62-75)
2-3 months	88 (86-89)	50 (45-55)
4 months	85 (83-86)	48 (41-54)
≥5 months	77 (76-78)	37 (34-40)



Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71:255-263. DOI: http://dx.doi.org/10.15585/mmwr.mm7107e2

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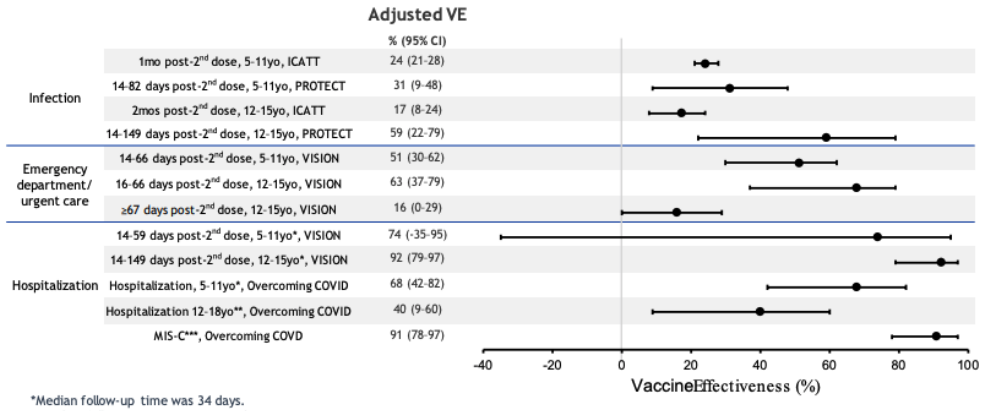
Summary: VE of 2 doses of mRNA vaccine during Omicron increases with increasing severity of outcome in children 5-18 years



*Median follow-up time was 34 days.
**Median follow-up time was 6 months.
***MIS-C VE estimates are from pre-Omicron.

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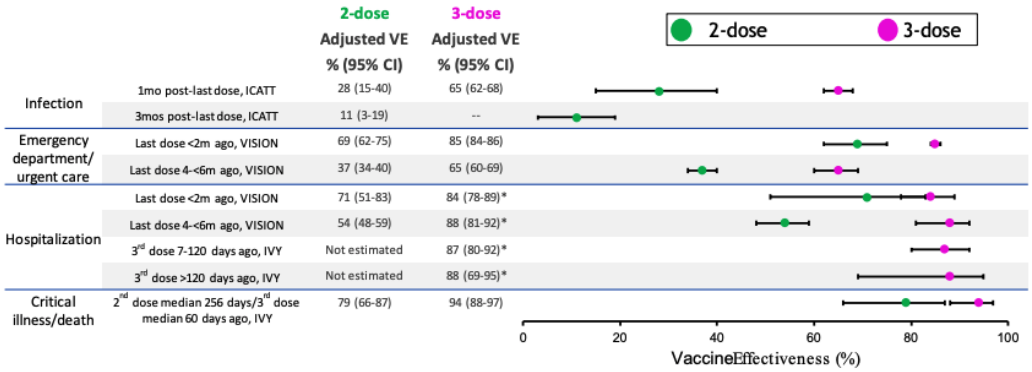
Summary: VE of 2 doses of mRNA vaccine increases with increasing severity of outcome during Omicron in adults ≥18 years; 3rd dose increases VE



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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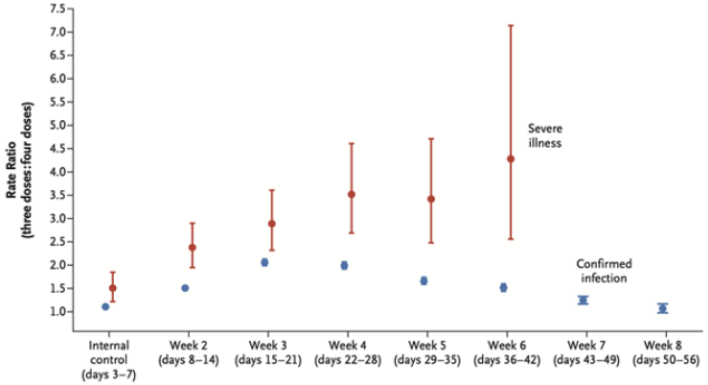
3. Protection by 4th dose of BNT 162b2 against Omicron in Israel (S. Alroy-Preis, MOH and R. Milo, Weizmann)

Protection as a function of time since 4th dose

Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression



Analysis period for confirmed infection: all infections confirmed between Jan-10 to Mar-2, 2022.

Severe illness: all infections confirmed during Jan-10 to Feb-18, 2022 that deteriorated to severe illness during 14 days after confirmation.

*Severe disease (NIH definition): resting respiratory rate >30 breaths per minute, or O2 saturation <94%, or PaO2/FiO2 <300

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An update to : https://www.medrxiv.org/content/10.1101/2022.02.01.22270232v1 6

Protection as a function of time since 4th dose

Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression

Table 3. Results of the Quasi-Poisson Regression Analysis of Severe Covid-19.*

Group (Days from Vaccination)	No. of Severe Cases (Person-Days at Risk)	Adjusted Rate Ratio (95% CI)		Adjusted Rate Difference (95% CI)	
		Comparison with Three-Dose Group	Comparison with Internal Control Group	Comparison with Three-Dose Group	Comparison with Internal Control Group
				cases/100,000 person-days at risk	
Three-dose group	1210 (24,857,976)	Reference	—	Reference	—
Internal control group (3–7)	114 (2,673,746)	1.5 (1.2 to 1.9)	Reference	1.8 (0.9 to 2.6)	Reference
Four-dose groups					
Week 2 (8–14)	125 (4,073,168)	2.4 (2.0 to 2.9)	1.6 (1.2 to 2.1)	3.2 (2.7 to 3.7)	1.3 (0.6 to 2.2)
Week 3 (15–21)	99 (3,868,314)	2.9 (2.3 to 3.6)	1.9 (1.4 to 2.6)	3.6 (3.1 to 4.2)	1.7 (1.0 to 2.7)
Week 4 (22–28)	66 (3,639,393)	3.5 (2.7 to 4.6)	2.3 (1.7 to 3.3)	3.9 (3.4 to 4.5)	2.1 (1.4 to 3.0)
Week 5 (29–35)	47 (3,277,662)	3.4 (2.5 to 4.7)	2.3 (1.6 to 3.3)	3.9 (3.3 to 4.5)	2.0 (1.2 to 3.0)
Week 6 (36–42)	18 (2,133,014)	4.3 (2.6 to 7.1)	2.8 (1.6 to 4.9)	4.2 (3.4 to 4.9)	2.4 (1.3 to 3.4)

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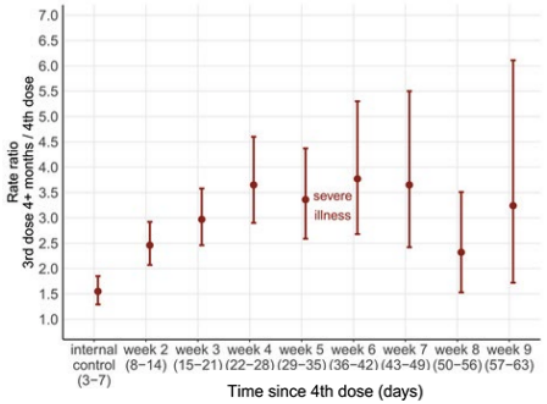
*Severe disease (NIH definition): resting respiratory rate >30 breaths per minute, or O2 saturation <94%, or PaO2/FiO2 <300 7

Extra follow up period since peer review -
Protection as a function of time since 4th dose

Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression



Analysis period: all infections confirmed during Jan-10 to Mar-12, 2022, that deteriorated to severe illness during 14 days after confirmation.

*Severe disease (NIH definition): resting respiratory rate >30 breaths per minute, or O2 saturation <94%, or PaO2/FiO2 <300

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4th dose protection against mortality in 60+ age group

(Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression)

Marginal VE against mortality:
76% [71%, 81%] (versus 3rd dose)
55% [35%, 69%] (versus 4th dose internal control group)

Mortality analysis period: all infections confirmed during Jan-10 to Mar-5, 2022 that resulted in mortality during 21 days after confirmation.

