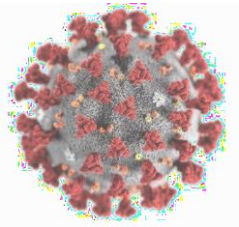
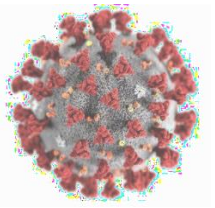
Pediatric Community Forum

"COVID-19 Boosters: Where from Here?"

Presenter:

Paul A. Offit, MD, FAAP
Attending Physician, Division of Infectious Diseases
Director, Vaccine Education Center
The Children's Hospital of Philadelphia

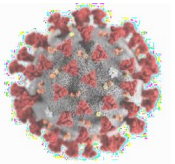




Session Learning Objectives:

As a result of participation in this activity, participants will be able to understand:

- The difference between a primary vaccine series and booster dosing.
- The immunological correlates of protection against mild vs. severe COVID-19.
- For whom COVID-19 vaccines are 2, 3, or 4-dose vaccines.



Pennsylvania Chapter
American Academy of Pediatrics
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This webinar will begin at 8:00 PM EST

CME/CEU is available for the live webinar. Information on how to obtain credit will be emailed to all participants following the webinar.

COVID-19 Boosters: Where from Here?

Paul A. Offit, MD

Division of Infectious Diseases

Vaccine Education Center

The Children's Hospital of Philadelphia

Perelman School of Medicine

The University of Pennsylvania

April 13, 2022

No disclosures

What is the goal of COVID-19 vaccines?

Goal #1:

Prevent severe illness

> medRxiv. 2021 Aug 9;2021.08.06.21261707. doi: 10.1101/2021.08.06.21261707. Preprint

Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence

Arjun Puranik [1], Patrick J Lenehan [1], Eli Silvert [1], Michiel J M Niesen [1], Juan Corchado-Garcia [1], John C O'Horo [2], Abinash Virk [2], Melanie D Swift [2], John Halamka [2], Andrew D Badley [2], A J Venkatakrishnan [1], Venky Soundararajan [1]

Affiliations + expand

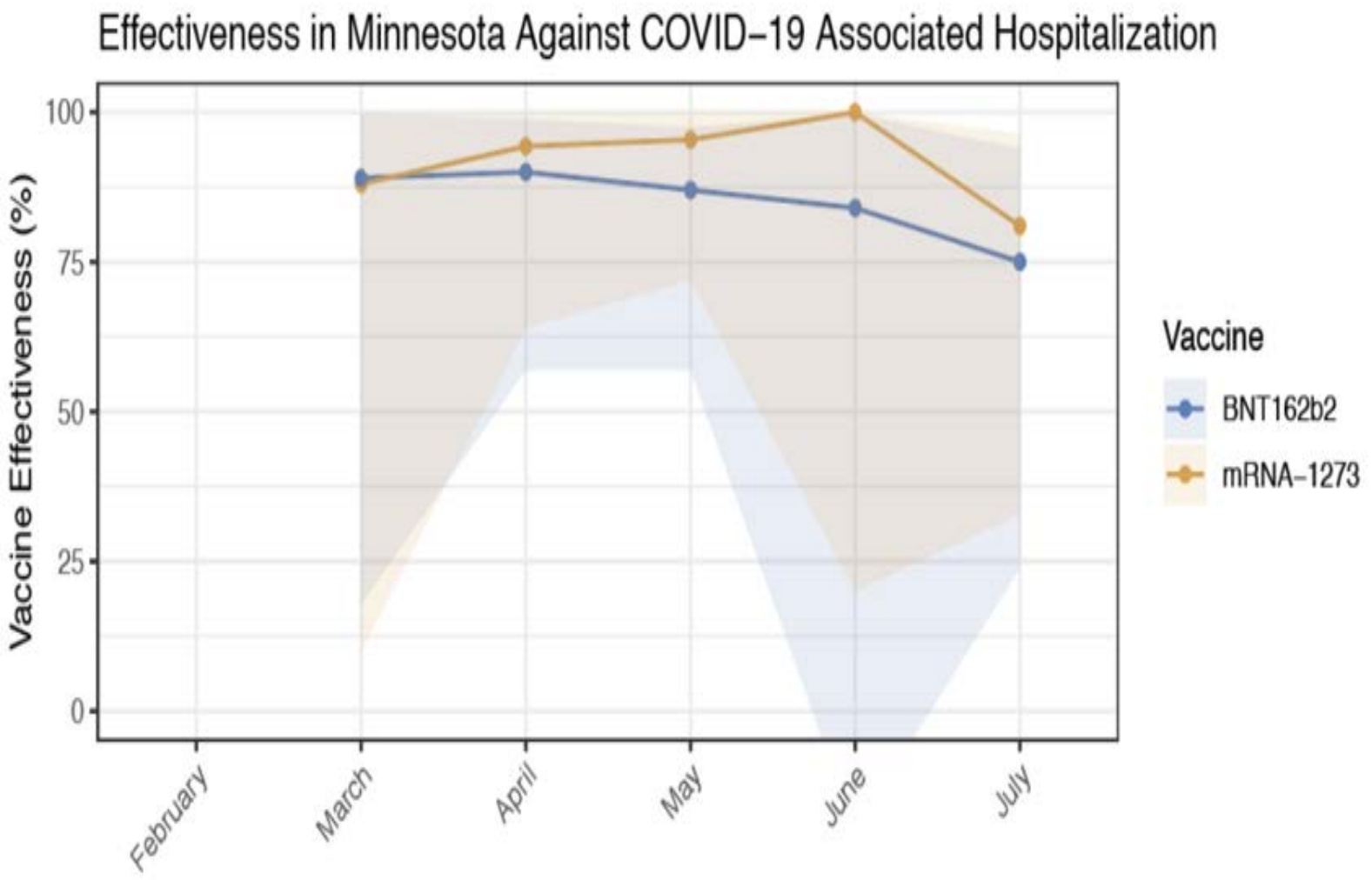
PMID: 34401884 PMCID: PMC8366801 DOI: 10.1101/2021.08.06.21261707

Free PMC article

Abstract

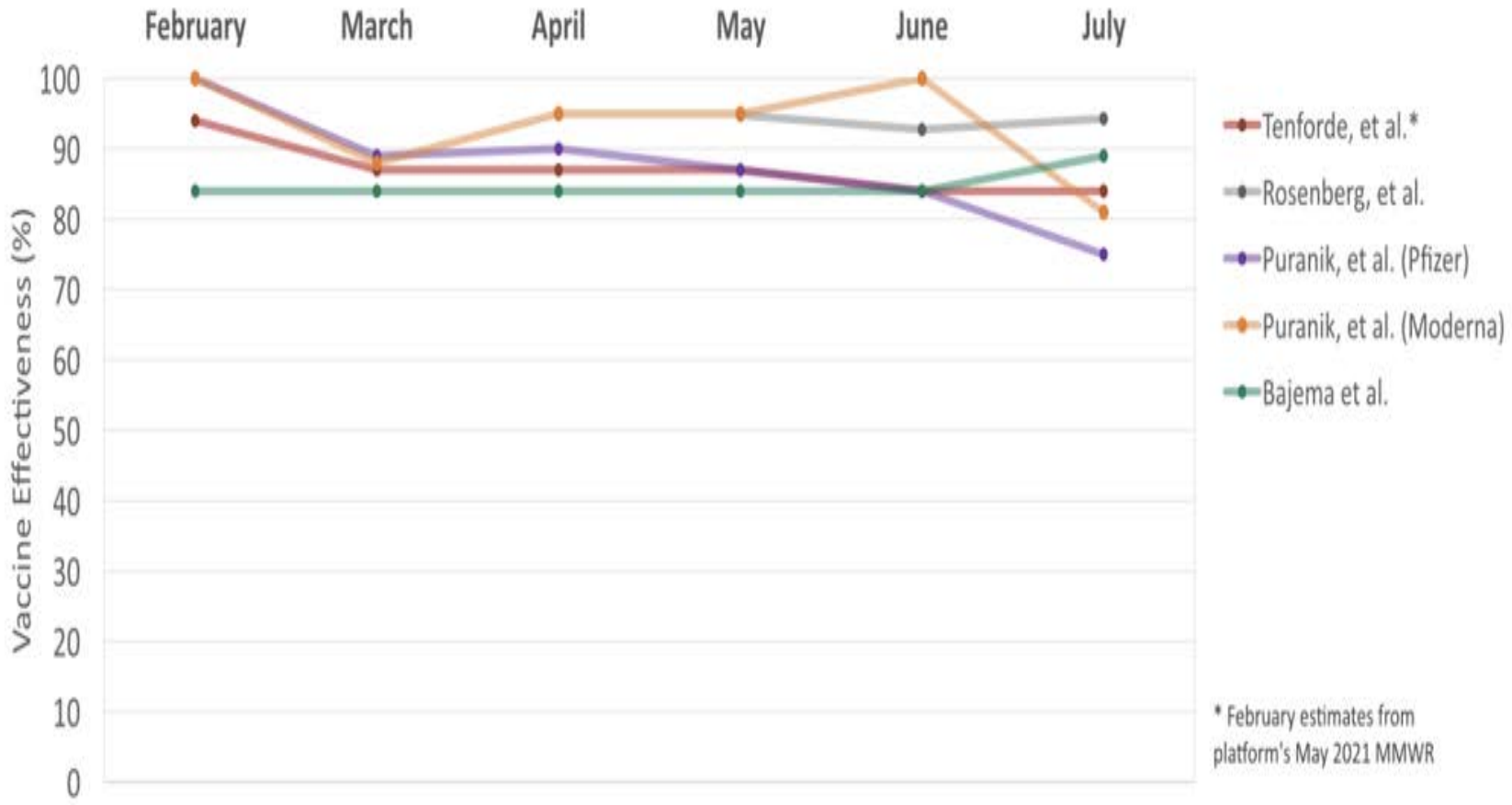
Although clinical trials and real-world studies have affirmed the effectiveness and safety of the FDA-authorized COVID-19 vaccines, reports of breakthrough infections and persistent emergence of new variants highlight the need to vigilantly monitor the effectiveness of these vaccines. Here we

B


Effectiveness in Minnesota Against COVID−19 Associated Hospitalization
Vaccine Effectiveness (%)
100
75
50
25
0
February
March
April
May
June
July
Vaccine
BNT162b2
mRNA−1273

Vaccine effectiveness against **hospitalization** over time

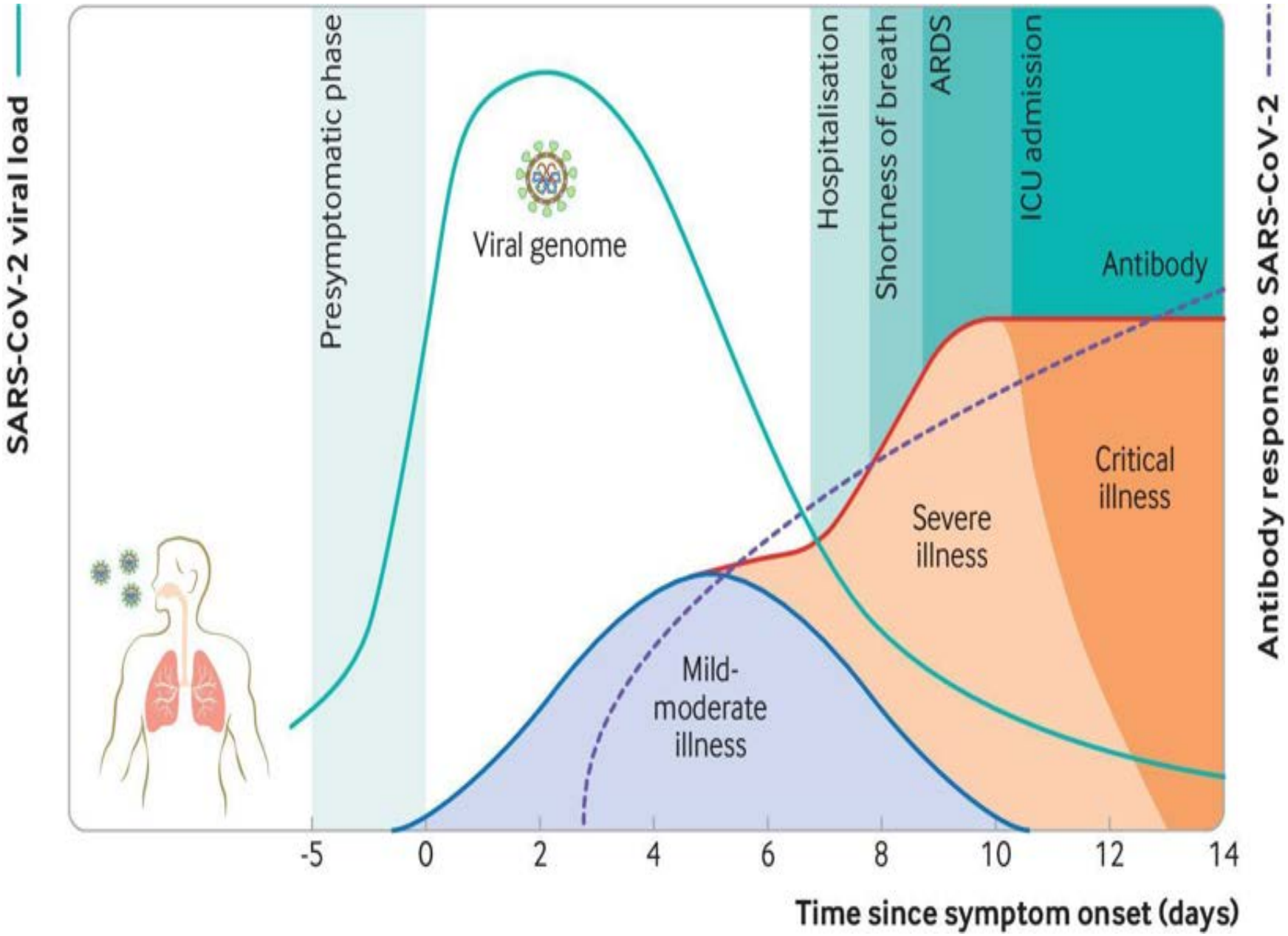
Adults ≥18 years of age



Efficacy of mRNA vaccines against severe disease in settings where Delta variant is circulating, Sept 2021