Mortality 3rd dose only (person-days at risk)	Mortality 4th dose day 12+ (person-days at risk)	Mortality internal control group (person-days at risk)	Adj. rate ratio for 4th dose day 12+ relative to 3rd dose [95% CI]	Adj. Rate ratio for 4th dose day 12+ relative to Internal control [95% CI]
453 (32,601,391)	95 (22,078,800)	35 (2,721,309)	**4.2** [3.4, 5.2]	**2.2** [1.6, 3.2]

Absolute rate difference per 100,000 risk-days: 1.3 (versus 3rd dose) and 0.5 (versus internal control group)

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Adverse events reported following 4th dose
(753,156 2nd booster doses administered)

Mild reports	Serious reports
442	12

Serious Adverse event (SAE) definition*

Any adverse event that:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in congenital anomaly
- Other important medical events which required intervention

*https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

Hospitalization and death reports following vaccination are examined by an independent clinical work group using available clinical data

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Data is based on adverse events reported to the MoH | Individuals may report more than 1 adverse event | There is an estimated under reporting

Number of reports by category

Adverse event category	number of reports
Systemic reactions	352
Local reactions	71
Neurologic reactions	14
Allergic reactions and Anaphylaxis	2
Other adverse events for surveillance	3*
Serious adverse events	12

Number of 4th dose vaccinees		
AstraZenica	Moderna	Pfizer
81	602	752,473

*All adverse events reported following 4th dose were of vaccine manufactured by Pfizer

* case 1 - Atrial fibrillation 3 days following vaccination – medical history includes cardiac disease (age group 75-79)
case 2 – Susp. Myocarditis (Troponin+ chest pain), hospitalization not needed, referred to MRI (age group 50-54)
case 3 – Increased liver enzymes found in routine screening, hospitalization not needed (age group 65-69)

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Serious adverse events reported following 4th dose

Medical history	Diagnosis	Days from vaccination	Age group
HTN, diabetes, chronic renal failure	Pericarditis	2 days	75-79
Dyslipidemia	Pericarditis	28 days	60-64
Chronic bronchitis, hypercholesterolemia, obesity, smoker	Pericarditis	17 days	70-74
HTN, diabetes, dyslipidemia	Pericarditis	1 day	70-74
HTN, diabetes, chronic renal failure	Renal failure exacerbation	8 days	70-74
Complex nursing patient - IHD, HTN, COPD, dementia, diabetes	Death	1 day	80-84

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Updated March 29th 2022

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Serious adverse events reported following 4th dose

Medical history	Diagnosis	Days from vaccination	Age group
CHF, cardiomyopathy, atrial fibrillation, HTN, dyslipidemia	Pneumonia	10 days	80-84
HTN, hypercholesterolemia, obesity, diabetes with target organ damage, IHD, asthma	CVA	3 days	80-84
Active corona virus at admission, COPD	Myocarditis	28 days	70-74
No known relevant medical history	Myocardial infarction	27 days	60-64
HTN, dyslipidemia	Acute kidney failure	21 days	65-69
Epilepsy, HTN, diabetes, hyperparathyroidism	Seizure	2 days	65-69

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Updated March 29th 2022

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Myocarditis & perimyocarditis cases and number of vaccinees (Pfizer) by age group and sex

Active surveillance. All cases reported in Israel Dec. 2020 - Mar. 29th, 2022[1]

Gender	Age Group	1st dose (0-21 days after the vaccine)			2nd dose (0-30 days after the vaccine)			3rd dose (0-30 days after the vaccine)			4th dose (0-30 days after the vaccine)		
		Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees
Female	5-11	158,185	0		113,218	0	0	23	0		0	0	
	12-15	212,762	0		177,909	1	177,909	50,449	0		0	0	
	16-19	257,503	0		231,241	2	115,621	145,530	2	72,765	421	0	
	20-24	269,472	1	269,472	248,780	5	49,756	183,186	0		1,603	0	
	25-29	252,008	0		234,265	2	117,133	167,328	0		2,510	0	
	30+	2,147,109	2	1,073,555	2,058,476	8	257,310	1,726,149	4	431,537	382,639	*2	191,320
Male	5-11	169,127	0		121,915	0	0	36	0		0	0	
	12-15	222,096	1	222,096	186,317	11	16,938	55,379	5	11,076	0	0	
	16-19	264,132	3	88,044	234,090	34	6,885	145,600	13	11,200	539	0	
	20-24	282,772	6	47,129	260,290	27	9,640	185,795	7	26,542	1,980	0	
	25-29	263,681	3	87,894	245,906	21	11,710	175,219	2	87,610	2,823	0	
	30+	2,006,779	6	334,463	1,929,859	28	68,924	1,622,533	17	95,443	359,066	0	
Total		**6,347,441**	**22**		**5,929,048**	**139**		**4,457,204**	**50**		**751,581**	**2**	

[1] Not including cases that have been ruled out by special committee

* Case 1 - Susp. Myocarditis – no hospitalization, to be confirmed by MRI in community. Case 2 – Active COVID-19 at admission

Two cases (Females) one of susp myocarditis reported 4 days following 4th dose, one case 28 days following 4th dose (active COVID-19 at admission)

Note: Sex unknown for 53,927 vaccine recipients, Age unknown for 329 vaccine recipients