Study Location (reference)	Vaccine	Effectiveness vs. severe disease or hospitalization	Lower limit of 95% CI	Upper limit of 95% CI
USA, Southern California KPSC (1)	BNT162b2 or mRNA-1273	93	84	96
USA, Minnesota (2)	BNT162b2	75	24	94
	mRNA-1273	81	33	96
USA, New York (3)	BNT162b2; mRNA-1273; Ad26.COV2.S	94.4	92.7	95.7
USA 13 jurisdictions (5)	BNT162b2; mRNA-1273; Ad26.COV2.S	90.4	87.7	92.5
USA, 7 locations VISION network (7)	BNT162b2	87	85	90
	mRNA-1273	91	83	93
USA, 9 States VISION network (8)	BNT162b2	80	73	85
	mRNA-1273	95	92	97
USA, 5 VA Medical Centers (9)	mRNA-1273	89	80	94
USA (14)	mRNA-1273	96	91	98
Israel, (4)	BNT162b2	88	94	91
Qatar (10)	BNT162b2	89.7	61	98.1
Qatar (11)	mRNA-1273	100	41.2	100
Singapore (12)	BNT162b2 or mRNA-1273	93	66	98
UK (13)	BNT162b2	96	86	99

Protection against severe illness is mediated by memory B cells, which are long-lived


SARS-CoV-2 viral load
Antibody response to SARS-CoV-2
Presymptomatic phase
Viral genome
Hospitalisation
Shortness of breath
ARDS
ICU admission
Antibody
Critical illness
Severe illness
Mild-moderate illness
-5
0
2
4
6
8
10
12
14
Time since symptom onset (days)


K

Do immunological studies support epidemiological studies?

> bioRxiv. 2021 Aug 23;2021.08.23.457229. doi: 10.1101/2021.08.23.457229. Preprint

mRNA Vaccination Induces Durable Immune Memory to SARS-CoV-2 with Continued Evolution to Variants of Concern

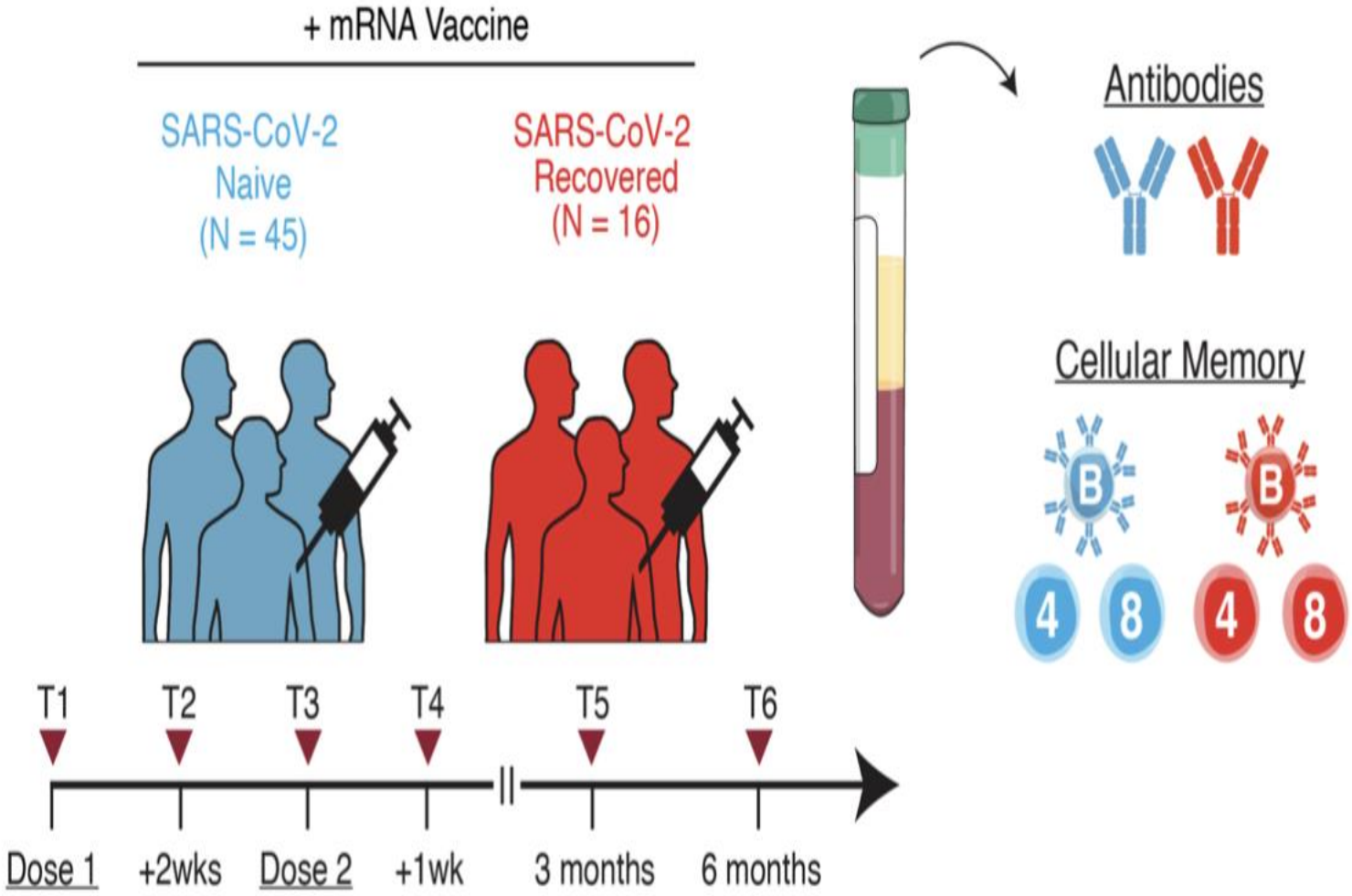
Rishi R Goel, Mark M Painter, Sokratis A Apostolidis, Divij Mathew, Wenzhao Meng, Aaron M Rosenfeld, Kendall A Lundgreen, Arnold Reynaldi, David S Khoury, Ajinkya Pattekar, Sigrid Gouma, Leticia Kuri-Cervantes, Philip Hicks, Sarah Dysinger, Amanda Hicks, Harsh Sharma, Sarah Herring, Scott Korte, Amy E Baxter, Derek A Oldridge, Josephine R Giles, Madison E Weirick, Christopher M McAllister, Moses Awofolaju, Nicole Tanenbaum, Elizabeth M Drapeau, Jeanette Dougherty, Sherea Long, Kurt D'Andrea, Jacob T Hamilton, Maura McLaughlin, Justine C Williams, Sharon Adamski, Oliva Kuthuru, UPenn COVID Processing Unit; Ian Frank, Michael R Betts, Laura A Vella, Alba Grifoni, Daniela Weiskopf, Alessandro Sette, Scott E Hensley, Miles P Davenport, Paul Bates, Eline T Luning Prak, Allison R Greenplate, E John Wherry

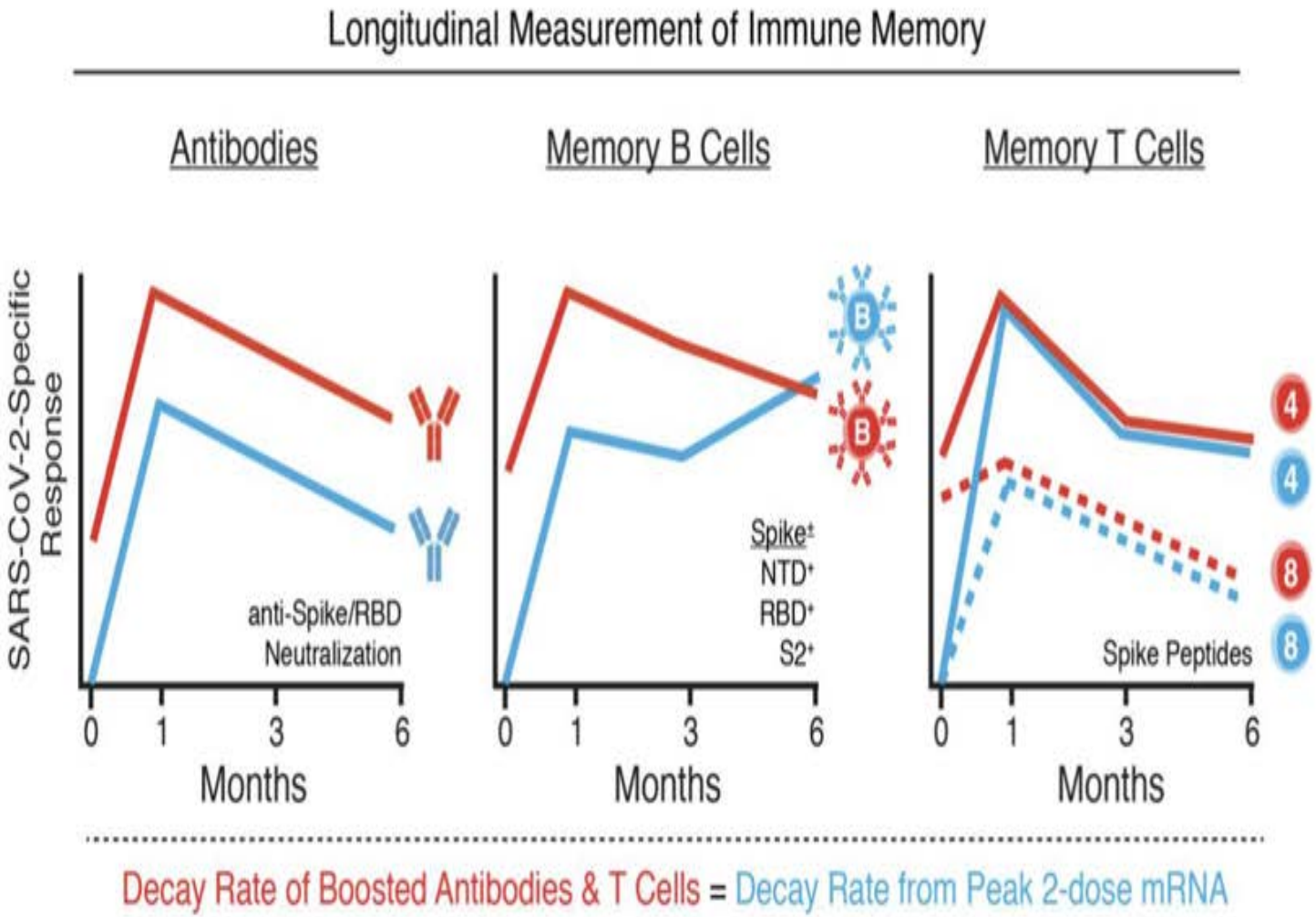
PMID: 34462751 PMCID: PMC8404899 DOI: 10.1101/2021.08.23.457229

Free PMC article

Abstract

SARS-CoV-2 mRNA vaccines have shown remarkable efficacy, especially in preventing severe illness and hospitalization. However, the emergence of several variants of concern and reports of


+ mRNA Vaccine
SARS-CoV-2
Naive
(N = 45)
SARS-CoV-2
Recovered
(N = 16)
Antibodies
Cellular Memory
B
B
4
8
4
8
T1
T2
T3
T4
T5
T6
Dose 1
+2wks
Dose 2
+1wk
3 months
6 months


Longitudinal Measurement of Immune Memory
Antibodies
Memory B Cells
Memory T Cells
SARS-CoV-2-Specific Response
anti-Spike/RBD Neutralization
Spike+
NTD+
RBD+
S2+
Spike Peptides
4
4
8
8
0 1 3 6
Months
0 1 3 6
Months
0 1 3 6
Months
Decay Rate of Boosted Antibodies & T Cells = Decay Rate from Peak 2-dose mRNA

Induction of memory cells

- At the beginning of the pandemic, experts believed that COVID vaccines would have to be given in 3 doses to generate high frequencies of memory B and T cells.
- Researchers believed that mRNA vaccines would be similar to purified protein vaccines (e.g., HBV, HPV) and whole inactivated viral vaccines (polio, HAV), where 4-6-month intervals were necessary to induce high frequencies of memory B and T cells.
- To date, this hasn’t been necessary for healthy young people.

Goal #2:

Prevent all symptomatic illness

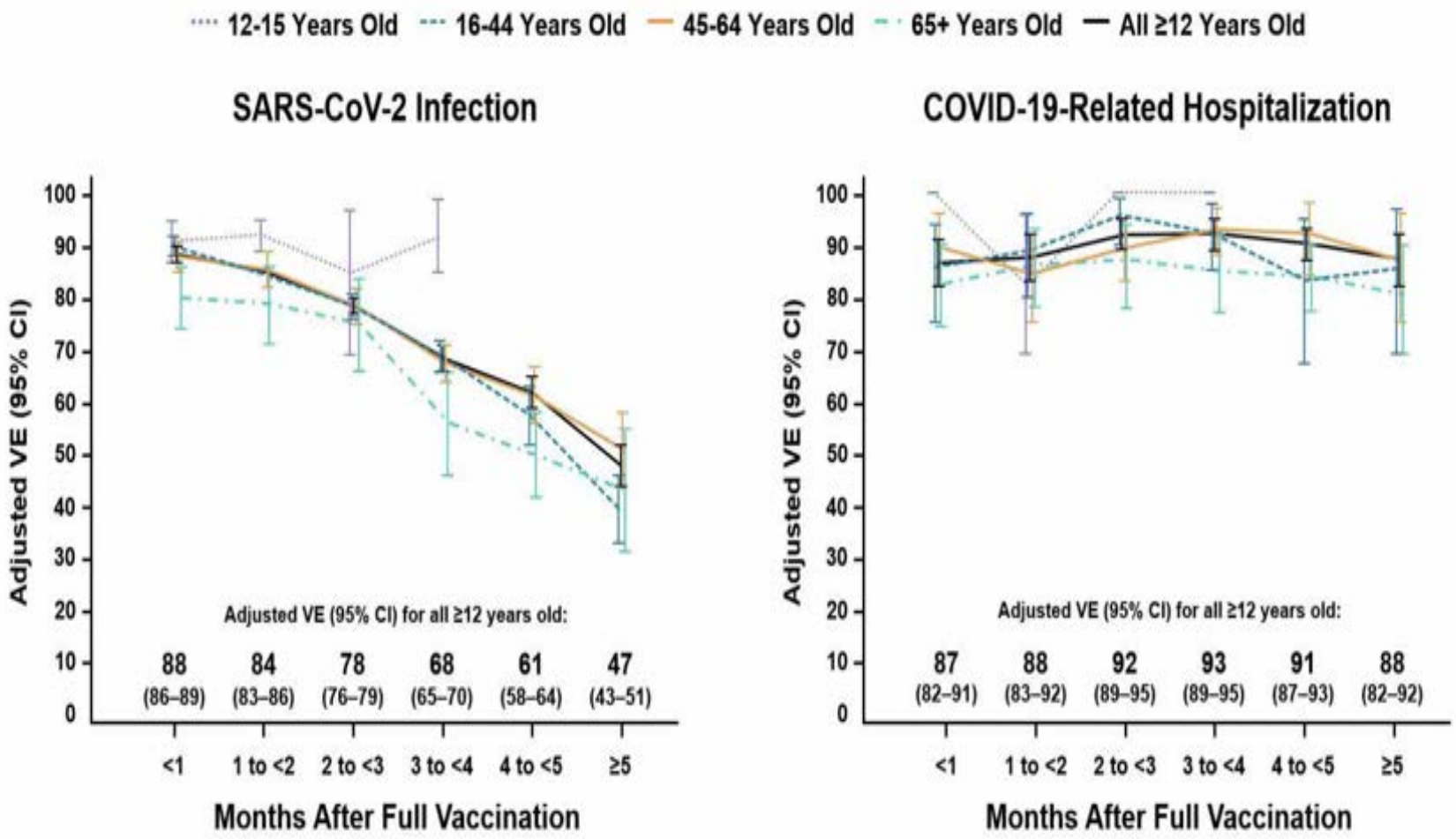
Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study

Sara Y Tartof, Jeff M Slezak, Heidi Fischer, Vennis Hong, Bradley K Ackerson, Omesh N Ranasinghe, Timothy B Frankland, Oluwaseye A Ogun, Joann M Zamparo, Sharon Gray, Srinivas R Valluri, Kaije Pan, Frederick J Angulo, Luis Jodar, John M McLaughlin

Summary

Background Vaccine effectiveness studies have not differentiated the effect of the delta (B.1.617.2) variant and potential waning immunity in observed reductions in effectiveness against SARS-CoV-2 infections. We aimed to evaluate overall and variant-specific effectiveness of BNT162b2 (tozinameran, Pfizer–BioNTech) against SARS-CoV-2 infections and COVID-19-related hospital admissions by time since vaccination among members of a large US health-care system.

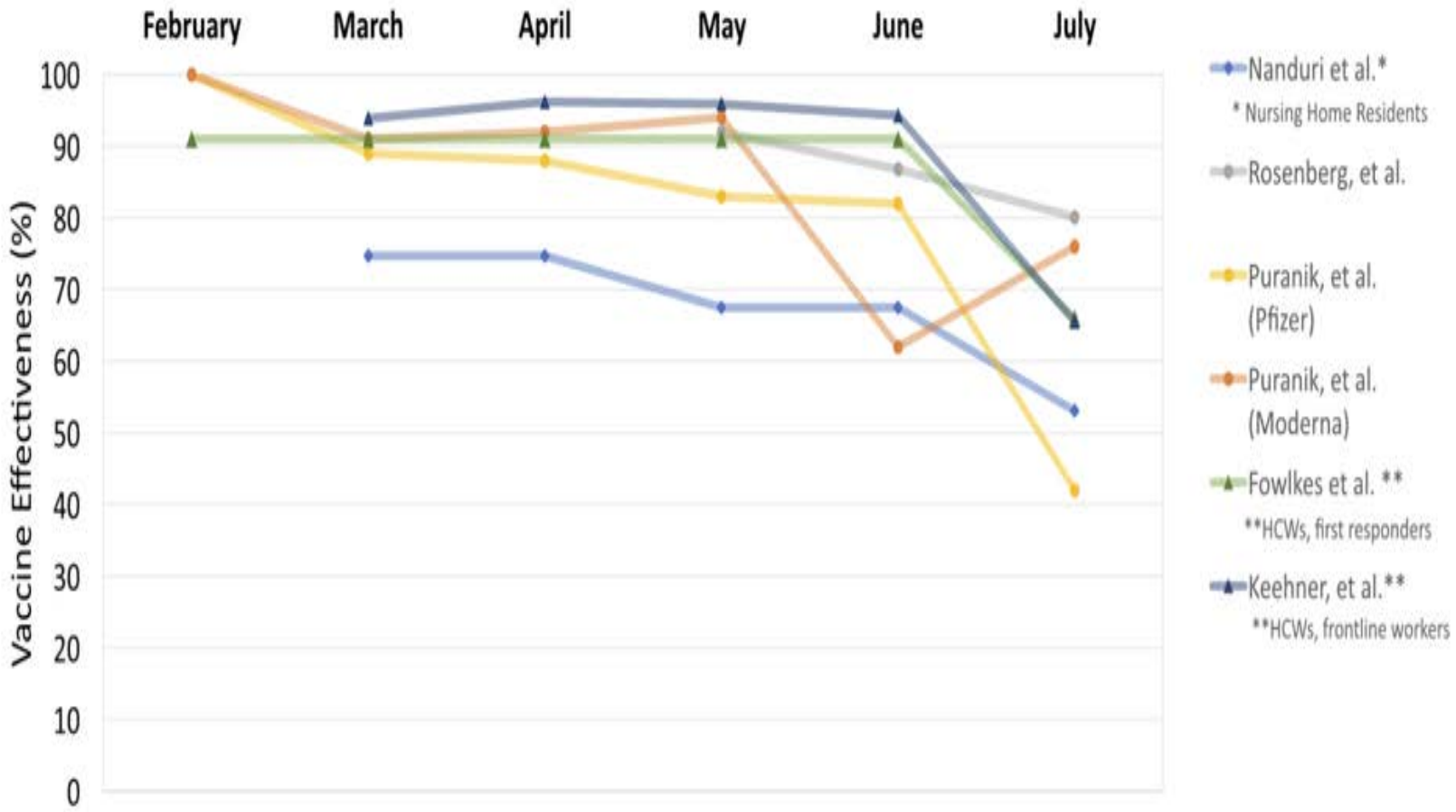
In All Age Groups, Vaccine Effectiveness Wanes Over Time Against Infections but Not Against Hospitalizations



Tartof SY, et al. Six-Month Effectiveness of BNT162B2 mRNA COVID-19 Vaccine in a Large US Integrated Health System: A Retrospective Cohort Study. Available at SSRN: https://dx.doi.org/10.2139/ssrn.3909743

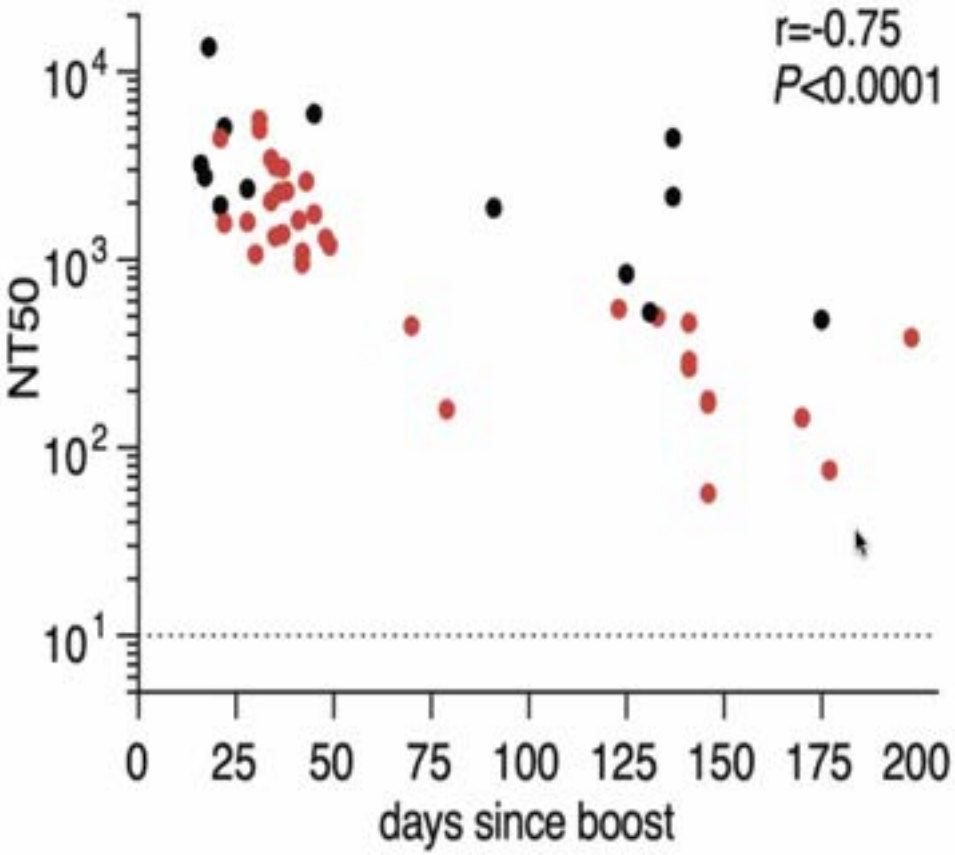
Vaccine effectiveness against **infection** over time

Adults ≥18 years of age

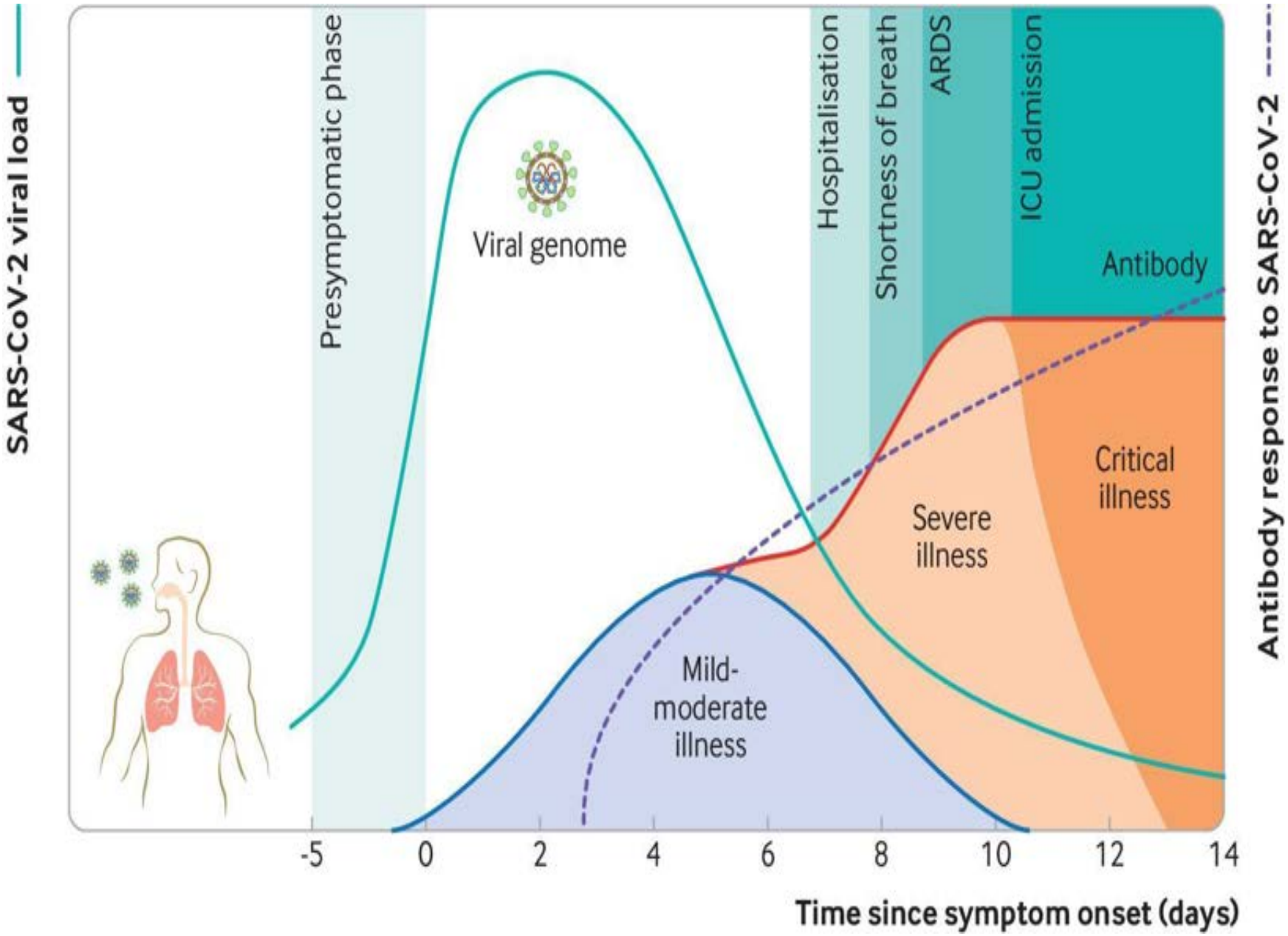


Protection against mild or asymptomatic infection is mediated by high-titers of circulating, virus neutralizing antibodies, which are relatively short-lived