MINISTRY OF HEALTH

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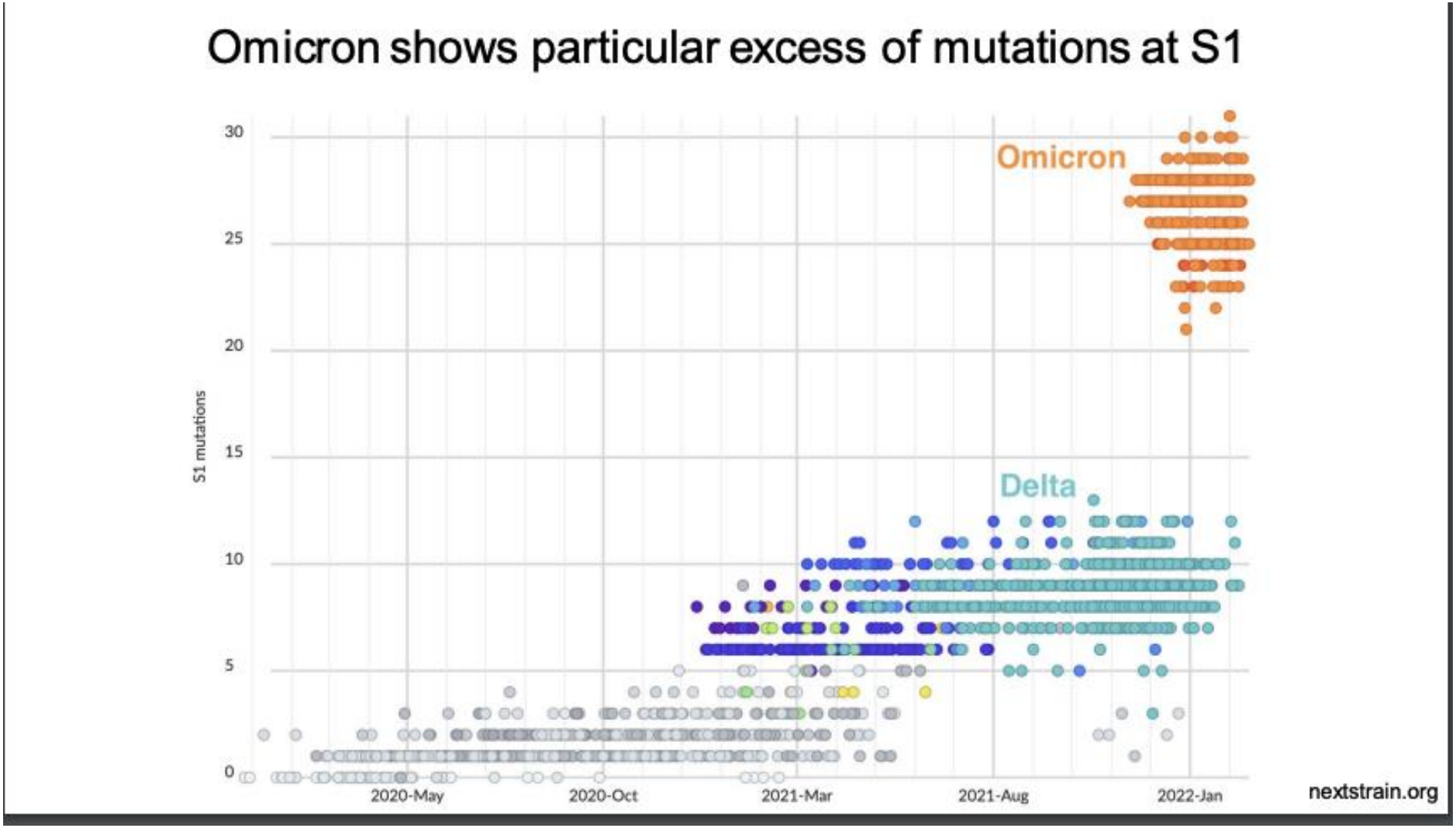
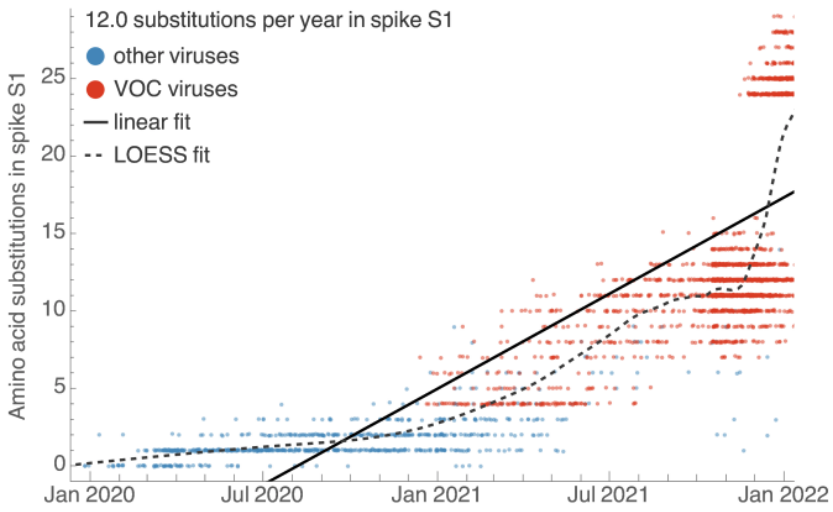
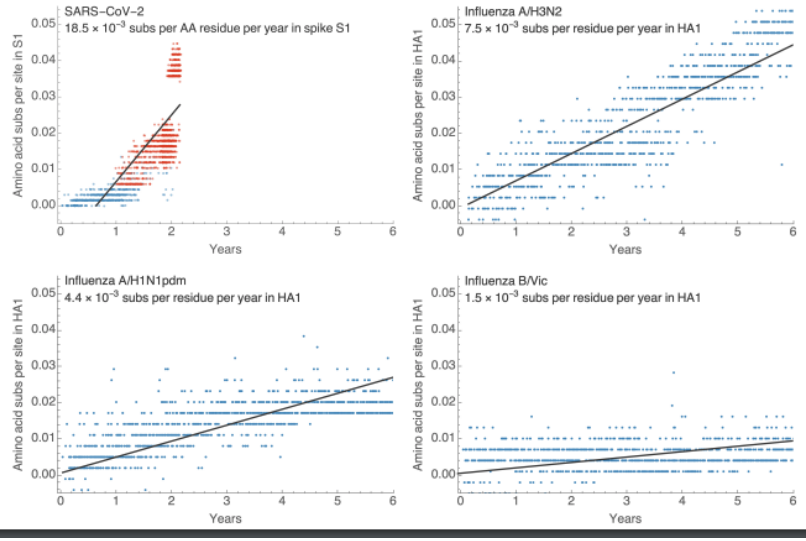
4. **Continuing SARS-C0V-2 evolution under population immune pressure (T. Bedford, Fred Hutch)**



S1 evolved at a rate of 12 amino acid changes per year in 2021



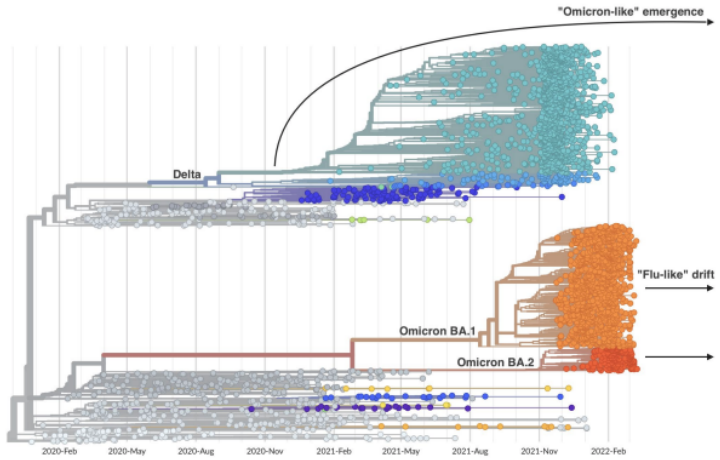
This is remarkably fast relative to seasonal influenza



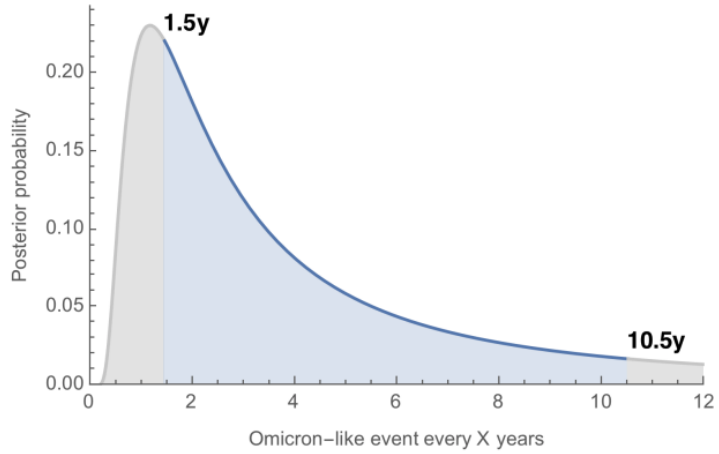
Omicron attack rate

1. We estimate US has seen 9.8% of the population as confirmed cases of Omicron through Mar 1, with the large majority accumulating after Dec 15
2. Assuming a case detection rate of 1 in 5 infections, we estimate almost 50% of the US infected with Omicron, most in the span of ~10 weeks

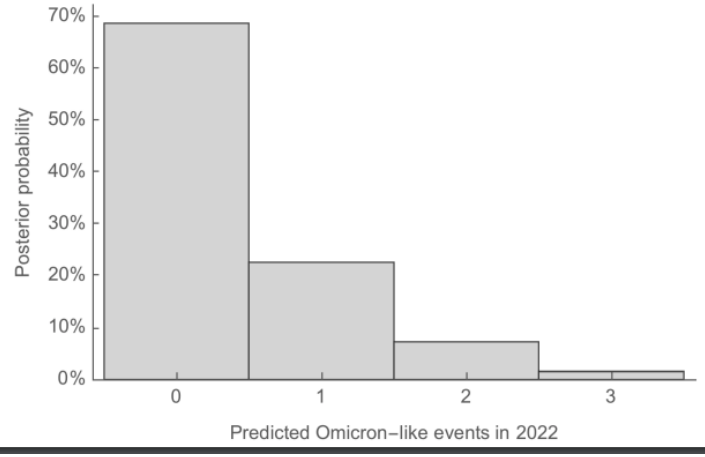
SARS-CoV-2 will continue to evolve to escape population immunity, though with multiple potential avenues



With 1 observation in 2.35 years of virus evolution, it's currently unclear how common Omicron-like events will be



This rate distribution gives a naive prediction of Omicron-like emergence events occurring in the next 12 months



Likely scenarios over the next 12 months

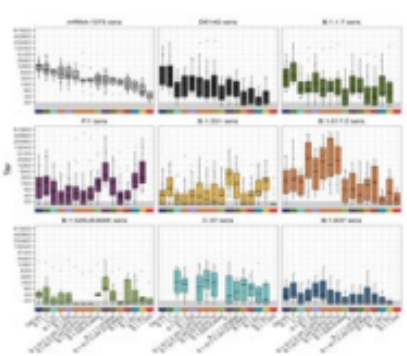
1. (More likely) Evolution within Omicron BA.2 to further increase intrinsic transmission and to escape from Omicron-derived immunity. This scenario sees lower attack rates with 2022-2023 epidemic driven by drift + waning + seasonality.