Decreasing Neutralizing Activity with Time



Cho et al Submitted


SARS-CoV-2 viral load
Antibody response to SARS-CoV-2
Presymptomatic phase
Viral genome
Hospitalisation
Shortness of breath
ARDS
ICU admission
Antibody
Critical illness
Severe illness
Mild-moderate illness
-5
0
2
4
6
8
10
12
14
Time since symptom onset (days)

Phase 3 trials created unrealistic expectations for protection against all symptomatic illness

mRNA vaccines:

Pfizer

First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

	BNT162b2 (30 µg) N=18,198		Placebo N=18,325				
Efficacy Endpoint	n	Surveillance Time (n)	n	Surveillance Time (n)	VE (%)	(95% CI)	Pr (VE >30%)
First COVID-19 occurrence ≥7 days after Dose 2	8	2.214 (17,411)	162	2.222 (17,511)	95.0	(90.3, 97.6)	>0.9999

Total surveillance time: 1000 person-years for all subjects within each group at risk for the endpoint..
Pr=Posterior probability

mRNA vaccines:

Moderna

Study 301: Primary Efficacy Objective Met, VE Against Confirmed, Symptomatic COVID-19 Cases is > 94%

Per Protocol

Confirmed, Symptomatic COVID-19 Cases	Interim Analysis		Primary Efficacy Analysis	
	mRNA-1273 N=13,934	Placebo N=13,883	mRNA-1273 N=14,134	Placebo N=14,073
Number of cases, n (%)	5 (< 0.1%)	90 (0.6%)	11 (< 0.1%)	185 (1.3%)
Vaccine efficacy based on hazard ratio (95% CI)	94.5% (86.5%, 97.8%)		94.1% (89.3%, 96.8%)	
p-value	< 0.0001		< 0.0001	
Incidence rate per 1000 person-years	1.8	33.4	3.3	56.5

The first communications error:

“breakthroughs”

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
July 30, 2021

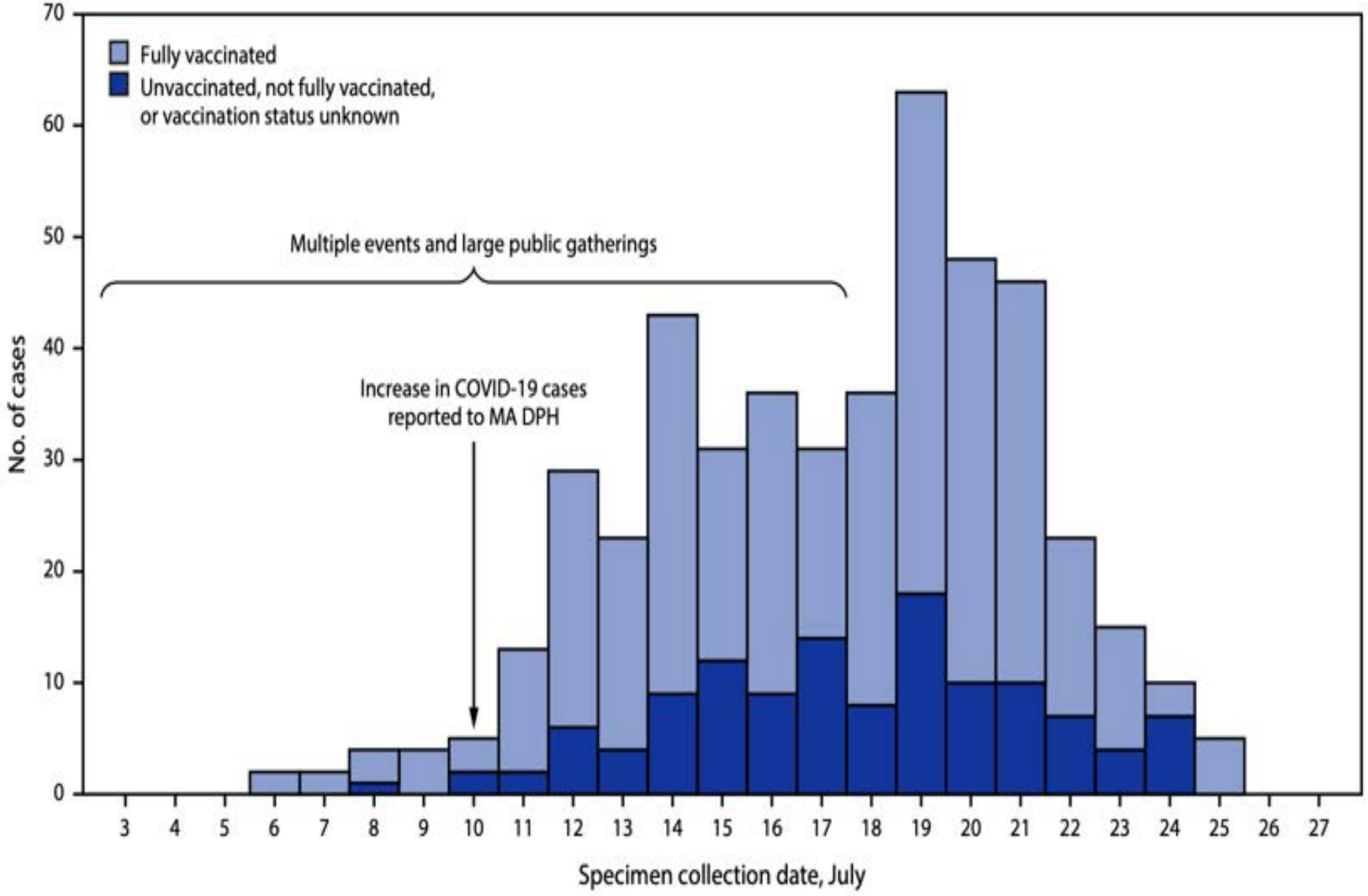
Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021

Catherine M. Brown, DVM[1]; Johanna Vostok, MPH[1]; Hillary Johnson, MHS[1]; Meagan Burns, MPH[1]; Radhika Gharpure, DVM[2]; Samira Sami, DrPH[2]; Rebecca T. Sabo, MPH[2]; Noemi Hall, PhD[2]; Anne Foreman, PhD[2]; Petra L. Schubert, MPH[1]; Glen R. Gallagher PhD[1]; Timelia Fink[1]; Lawrence C. Madoff, MD[1]; Stacey B. Gabriel, PhD[3]; Bronwyn MacInnis, PhD[3]; Daniel J. Park, PhD[3]; Katherine J. Siddle, PhD[3]; Vaira Harik, MS[4]; Deirdre Arvidson, MSN[4]; Taylor Brock-Fisher, MSc[5]; Molly Dunn, DVM[5]; Amanda Kearns[5]; A. Scott Laney, PhD[2]

During July 2021, 469 cases of COVID-19 associated with multiple summer events and large public gatherings in

transmission might consider expanding prevention strategies, including masking in indoor public settings regardless of vac-

FIGURE 1. SARS-CoV-2 infections (N = 469) associated with large public gatherings, by date of specimen collection and vaccination status* — Barnstable County, Massachusetts, July 2021



The second communications error:

“boosters for all”

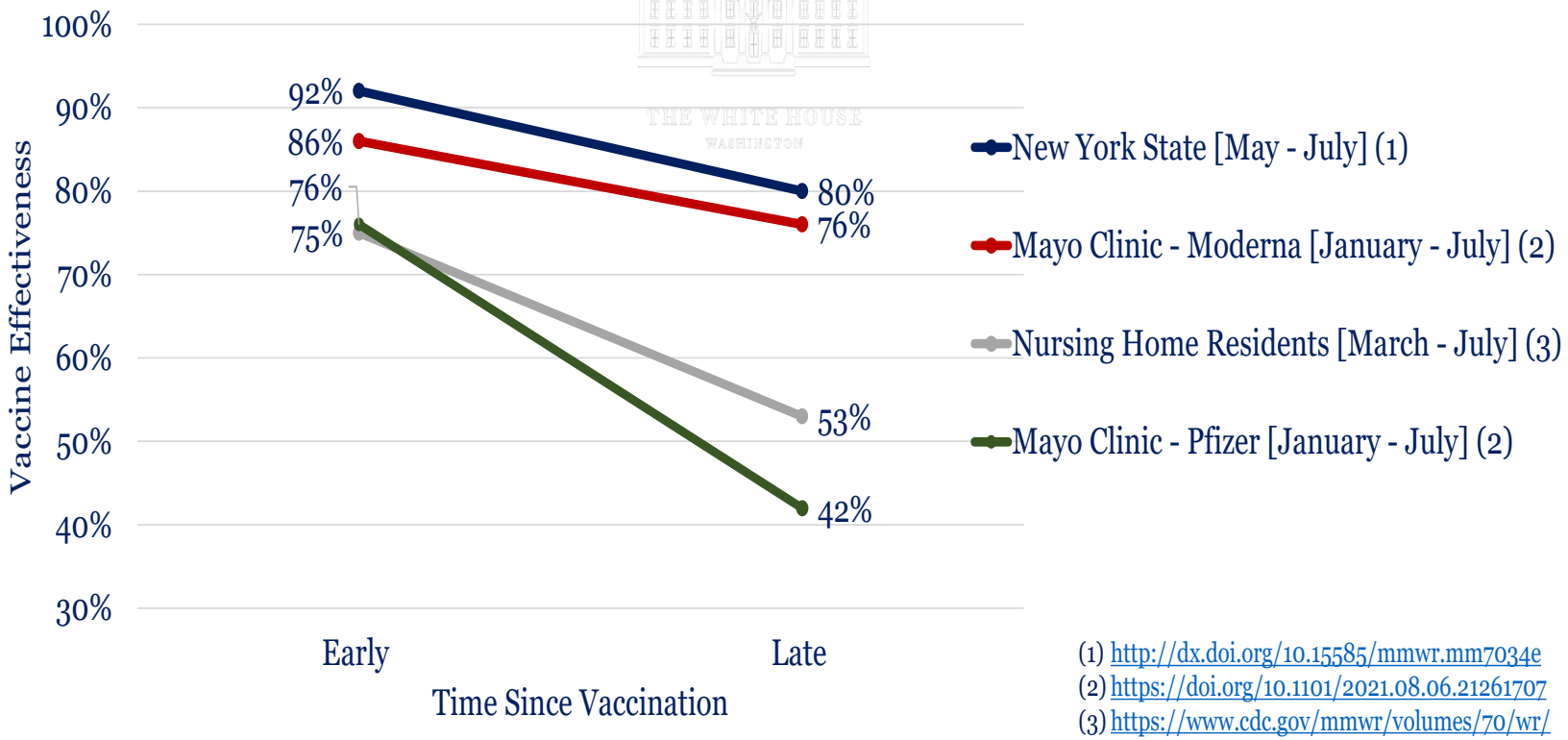
President Biden said on Aug. 18 that after Sept. 20, vaccinated Americans can get booster shots against coronavirus eight months after their second injection. (The Washington Post)

THE WHITE HOUSE
WASHINGTON

COVID-19 Vaccine Effectiveness

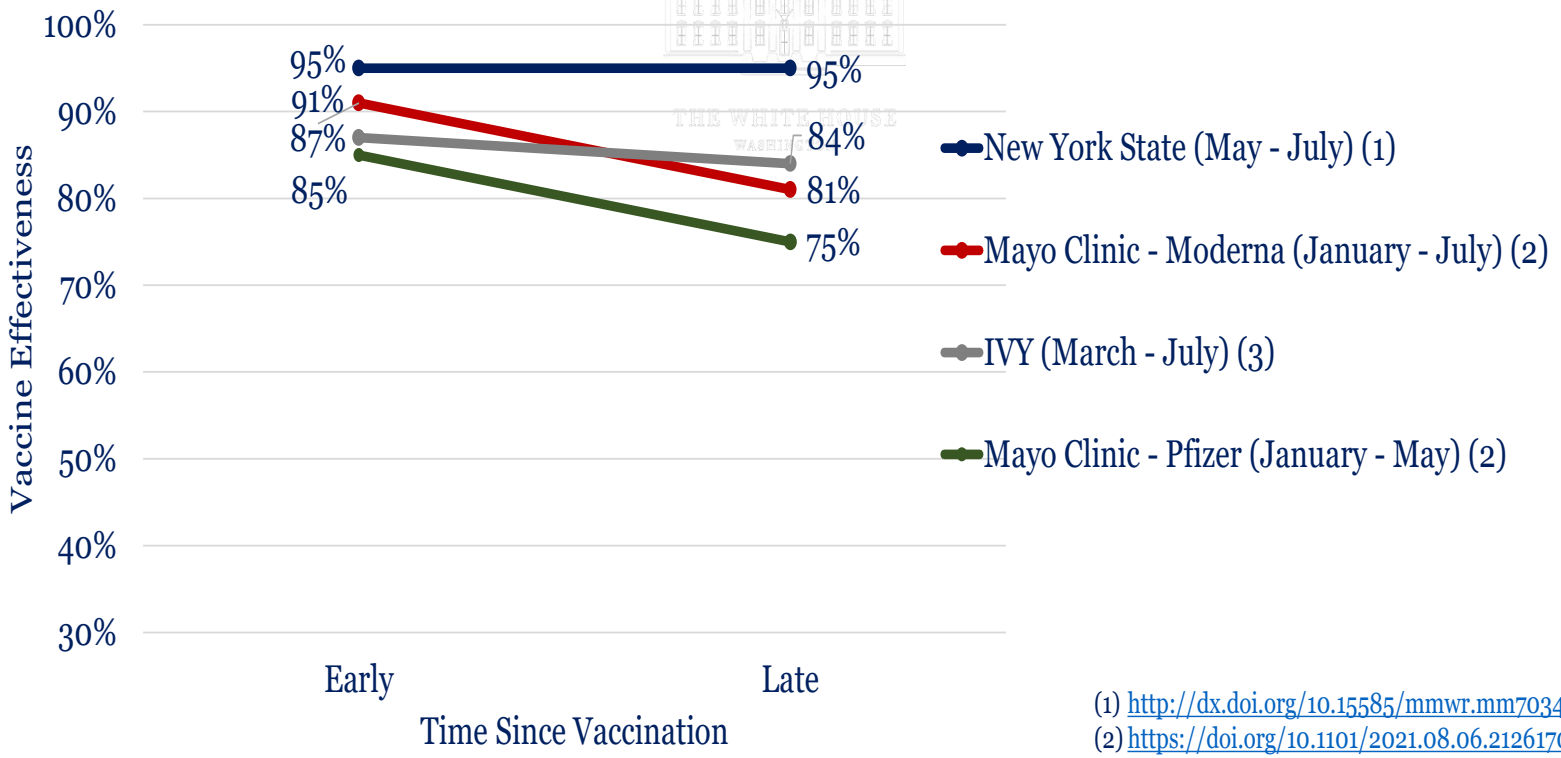
August 18, 2021

Vaccine Effectiveness against Infection has Decreased over Time



(1) http://dx.doi.org/10.15585/mmwr.mm7034e
(2) https://doi.org/10.1101/2021.08.06.21261707
(3) https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e3.htm?s_cid=mm7034e3_w

Vaccine Effectiveness against Hospitalizations Remains Relatively High



(1) http://dx.doi.org/10.15585/mmwr.mm7034e
(2) https://doi.org/10.1101/2021.08.06.21261707
(3) http://dx.doi.org/10.15585/mmwr.mm7034e2

Summary

- Vaccine effectiveness against infection (symptomatic and asymptomatic) is decreasing over time
- Vaccine effectiveness against severe disease, hospitalization, and death remains relatively high
- Vaccine effectiveness is decreased for the Delta variant
- Anticipating further waning immunity and the ongoing Delta surge, we are preparing for a booster vaccine

By “further waning of immunity,” was the administration referring to waning of protection against all symptomatic illness or severe disease?

FDA vaccine advisory committee (VRBPAC) convenes on

September 17, 2021

The Israeli experience:

Erosion in protection against severe disease?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel

Yinon M. Bar-On, M.Sc., Yair Goldberg, Ph.D., Micha Mandel, Ph.D., Omri Bodenheimer, M.Sc., Laurence Freedman, Ph.D., Nir Kalkstein, B.Sc., Barak Mizrahi, M.Sc., Sharon Alroy-Preis, M.D., Nachman Ash, M.D., Ron Milo, Ph.D., and Amit Huppert, Ph.D.

ABSTRACT

BACKGROUND

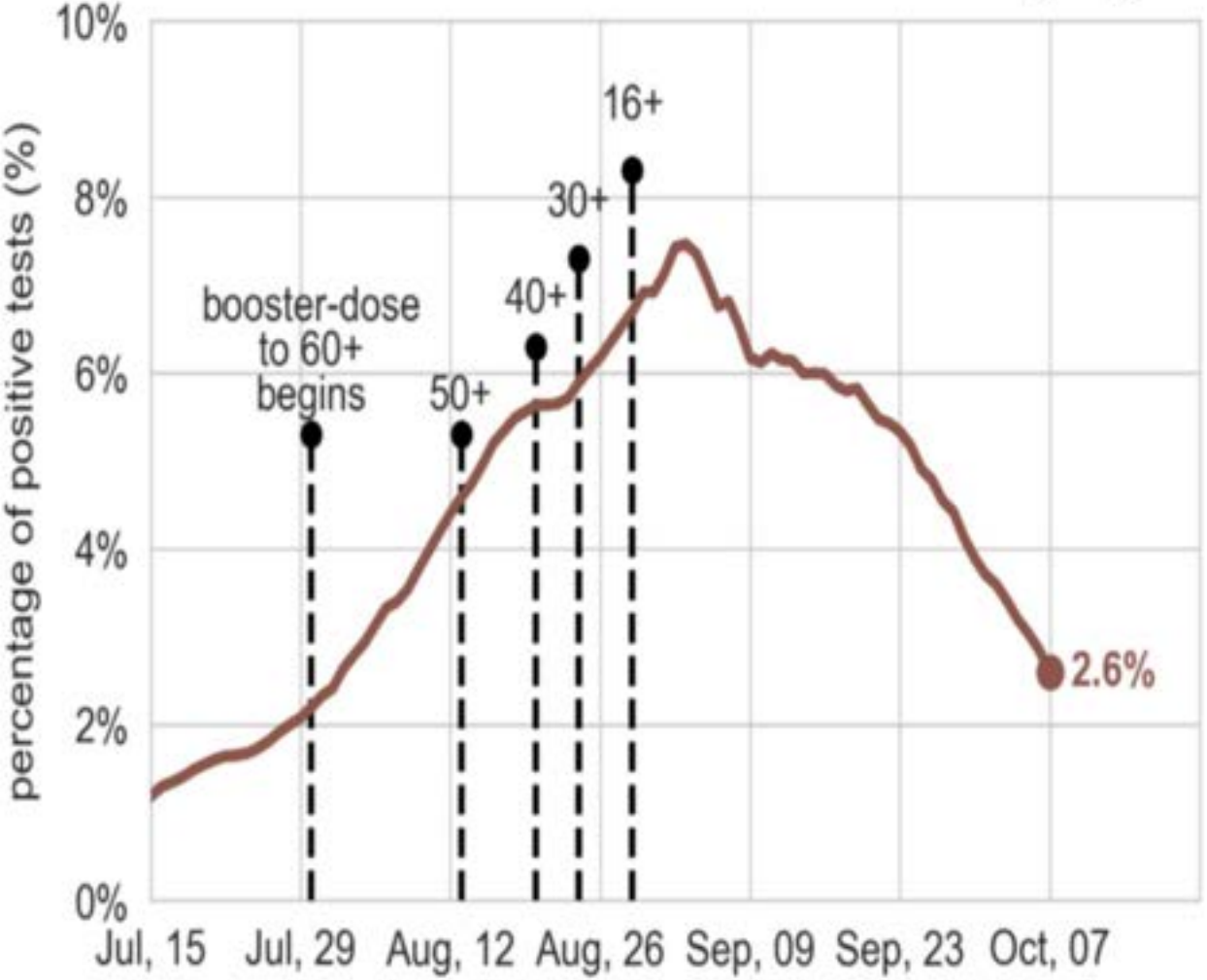
On July 30, 2021, the administration of a third (booster) dose of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) was approved in Israel for persons who

The Israeli Experience

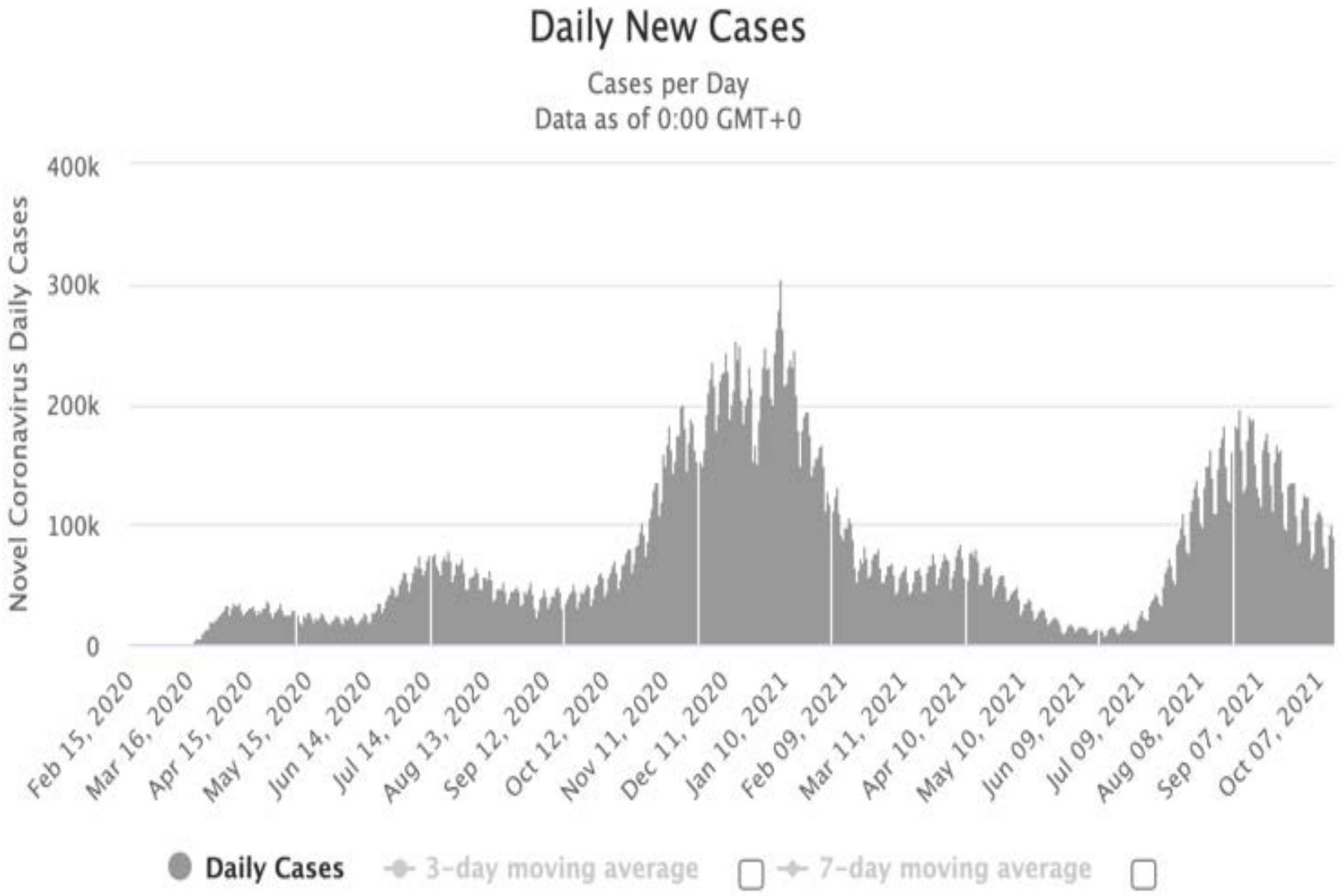
- 75% of participants greater than 70 years old.
- 60-69-year-olds: Incidence of severe illness was 2.8% in the non-booster group and 1.3% in the booster group.
- 70-79-year-olds: Incidence of severe illness was 7.5% in the non-booster group and 1.3% in the booster group.
- >80-years-old: Incidence of severe illness was 18.2% in the non-booster group and 7.9% in the booster group.

Nationwide decrease in percentage of positive tests began only after boosters were administered to most age groups

Percentage of positive tests is more reliable than number of cases due to high-holidays in Israel during Sept.



Daily New Cases in the United States



FDA Vaccine Advisory Committee

- Pfizer's mRNA vaccine could be distributed as a third dose for those over 65 years of age.
- The committee voted "no" on the question of whether a booster dose should be approved for those 16 years of age and older.