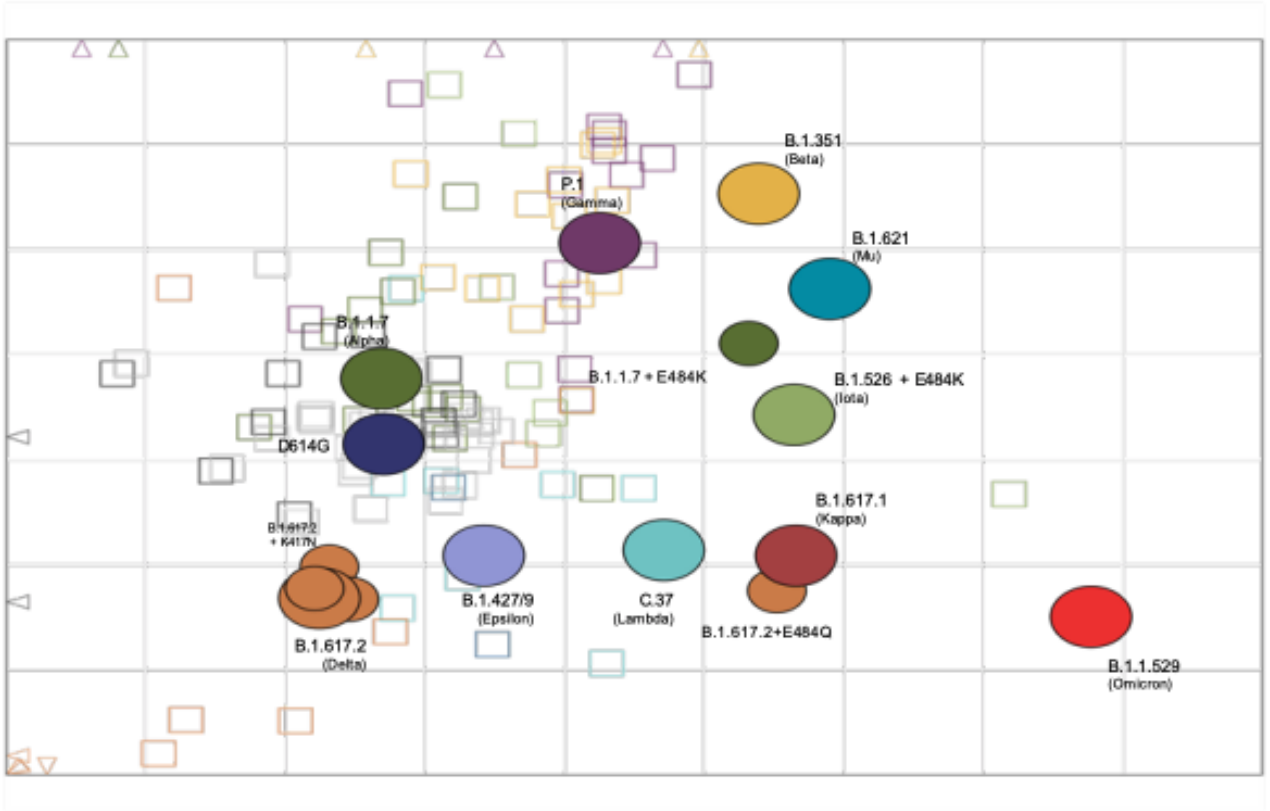
2. (Less likely) Another Omicron-like emergence event in which a chronic infection initiated in ~2021 incubates a new wildly divergent virus. This scenario sees high attack rates with epidemic driven by variant emergence.

5. SARS-CoV-2 Antigenic Space (J. Beigel NIAID)

Work by NIAID collaborators (SAVE and others) use neutralization assays coupled with antigenic cartography to describe antibody response.

- These maps are visualization tools for neutralization data to help understand antigenic spaces and risks.
- Antigenic cartography and antigenic landscapes are a common tool for strain selection for influenza.





Samuel Wilks & Derek Smith (Cambridge)

PsVNA by Shen & Montefiori (Duke)

NIH COVAIL Trial

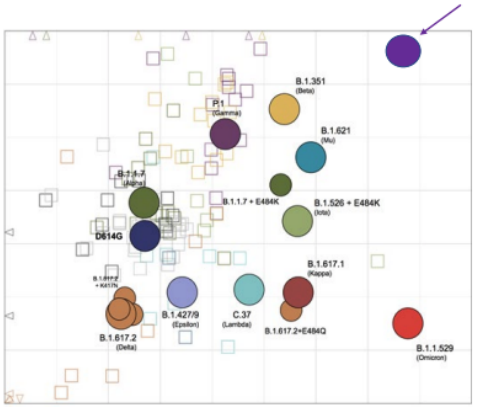
- Population:
  - Any COVID-19 primary vaccine and boost
  - Homologous or heterologous
- Two age strata:
  - 18-64 years
  - ≥ 65 years (>45% in ≥ 65 years).
- Two infection strata:
  - Confirmed prior COVID-19 (>35%)
  - No known history of prior infection.
- Primary endpoint:
  - Humoral immune responses
    - PsVNA and binding
  - D614G, beta, delta, omicron
- 24 sites
  - Began enrollment last week

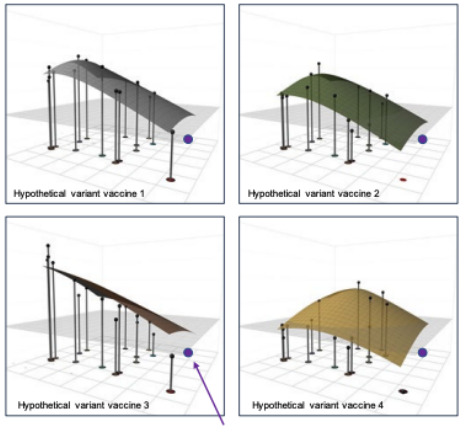
First stage

Arms	Sample Size	Vaccine Candidate	Interval (weeks)	Timing of First Dose	Second Dose	
1	100	Prototype	≥16	D1		Moderna
2	100	Beta + Omicron	≥16	D1		
3	100	Beta + Omicron	≥16	D1	D56	
4	100	Delta + Omicron	≥16	D1		
5	100	Omicron	≥16	D1		
6	100	Omicron + Prototype	≥16	D1		

https://clinicaltrials.gov/ct2/show/NCT05289037

If (when) a new variant emerges, we can test serum to the new antigen
- will inform of vaccine options to use with previously tested variant vaccines





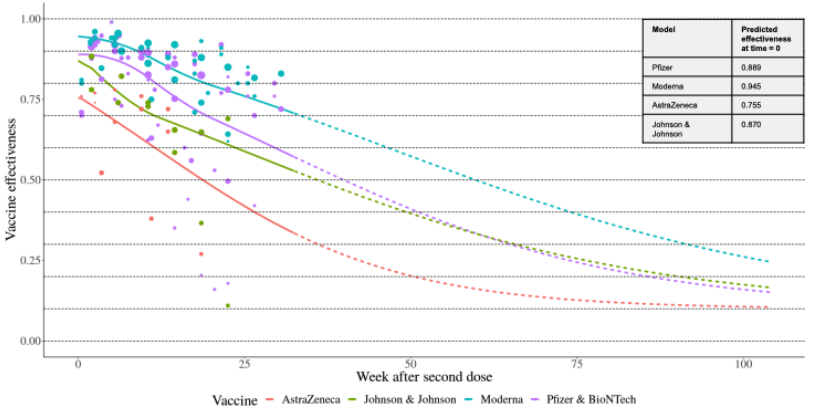
Conclusion

- There is likely to be continued evolution of the SARS-CoV-2 virus.
  - Evolution within Omicron BA.2, or
  - Another Omicron-like emergence event
- Ideally we learn to pick vaccine strains based on anticipated evolution.
- We also need to understand how to use available vaccines (prototype and variant) to modify antibody responses and target different antigenic spaces.