ACIP convenes on

September 23, 2021

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Proposed recommendations for booster doses of COVID-19 vaccines

Age	mRNA COVID-19 vaccine primary series			Janssen COVID-19 vaccine primary series
	No risk factors	Underlying medical conditions	Resident of LTCF	
≥65 years	**Should** receive a booster	**Should** receive a booster	**Should** receive a booster	**Should** receive a booster
50–64 years	**May** receive a booster			
18–49 years		**May** receive a booster		

HEALTH AND SCIENCE

FDA clears Moderna's and Pfizer's Covid vaccine booster shots for all U.S. adults

PUBLISHED FRI, NOV 19 2021•8:15 AM EST | UPDATED FRI, NOV 19 2021•8:33 PM EST

Spencer Kimball
@SPENCEKIMBALL

SHARE

November 19, 2021

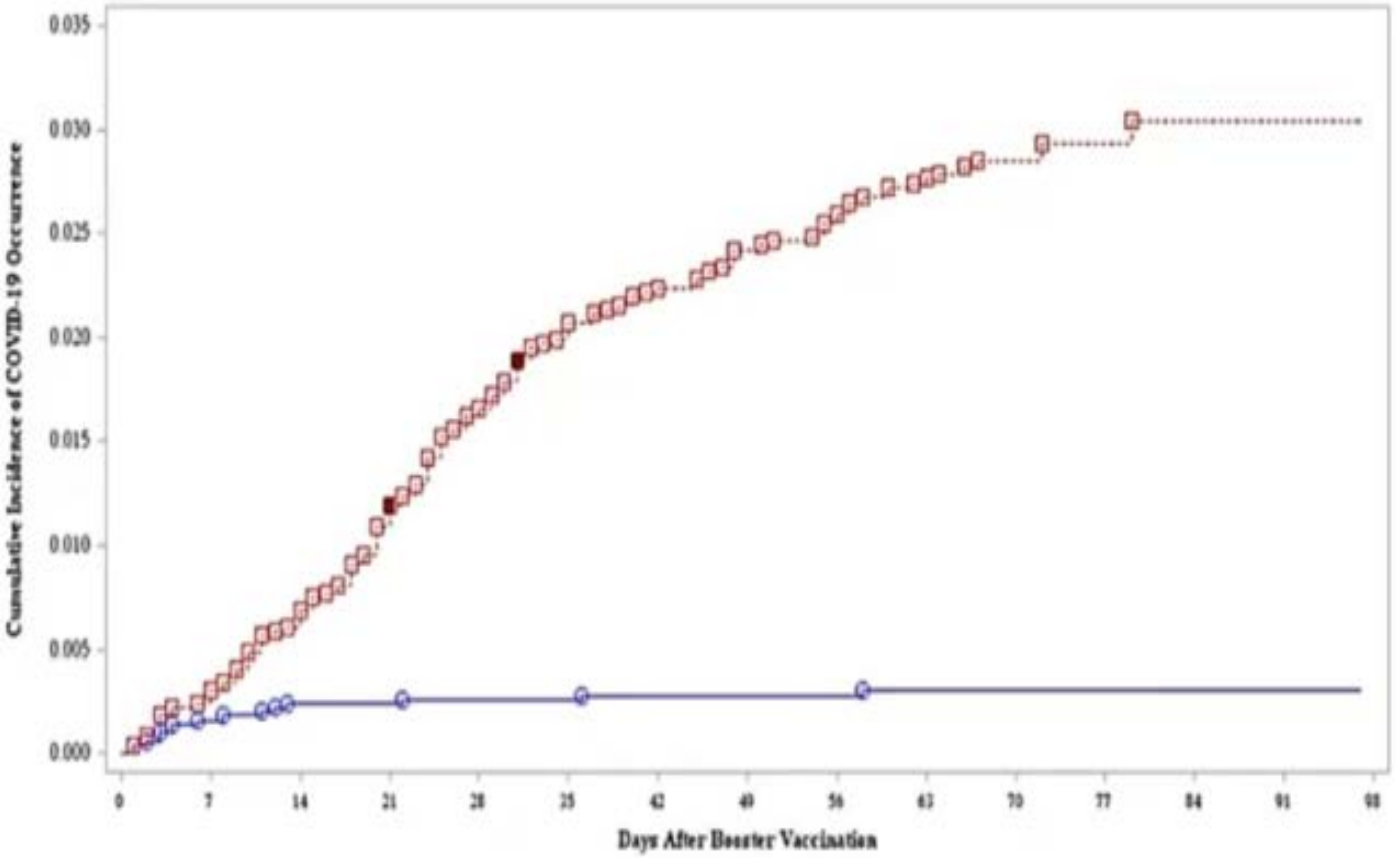
ACIP reconvenes on

November 19, 2021

Pfizer Booster Study

Cumulative Incidence Curve for First COVID-19 Occurrence After Booster Vaccination – All Available Efficacy Population

Curves diverge rapidly, starting even before 7 days after booster



Note the 2 severe cases met the FDA definition only, based only on SpO2 <93%. They were not hospitalized

Relative Vaccine efficacy during blinded follow-up period

Booster dose was highly effective against symptomatic COVID-19

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

	BNT162b2 (30 µg) N=4695		Placebo N=4671			
Efficacy Endpoint	n	Surveillance Time (n)	n	Surveillance Time (n)	RVE (%)	(95% CI)
First COVID-19 occurrence from ≥7 days after booster vaccination to <2 months after booster vaccination	6	0.823 (4659)	123	0.792 (4614)	95.3	(89.5,98.3)

Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint
RVE = relative vaccine efficacy of the BNT162b2 booster group relative to the placebo group (nonbooster)

Proposed recommendations for booster doses of COVID-19 vaccines

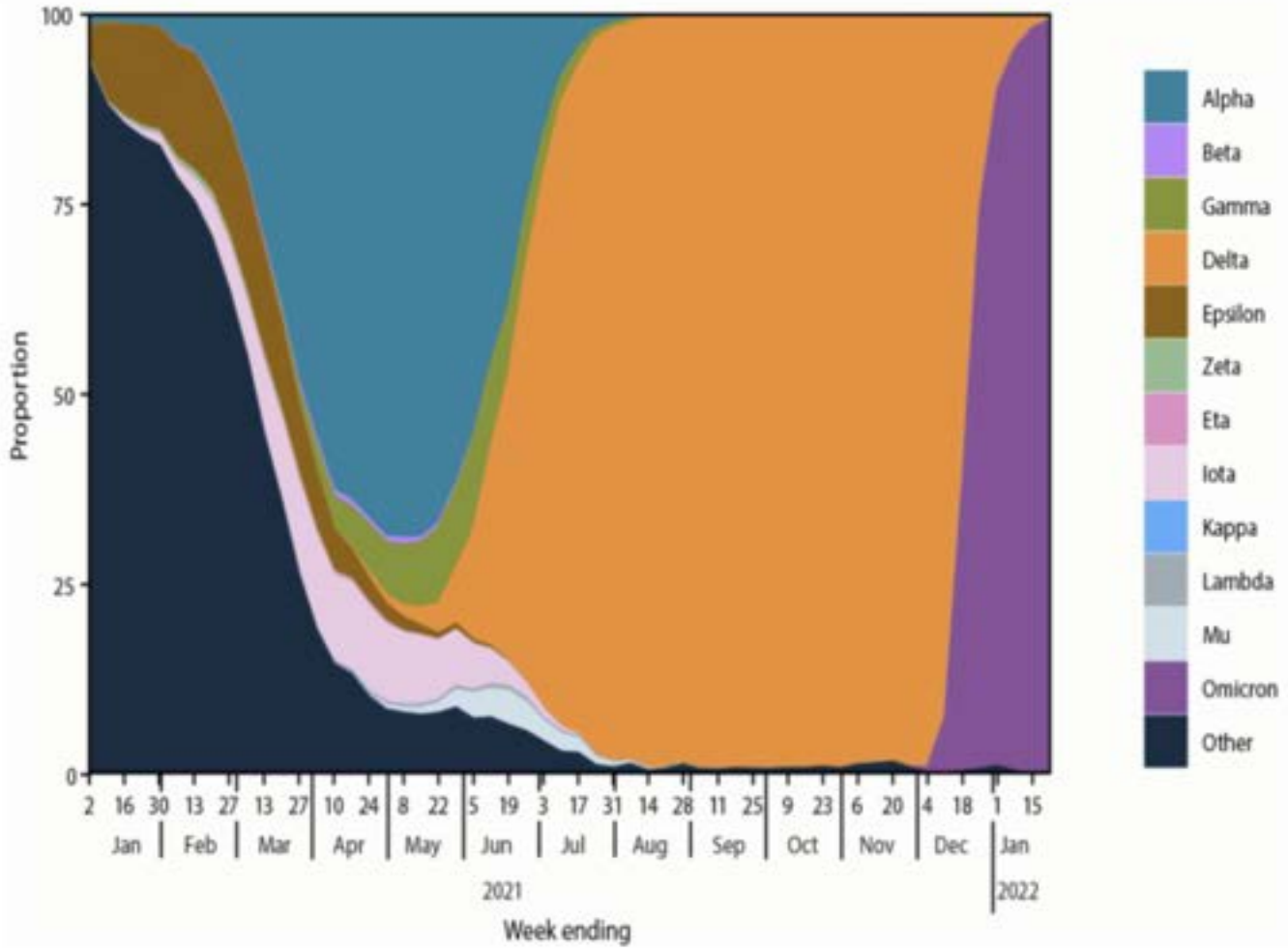
Age	mRNA COVID-19 vaccine primary series			Janssen COVID-19 vaccine primary series
	No risk factors	Underlying medical conditions	Resident of LTCF	
≥65 years	**Should** receive a booster	**Should** receive a booster	**Should** receive a booster	**Should** receive a booster
50–64 years	May receive a booster			
18–49 years		May receive a booster		

November 29, 2021:

Omicron variant

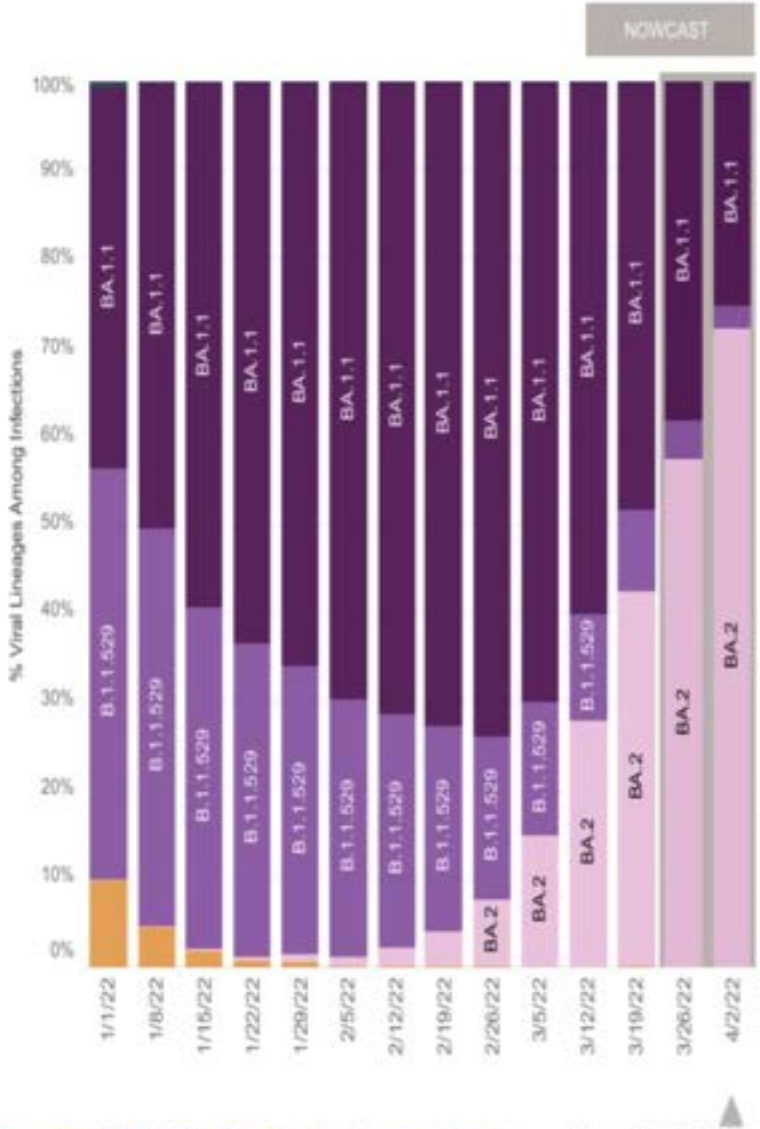
Changing Landscape of Circulating Variants

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

Recent Trends in Weighted Variant Proportion Estimates & Nowcast



USA

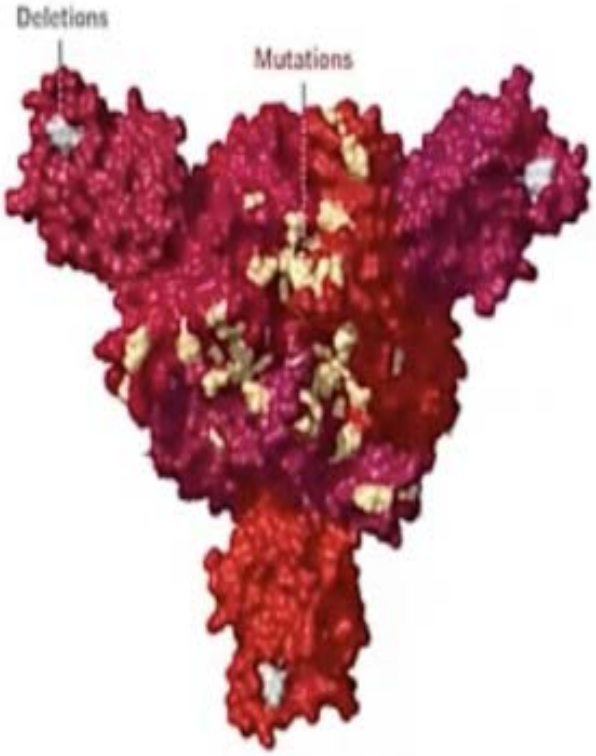
WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.2	VOC	72.2%	68.1-75.9%
	BA.1.1	VOC	25.3%	21.9-29.1%
	B.1.1.529	VOC	2.5%	2.0-3.2%
Delta	B.1.617.2	VOC	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
\# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. BA.1 and BA.3 are aggregated with B.1.1.529. For regional data, BA.1.1 is also aggregated with B.1.1.529, as it currently cannot be reliably called in each region.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions Accessed April 4, 2022