6. IHME COVID-19 modeling update (C. Murray, IHME)

Vaccine effectiveness at preventing infection

Combined Pfizer Infection 3-4 weeks and >5 weeks interval between doses



Model	Predicted effectiveness at time = 0
Pfizer	0.889
Moderna	0.945
AstraZeneca	0.755
Johnson & Johnson	0.870

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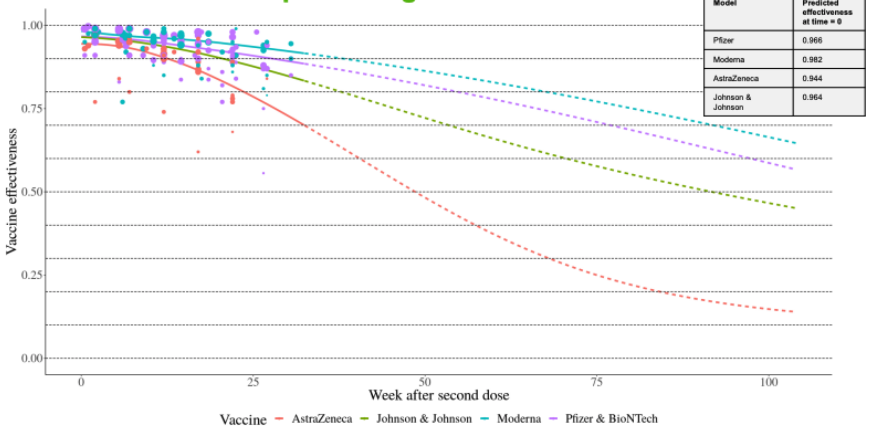
Vaccine effectiveness at preventing severe disease



Model	Predicted effectiveness at time = 0
Pfizer	0.966
Moderna	0.982
AstraZeneca	0.944
Johnson & Johnson	0.964

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Vaccine effectiveness: lower for Omicron

Table 3. Estimates of vaccine effectiveness for specific vaccines used in the model at preventing severe disease and infection. We use data from clinical trials directly, where available, and make estimates otherwise. More information can be found on our website.

	Effectiveness at preventing											
	Ancestral		Alpha		Beta		Gamma		Delta		Omicron	
Vaccine	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection
AstraZeneca	94%	63%	94%	63%	94%	69%	94%	69%	94%	69%	71%	36%
CanSino	66%	62%	66%	62%	64%	61%	64%	61%	64%	61%	48%	32%
CoronaVac	50%	47%	50%	47%	49%	46%	49%	46%	49%	46%	37%	24%
Covaxin	78%	73%	78%	73%	76%	72%	76%	72%	76%	72%	57%	38%
Johnson & Johnson	86%	72%	86%	72%	76%	64%	76%	64%	76%	64%	57%	33%
Moderna	97%	92%	97%	92%	97%	91%	97%	91%	97%	91%	73%	48%
Novavax	89%	83%	89%	83%	86%	82%	86%	82%	86%	82%	65%	43%
Pfizer/BioNTech	95%	86%	95%	86%	95%	84%	95%	84%	95%	84%	72%	44%
Sinopharm	73%	68%	73%	68%	71%	67%	71%	67%	71%	67%	53%	35%
Sputnik-V	92%	86%	92%	86%	89%	85%	89%	85%	89%	85%	67%	44%
Other vaccines	75%	70%	75%	70%	73%	69%	73%	69%	73%	69%	55%	36%
Other vaccines (mRNA)	91%	86%	91%	86%	88%	85%	88%	85%	88%	85%	67%	45%

- These are initial effectiveness after 2 doses of vaccine.
- Effectiveness wanes overtime.
- Effectiveness against preventing Omicron infection wanes very quickly; 10-15% effectiveness at 20 weeks.

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Omicron key attributes

- Highly infectious – several multiples of Delta
- 80-90% asymptomatic or mild symptoms – South African trial enrollees 31% point prevalence in early December, pre-hospital admission screening in asymptomatic patients as high as 10% in US hospitals, ONS infection survey 12% prevalence in some regions in late December.
- 40-60% reduction in the case-hospitalization rate
- 80% reduction in hospital-fatality rate in South Africa, Canada.
- Immune escape – 50% of previously infected getting infected

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BA2 shoulder

- Some countries in Europe (not all) including UK, France, Germany, Netherlands, have had a secondary BA2 wave.
- These waves have lasted approximately 18-22 days.
- A BA2 wave is quite possible in the US but we may have a minimal BA2 wave such as in Spain due to higher levels of past infection in the US.

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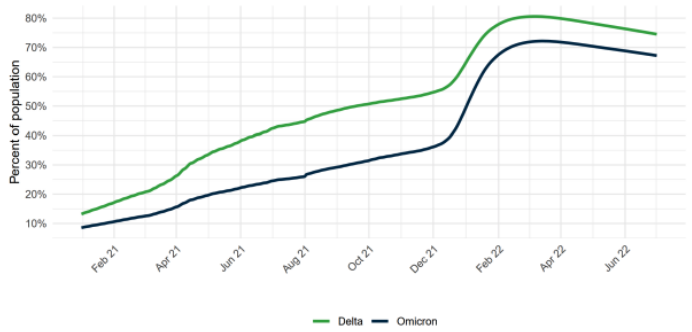
Immunity has peaked and will begin to decline

Figure 21.1: Percent of people who are immune to Delta or Omicron. Immunity is based on protection due to prior vaccination and infection(s). Moreover, variant-specific immunity is also based on variant-variant specific protection.



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Next variants?

- New variants are highly likely to emerge.
- Even variants that have higher severity than the omicron lineage may not lead to government social distancing mandates.
- Combination of enhanced levels of immunity, ongoing vaccination including the appropriate timing of boosters, availability of anti-virals and knowledge that vulnerable can protect themselves through high-quality mask use and social distancing should greatly reduce the future death toll.
- COVID-19 will become a disease that health systems need to manage on an ongoing basis.

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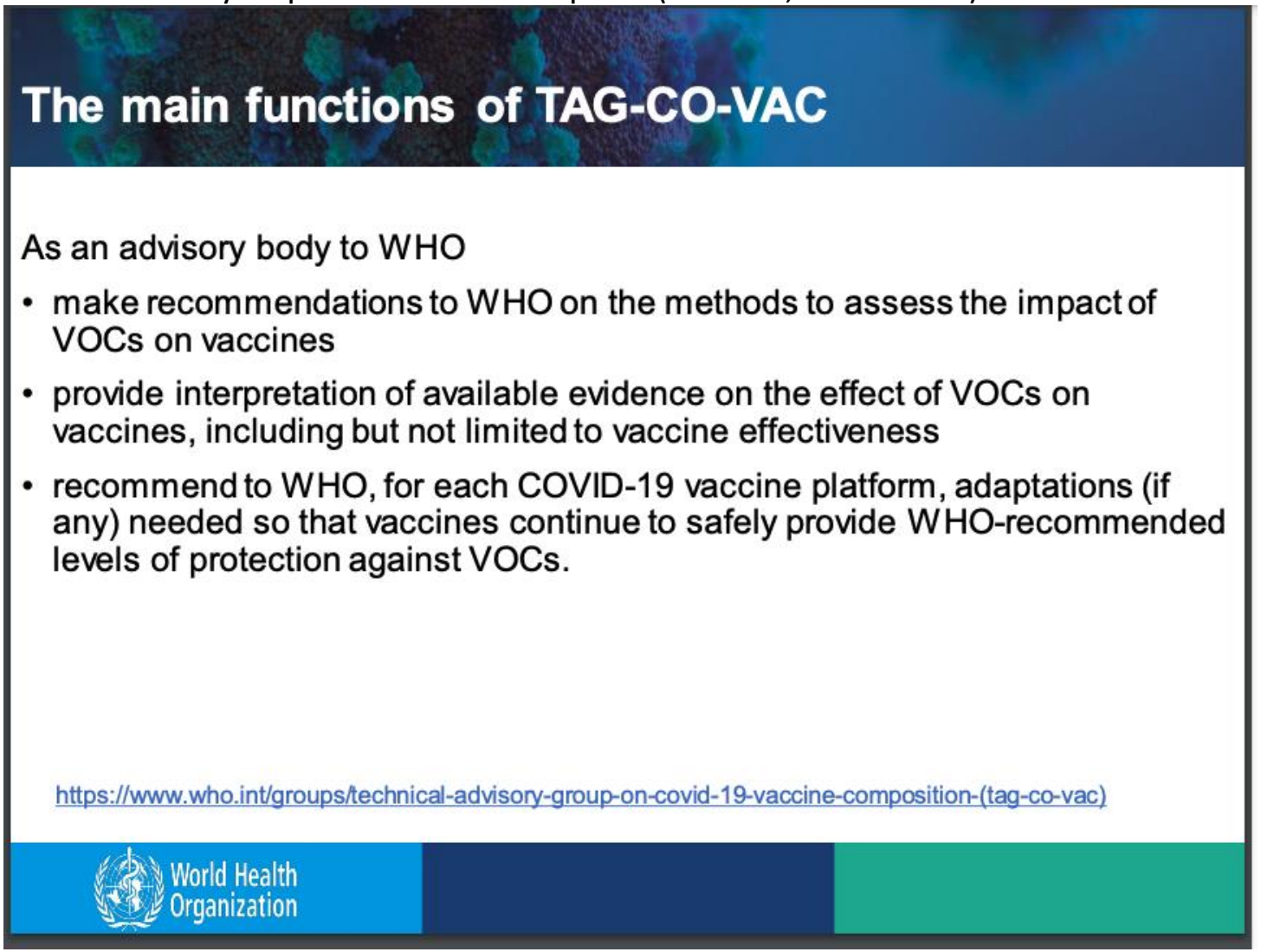
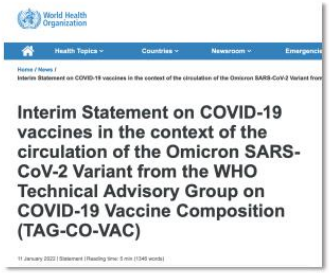
7. Technical Advisory Group on COVID-19 Vaccine Composition (K. Subbara0, WHO Melbourne)



TAG-CO-VAC statement on COVID-19 Vaccines – 11 Jan 2022

Key messages

- Indicates **protection against severe disease and death is more likely to be preserved** than protection against infection by current COVID-19 vaccines for the Omicron variant.
- Urges the world to **accelerate broader access to primary vaccination**, particularly for groups at greater risk.
- Calls for the development of COVID-19 vaccines that have high impact on prevention of **infection and transmission,** in addition to protection against severe disease and death.
- Specifies until such vaccines are available and as the virus continues to evolve, **the composition of current COVID-19 vaccines may need to be updated** to ensure WHO-recommended levels of protection.



https://www.who.int/news/item/11-01-2022-interim-statement-on-covid-19-vaccines-in-the-context-of-the-circulation-of-the-omicron-sars-cov-2-variant-from-the-who-technical-advisory-group-on-covid-19-vaccine-composition

World Health Organization

TAG-CO-VAC statement on COVID-19 Vaccines – 11 Jan 2022 (cont.)

Options to consider

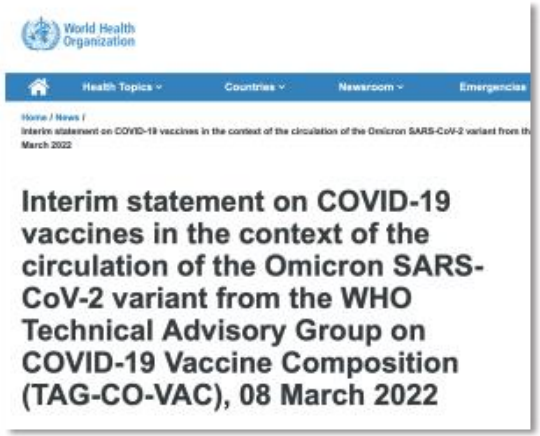
- **monovalent vaccine** that elicits an immune response against the predominant circulating variant(s), although this option faces the challenge of the rapid emergence of SARS-CoV-2 variants and the time needed to develop a modified or new vaccine;
- **multivalent vaccine** containing antigens from different SARS-CoV-2 VOCs;
- **pan SARS-CoV-2 vaccine**: a more sustainable long-term option that would effectively be variant-proof.

TAG-CO-VAC statement on COVID-19 Vaccines – 8 March 2022

In the context of Omicron variant, the TAG-CO-VAC highlighted the substantial uncertainties around the evolution of SARS-CoV-2, the challenges linked to updating COVID-19 vaccines and the paucity of data on variant-specific vaccines.

Key messages

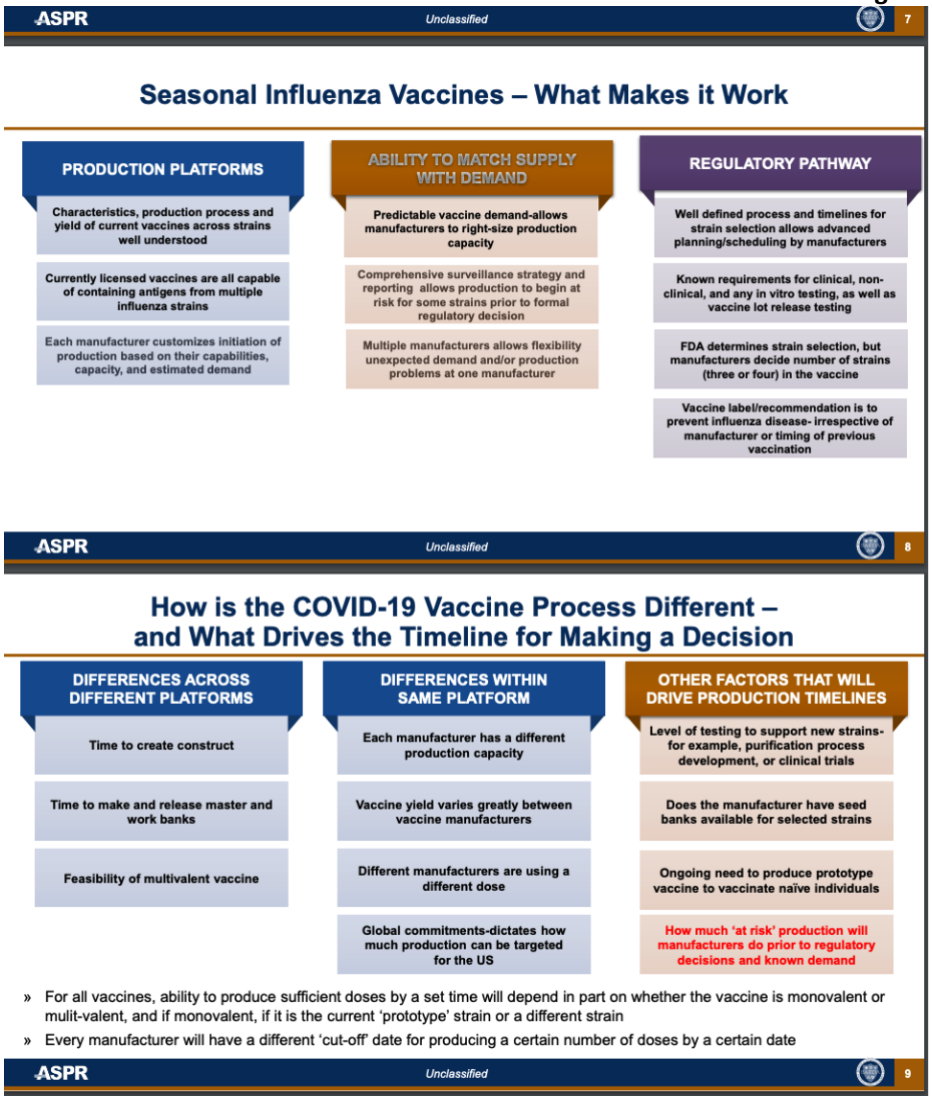
- Continues to review available data to **optimize vaccine mediated protection** against prevalent circulating Variants of Concern
- Strongly supports **urgent and broad access to current COVID-19 vaccines for primary series and booster doses**, particularly for groups at risk of developing severe disease
- Continues to encourage COVID-19 vaccine manufacturers to generate and provide data to WHO on **performance of current and variant-specific COVID-19 vaccines**