Characteristics of SARS-CoV-2 Omicron variant of concern

- Detection of cases in multiple countries
- Potential increased transmissibility
- 30 mutations in spike gene (S-gene)
  – 15 in receptor binding domain
- Potential reduction in efficacy of some antibody treatments
- Potential reduction in neutralization by sera from vaccinated or convalescent individuals



Key mutations (yellow) in the Omicron spike protein (top view)
Source: New York Times

https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html
https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html

Article

Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2

https://doi.org/10.1038/s41586-021-04388-0

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Check for updates

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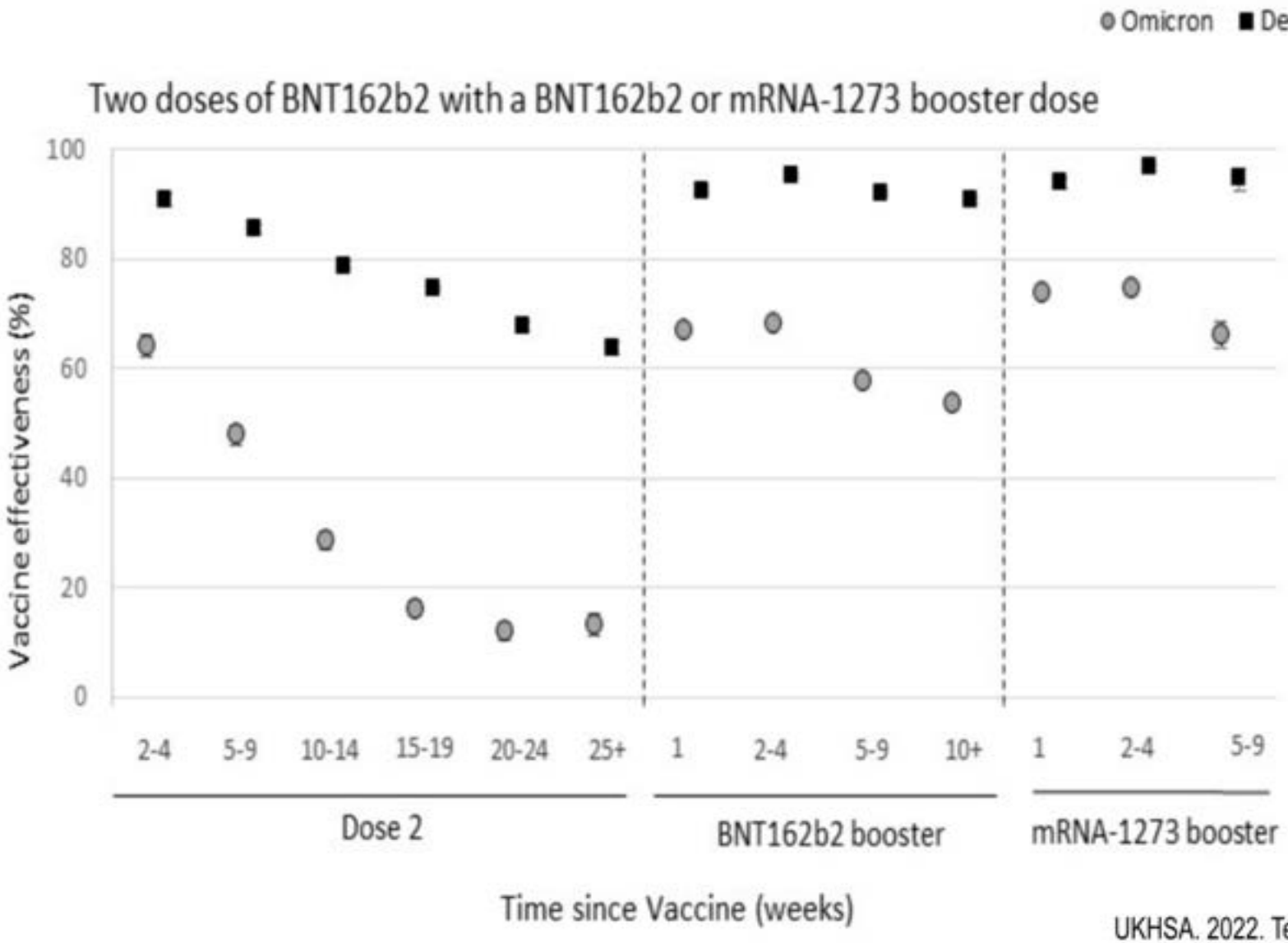
The B.1.1.529/Omicron variant of SARS-CoV-2 was only recently detected in southern Africa, but its subsequent spread has been extensive, both regionally and globally[1]. It is expected to become dominant in the coming weeks[2], probably due to enhanced transmissibility. A striking feature of this variant is the large number of spike mutations[3] that pose a threat to the efficacy of current COVID-19 vaccines and antibody therapies[4]. This concern is amplified by the findings of our study. Here we found that B.1.1.529 is markedly resistant to neutralization by serum not only from patients who recovered from COVID-19, but also from individuals who were vaccinated with one of the four widely used COVID-19 vaccines. Even serum from individuals who were vaccinated and received a booster dose of mRNA-based vaccines exhibited substantially diminished neutralizing activity against B.1.1.529. By evaluating a panel of monoclonal antibodies

Omicron spike mutations substantially drop VE against infection



UKHSA. 2022. Technical Report.

CDC Expands COVID-19 Booster Recommendations

Media Statement

For Immediate Release: Monday, November 29, 2021

Contact: Media Relations

(404) 639-3286

The following is attributable to CDC Director, Dr. Rochelle Walensky

Today, CDC is strengthening its recommendation on booster doses for individuals who are 18 years and older. Everyone ages 18 and older should get a booster shot either when they are 6 months after their initial Pfizer or Moderna series or 2 months after their initial J&J vaccine.

CDC Expands Booster Shot Eligibility and Strengthens Recommendations for 12–17 Year Olds

Español (Spanish)

Media Statement

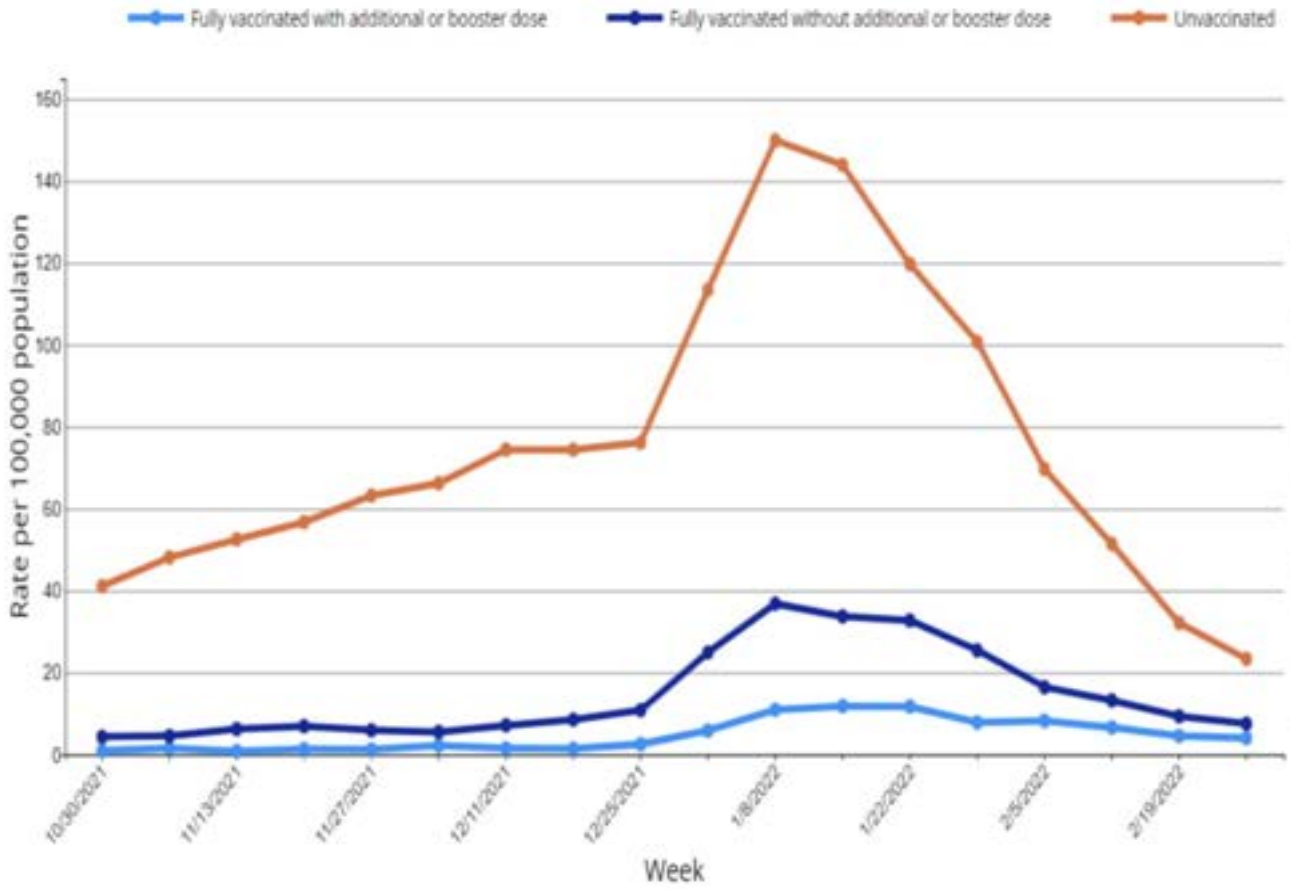
For Immediate Release: Wednesday, January 5, 2022

Contact: Media Relations

(404) 639-3286

Today, CDC is endorsing the Advisory Committee on Immunization Practices' (ACIP) recommendation to expand eligibility of booster doses to those 12 to 15 years old. CDC now recommends that adolescents age 12 to 17 years old should receive a booster shot 5 months after their initial Pfizer-BioNTech vaccination series.

Age-Adjusted Rates of COVID-19-Associated Hospitalizations by Vaccination Status in Adults Ages ≥18 Years, October 2021-February 2022



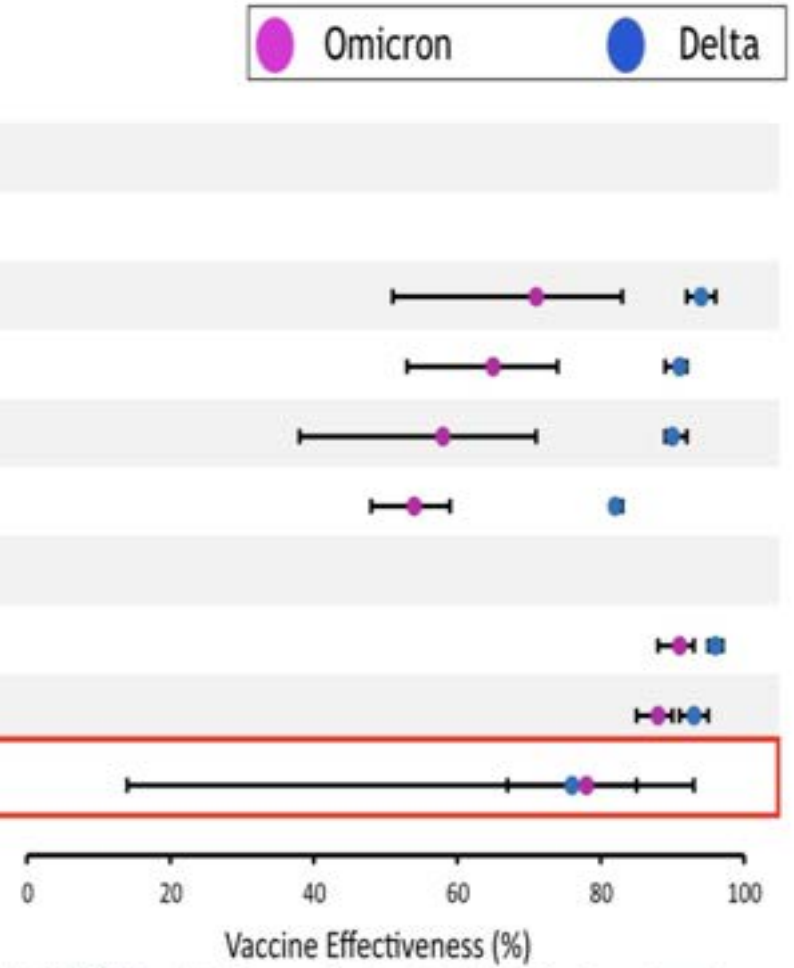
In February, compared to fully vaccinated adults ages ≥18 years with additional or booster doses, monthly rates of COVID-19-associated hospitalizations were **7X** higher in unvaccinated adults

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed March 17, 2022

Endpoint: hospitalization | Population: adults

VISION: mRNA VE against hospitalization 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	94 (92-96)	71 (51-83)
2-3 months	91 (89-92)	65 (53-74)
4 months	90 (89-92)	58 (38-71)
≥5 months	82 (82-83)	54 (48-59)
3 doses		
<2 months	96 (95-97)	91 (88-93)
2-3 months	93 (91-95)	88 (85-90)
≥4 months	76 (14-93)	78 (67-85)



No routine booster recommendations in this time frame; vaccinated individuals may be primarily immunocompromised individuals.