https://www.who.int/news/item/08-03-2022-interim-statement-on-covid-19-vaccines-in-the-context-of-the-circulation-of-the-omicron-sars-cov-2-variant-from-the-who-technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)-08-march-2022

World Health Organization

8. COVID-19 Vaccine Strain Selection – Points to Consider for Manufacturing Timelines (R. Johnson, BARDA)



ASPR Unclassified 7

Seasonal Influenza Vaccines – What Makes it Work

PRODUCTION PLATFORMS	ABILITY TO MATCH SUPPLY WITH DEMAND	REGULATORY PATHWAY
Characteristics, production process and yield of current vaccines across strains well understood	Predictable vaccine demand-allows manufacturers to right-size production capacity	Well defined process and timelines for strain selection allows advanced planning/scheduling by manufacturers
Currently licensed vaccines are all capable of containing antigens from multiple influenza strains	Comprehensive surveillance strategy and reporting allows production to begin at risk for some strains prior to formal regulatory decision	Known requirements for clinical, non-clinical, and any in vitro testing, as well as vaccine lot release testing
Each manufacturer customizes initiation of production based on their capabilities, capacity, and estimated demand	Multiple manufacturers allows flexibility unexpected demand and/or production problems at one manufacturer	FDA determines strain selection, but manufacturers decide number of strains (three or four) in the vaccine
		Vaccine label/recommendation is to prevent influenza disease- irrespective of manufacturer or timing of previous vaccination

ASPR Unclassified 8

How is the COVID-19 Vaccine Process Different – and What Drives the Timeline for Making a Decision

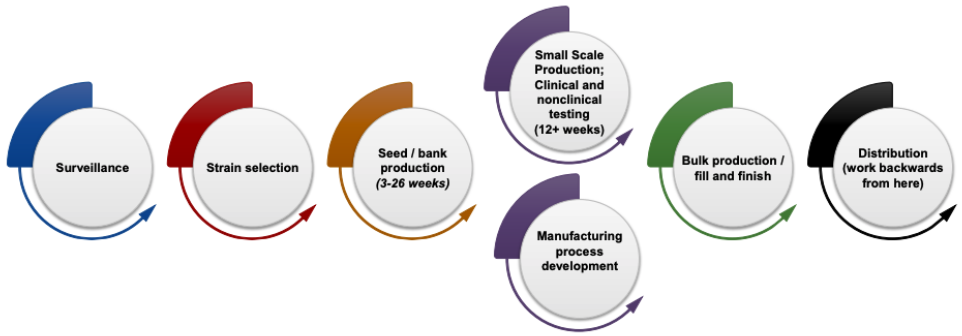
DIFFERENCES ACROSS DIFFERENT PLATFORMS	DIFFERENCES WITHIN SAME PLATFORM	OTHER FACTORS THAT WILL DRIVE PRODUCTION TIMELINES
Time to create construct	Each manufacturer has a different production capacity	Level of testing to support new strains- for example, purification process development, or clinical trials
Time to make and release master and work banks	Vaccine yield varies greatly between vaccine manufacturers	Does the manufacturer have seed banks available for selected strains
Feasibility of multivalent vaccine	Different manufacturers are using a different dose	Ongoing need to produce prototype vaccine to vaccinate naïve individuals
	Global commitments-dictates how much production can be targeted for the US	How much 'at risk' production will manufacturers do prior to regulatory decisions and known demand

» For all vaccines, ability to produce sufficient doses by a set time will depend in part on whether the vaccine is monovalent or mulit-valent, and if monovalent, if it is the current 'prototype' strain or a different strain

» Every manufacturer will have a different 'cut-off' date for producing a certain number of doses by a certain date

ASPR Unclassified 9

Multi-strain/Strain Change Life-Cycle Steps



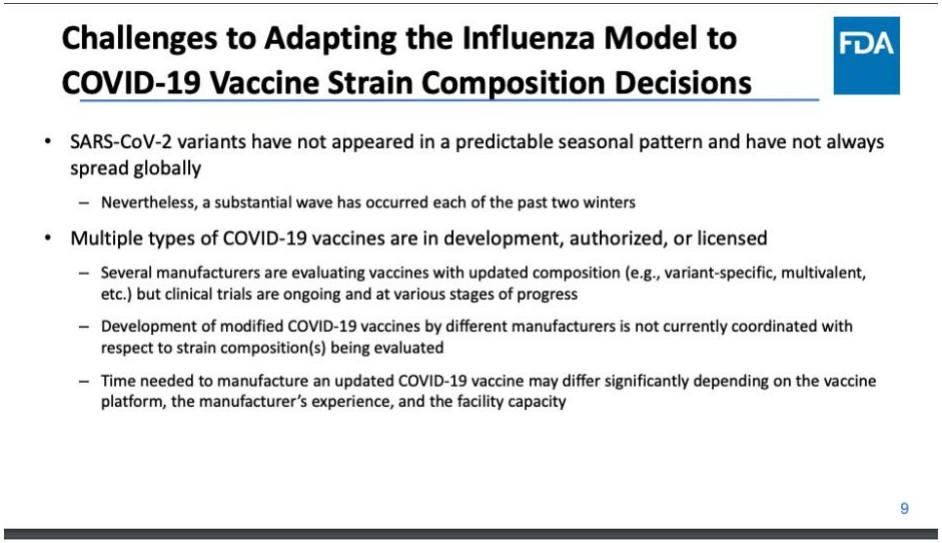
ASPR Unclassified 10

Regulatory Factors Beyond Strain Selection that Will Determine Vaccine Availability by a Given Date

Decision Points/Timelines	
Identify strains under consideration to provide opportunity for seed stock/bank generation	Clarifying if there will be any requirements differences between platforms
Clear expectations for clinical and non clinical testing requirements	Will primary series and/or "first boost" still be prototype strain?
Decision process/who makes decision regarding strains and number of strains/vaccine	Will timing of boost be in the context of previous dose, or in the context of just getting a 'routine annual vaccination' similar to seasonal influenza?

ASPR Unclassified 11

8. Proposed Framework for Addressing Future COVID-19 Vaccine Strain Composition (J. Weir, CBER)

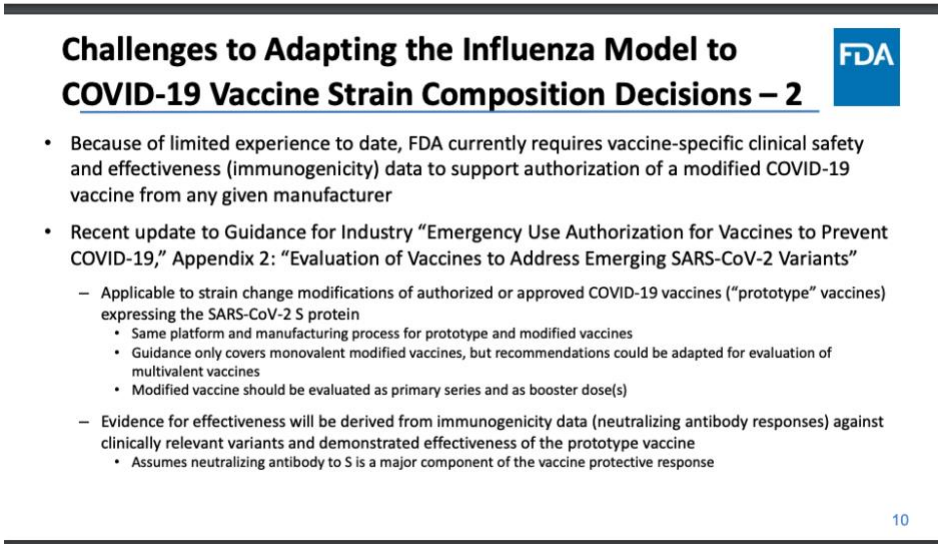


Challenges to Adapting the Influenza Model to COVID-19 Vaccine Strain Composition Decisions

FDA

- SARS-CoV-2 variants have not appeared in a predictable seasonal pattern and have not always spread globally
  - Nevertheless, a substantial wave has occurred each of the past two winters
- Multiple types of COVID-19 vaccines are in development, authorized, or licensed
  - Several manufacturers are evaluating vaccines with updated composition (e.g., variant-specific, multivalent, etc.) but clinical trials are ongoing and at various stages of progress
  - Development of modified COVID-19 vaccines by different manufacturers is not currently coordinated with respect to strain composition(s) being evaluated
  - Time needed to manufacture an updated COVID-19 vaccine may differ significantly depending on the vaccine platform, the manufacturer's experience, and the facility capacity

9



Challenges to Adapting the Influenza Model to COVID-19 Vaccine Strain Composition Decisions – 2

FDA

- Because of limited experience to date, FDA currently requires vaccine-specific clinical safety and effectiveness (immunogenicity) data to support authorization of a modified COVID-19 vaccine from any given manufacturer
- Recent update to Guidance for Industry "Emergency Use Authorization for Vaccines to Prevent COVID-19," Appendix 2: "Evaluation of Vaccines to Address Emerging SARS-CoV-2 Variants"
  - Applicable to strain change modifications of authorized or approved COVID-19 vaccines ("prototype" vaccines) expressing the SARS-CoV-2 S protein
    - Same platform and manufacturing process for prototype and modified vaccines
    - Guidance only covers monovalent modified vaccines, but recommendations could be adapted for evaluation of multivalent vaccines
    - Modified vaccine should be evaluated as primary series and as booster dose(s)
  - Evidence for effectiveness will be derived from immunogenicity data (neutralizing antibody responses) against clinically relevant variants and demonstrated effectiveness of the prototype vaccine
    - Assumes neutralizing antibody to S is a major component of the vaccine protective response

10

Challenges to Adapting the Influenza Model to COVID-19 Vaccine Strain Composition Decisions – 3

FDA

- Ideally, the process of changing the COVID-19 vaccine would be coordinated globally
- Global coordination may be challenging due to:
  - The unpredictable nature of SARS-CoV-2 evolution
  - Regional differences in VOC circulation or dominance
  - Different regional levels of vaccination coverage and types of vaccines in use
  - Variable timeliness of availability of clinical data for different vaccines to support a need for a modified vaccine
  - Implementing a coordinated global process will likely take some time
- A process for updating the composition of COVID-19 vaccines in the U.S. will need to be flexible, as well as orderly, transparent, and data driven
  - Consideration could be given to scheduling a periodic review of the COVID-19 epidemiology and available clinical data for vaccines against VOC

11

Conditions Necessary to Make a Recommendation for Changing COVID-19 Vaccine Strain Composition

FDA

- Epidemiology data identifies an antigenically distinct variant(s) that is or will likely become dominant
- Immunogenicity and effectiveness data indicate that current COVID-19 vaccines provide insufficient protection against circulating variant viruses
- Data to justify a recommendation for a strain composition change is available for at least one (and ideally more than one) COVID-19 vaccine
- Vaccine manufacturers have clinical data to support the safety and effectiveness of modified vaccines for their respective products
- Vaccine manufacturers are able to manufacture and deliver a modified vaccine in sufficient quantities, and within a sufficient timeframe, to make an impact

12

Some Additional Questions to be Considered in a COVID-19 Vaccine Strain Composition Decision

FDA

- Does the available clinical data support changing the strain composition of vaccines currently in use?
  - Should modified vaccines be mono-valent or multi-valent?
  - What strain(s) should be included?
- Does the available clinical data indicate how well a modified vaccine would impact breadth of coverage against circulating and potentially emergent viruses?
  - Are breadth of coverage considerations different for vaccines used as primary series vs. booster doses?

13

Some Additional Questions to be Considered in a COVID-19 Vaccine Strain Composition Decision – 2

FDA

- How often should the composition of COVID-19 vaccines be reviewed for possible composition update?
  - Yearly, as for influenza? As VOCs appear and become dominant?
  - What contingency plans should be considered if a novel SARS-CoV-2 variant emerges and is not well covered by available vaccines?
- If a strain composition change is recommended, how is a smooth transition to use modified vaccines implemented?
  - Recommendations for seasonal influenza vaccines apply to all vaccines, and vaccines have a dating period that eliminates any potential confusion
- What additional data or experience could expedite the process for COVID-19 vaccine composition changes by limiting or obviating the need for clinical data?

14

A Tentative Framework for Considering COVID-19 Vaccine Composition in the U.S.

FDA

- The FDA would seek the advice of the VRBPAC to make recommendations for any change in composition of authorized or approved COVID-19 vaccines in the U.S.
  - On a routine basis (TBD), the FDA and VRBPAC will review the epidemiology of circulating SARS-CoV-2 variants in the U.S., the effectiveness of available vaccines in use, and the available clinical data and manufacturing concerns for modified vaccines, in order to determine whether to recommend an updated vaccine for use in the U.S.
  - A collaborative plan including manufacturers, FDA, and other public health agencies, should be developed to provide the necessary clinical data needed for future vaccine composition decisions
  - Contingency plans should be developed to respond to an emerging variant that escapes protection provided by currently available vaccines
- If the WHO does make a COVID-19 vaccine composition recommendation, the FDA and VRBPAC will evaluate whether that recommendation should be implemented for U.S. COVID-19 vaccines, with consideration given to:
  - Epidemiology of circulating SARS-CoV-2 variants in the U.S.
  - Capability of manufacturers of authorized vaccines to implement the recommendation in a timely fashion
  - Availability of clinical data to support safety and effectiveness of recommended modified vaccine

15

Considerations for Use of Additional Booster Doses

FDA

- A recommendation for an additional booster dose might follow a recommendation for changing COVID-19 vaccine strain composition that occurs as the result of either a scheduled or ad hoc review of COVID-19 epidemiology and vaccine effectiveness
- Even if available data continue to support use of prototype vaccines going forward, periodic use of additional booster doses (e.g., annually, similar to seasonal influenza vaccines) may be needed to maintain adequate immunity
- Recommendations for use and timing of additional booster doses should consider:
  - Goals of vaccination program (e.g., preventing significant morbidity and mortality, as opposed to preventing mild disease, infection, and transmission)
  - In which population(s) additional booster doses are warranted
  - Practical/operational aspects of public health vaccination programs

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Topics for Discussion

FDA

Following the open public hearing, the VRBPAC will be asked to discuss and provide input on the following topics (no voting questions):

- What considerations should inform strain composition decisions to ensure that available COVID-19 vaccines continue to meet public health needs, e.g.:
  - Role of VRBPAC and FDA in coordinating strain composition decisions
  - Timelines needed to implement strain composition updates
  - Harmonization of strain composition across available vaccines
- How often should the adequacy of strain composition for available vaccines be assessed?
- What conditions would indicate a need for updated COVID-19 vaccine strain composition, and what data would be needed to support a decision on a strain composition update?
- What considerations should inform the timing and populations for use of additional COVID-19 vaccine booster doses?

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Safety Platforms for Emergency vACcines (SPEAC)
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