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

COVID-19-associated Hospitalizations Among Vaccinated Adults ≥18 Years with COVID-19 as Primary Reason for Admission – COVID-NET

January 1, 2021-January 31, 2022

- Fully vaccinated cases more likely to be:
  - Older
  - Long-term care facility resident
  - DNR/DNI/CMO code
- More underlying medical conditions

Category	Unvaccinated weighted % N=8,013	Fully vaccinated weighted % N=1,768
Age group (median, IQR)	58 (46-70)	70 (59-80)
18-49 years	31	11
50-64 years	33	16
≥65 years	37	72
LTCF residence	4	12
DNR/DNI/CMO	6	14
Underlying medical conditions*		
Chronic lung disease	28	42
Cardiovascular disease	33	56
Neurologic disease	15	29
Renal disease	14	30
Immunosuppressive condition	11	24
≥3 Underlying medical conditions	50	76

* Conditions significantly different in multivariable model of factors associated with hospitalization

DNI = do not intubate; DNR = do not resuscitate; CMO=comfort measure only

Unpublished data, as described at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html

Protection against mild illness fades after dose 2 or 3

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

Jill M. Ferdinands, PhD[1]; Suchitra Rao, MBBS[2]; Brian E. Dixon, PhD[3,4]; Patrick K. Mitchell, ScD[5]; Malini B. DeSilva, MD[6]; Stephanie A. Irving, MHS[7]; Ned Lewis, MPH[8]; Karthik Natarajan, PhD[9,10]; Edward Stenehjem, MD[11]; Shaun J. Grannis, MD[3,12]; Jungmi Han[9]; Charlene McEvoy, MD[6]; Toan C. Ong, PhD[2]; Allison L. Naleway, PhD[7]; Sarah E. Reese, PhD[5]; Peter J. Embi, MD[3,12,13]; Kristin Dascomb, MD[11]; Nicola P. Klein, MD[8]; Eric P. Griggs, MPH[1]; Deepika Konatham[14]; Anupam B. Kharbanda, MD[15]; Duck-Hye Yang, PhD[5]; William F. Fadel, PhD[3,4]; Nancy Grisel, MPP[11]; Kristin Goddard, MPH[8]; Palak Patel, MBBS[1]; I-Chia Liao MPH[14]; Rebecca Birch, MPH[5]; Nimish R. Valvi, DrPH[3]; Sue Reynolds, PhD[1]; Julie Arndorfer, MPH[11]; Ousseny Zerbo, PhD[8]; Monica Dickerson[1]; Kempapura Murthy, MBBS[14]; Jeremiah Williams, MPH[1]; Catherine H. Bozio, PhD[1]; Lenee Blanton, MPH[1]; Jennifer R. Verani, MD[1]; Stephanie J. Schrag, DPhil[1]; Alexandra F. Dalton, PhD[1]; Mehiret H. Wondimu, MPH[1]; Ruth Link-Gelles, PhD[1]; Eduardo Azziz-Baumgartner, MD[1]; Michelle A. Barron, MD[2]; Manjusha Gaglani, MBBS[14,16]; Mark G. Thompson, PhD[1]; Bruce Fireman[8]

On February 11, 2022, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

CDC recommends that all persons aged ≥12 years receive a booster dose of COVID-19 mRNA vaccine ≥5 months after

variant accounted for ≥50% of sequenced isolates).[¶] Persons categorized as having received 3 doses included those who received a third dose in a primary series or a booster dose after a 2 dose primary series (including the reduced-dosage Moderna

Booster dosing

- At this point, we needed to define which groups benefited from a 3-dose vaccine for protection against serious illness.
- If the goal of a booster dose is to afford better protection against mild illness (as was the case with immune evasive strains like omicron or BA-2), then booster doses would need to be repeated every 6 months.
- To date, no clear evidence exists that booster dosing affords better protection against serious illness in otherwise healthy young people < 50 years of age.

Pfizer’s fourth dose:

March 28, 2022

Original Article

DE:
ME:

Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting

Ori Magen, M.D., Jacob G. Waxman, M.D., Maya Makov-Assif, M.D., Roni Vered, M.D., Dror Dicker, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Y. Reis, Ph.D., Ran D. Balicer, M.D., and Noa Dagan, M.D.

From the Clalit Research Institute, Innovation Division (O.M., J.G.W., M.M.-A., R.D.B., N.D.), and the Tel-Aviv District, Community Division (R.V.), Clalit Health Services, and the Sackler Faculty of Medicine, Tel-Aviv University (D.D.), Tel Aviv, the Department of Internal Medicine D, Hasharon Hospital Rabin Medical Center, Petah Tikva (D.D.), and the School of Public Health, Faculty of Health Sciences (R.D.B.), and the Department of Software and Information Systems Engineering (N.D.), Ben Gurion University of the Negev, Be'er Sheva — all in Israel; and the Departments of Epidemiology and Biostatistics and CAUSALab (M.A.H.) and the Center for Communicable Disease Dynamics, Departments of Epidemiology and of Immunology and Infectious Diseases (M.L.), Harvard T.H. Chan School of Public Health, the Ivan and Francesca Berkowitz Family Living Laboratory Collaboration at Harvard Medical School and Clalit Research Institute (B.Y.R., R.D.B., N.D.), the Predictive Medicine Group, Computational Health Informatics Program, Boston Children's Hospital (B.Y.R.), and the Departments of Pediatrics (B.Y.R.) and Biomedical Informatics (B.Y.R., N.D.), Harvard Medical School — all in Boston.

Dr. Dagan can be contacted at noada@clalit.org.il or at the Clalit Research Institute, Innovation Division, Clalit Health Services, 101 Arlozorov St., 6209804, Tel Aviv, Israel.

Drs. Magen, Waxman, and Makov-Assif contributed equally to this article.

Abstract

Background

With large waves of infection driven by the B.1.1.529 (omicron) variant of severe

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)

MINISTRY OF HEALTH

Weakness of the Israeli study

- Israel offered a fourth dose for anyone who chose to take it, targeting those with multiple comorbidities.
- This was a retrospective study; some participants chose to take the fourth dose, others didn’t. Average age was 72 years.
- Researchers assumed that both groups were the same in terms of attentiveness to their health, protective measures, and risky behavior.

Second Booster (4th Dose) - Indications

- Age 60 years and older
- Individuals ≥ 18 years old with comorbidities and risk factors for developing severe COVID-19 and their caretakers
- Facility residents and their caretakers ≥ 18 years old
- Caretakers of elderly ≥ 18 years old
- Health care workers or other workers with significant exposure to COVID-19 in their workplace ≥ 18 years old

MINISTRY OF HEALTH

CDC Recommends Additional Boosters for Certain Individuals

Media Statement

For Immediate Release: March 29, 2022
Contact: Media Relations
(404) 639-3286

Data continue to show the importance of vaccination and booster doses to protect individuals both from infection and severe outcomes of COVID-19. For adults and adolescents eligible for a first booster dose, these shots are safe and provide substantial benefit. During the recent Omicron surge, those who were boosted were 21-times less likely to die from COVID-19 compared to those who were unvaccinated, and 7-times less likely to be hospitalized. CDC continues to recommend that all eligible adults, adolescents, and children 5 and older be up to date on their COVID-19 vaccines, which includes getting an initial booster when eligible.

Following FDA's regulatory action today, CDC is updating its recommendations to allow certain immunocompromised individuals and people over the age of 50 who received an initial booster dose at least 4 months ago to be eligible for another mRNA booster to increase their protection against severe disease from COVID-19. Separately and in addition,

ECDC and EMA on 4th dose

- European Centre for Disease Prevention and Control (ECDC) and European Medicines Agency (EMA)
- "Fourth dose can be given to adults 80 years of age and older."
- "No clear evidence in the EU that vaccine protection against severe disease is waning substantially in adults with normal immune systems aged 60 to 79."
- "For adults less than 60 years of age with normal immune systems, not conclusive evidence that vaccine protection against severe disease is waning."

Booster dosing

- We need to define for whom COVID-19 vaccines are 2-dose, 3-dose or 4-dose vaccines and stop using the word "booster."
- Consistent with published studies, mRNA vaccines are: 1) a 4-dose vaccine for those who are immune compromised; 2) a 4-dose vaccine for those who are over 65 who have multiple co-morbidities; 3) a 3-dose vaccine for everyone over 12 with comorbidities; and 4) a 2-dose vaccine for healthy people less than 65 (but this ship has probably sailed).

Comorbidities

- Chronic heart, lung, kidney or liver disease.
- Obesity, which comprises about 30 percent of US population.
- Diabetes, types 1 or 2.
- Chronic neurological conditions.
- Pregnancy and recent pregnancy.
- Smoking.
- Tuberculosis

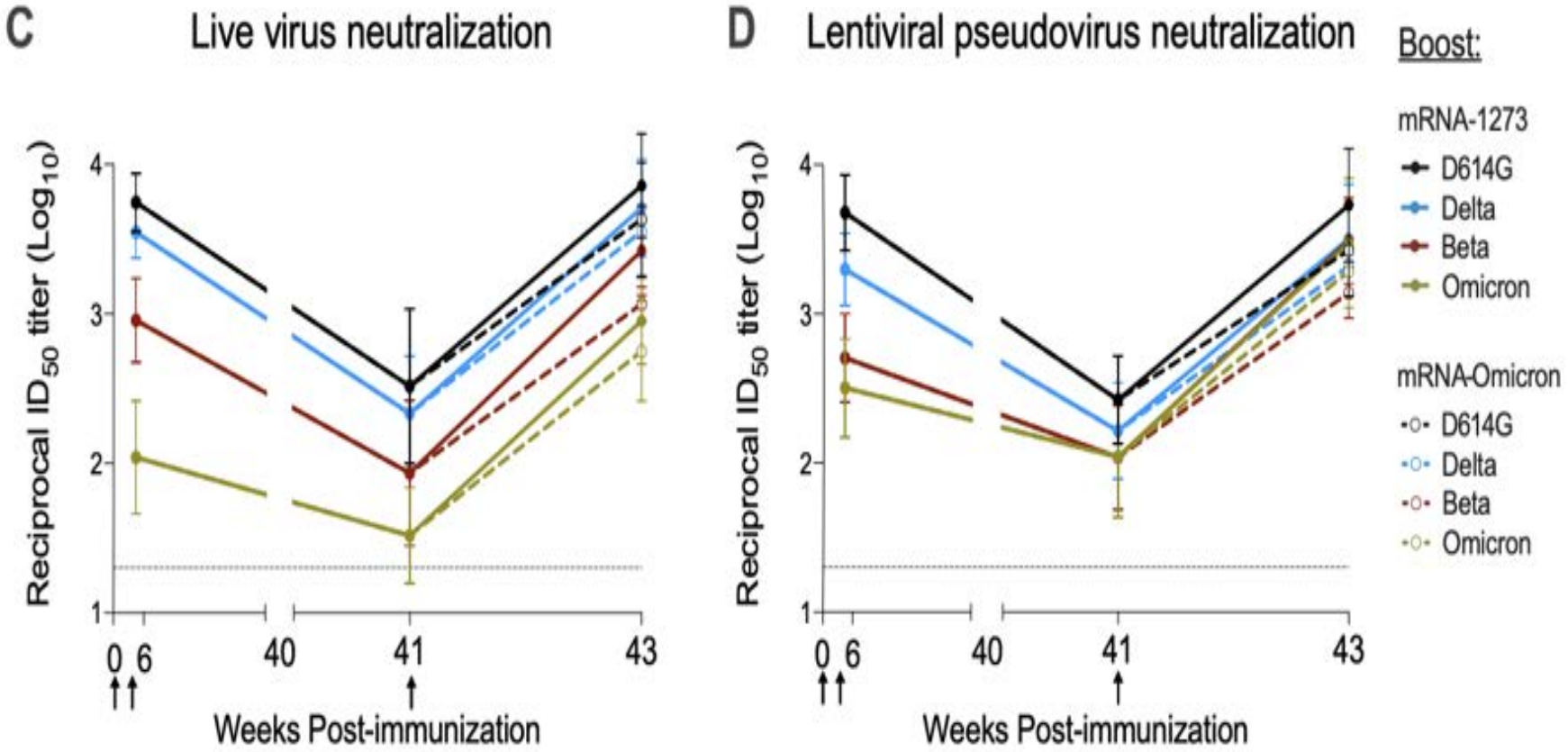
Potential harms from frequent booster dosing

“Original antigenic sin”

mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits comparable B cell expansion, neutralizing antibodies and protection against Omicron

Authors:

Matthew Gagne[1,9], Juan I. Moliva[1,9], Kathryn E. Foulds[1,9], Shayne F. Andrew[1,9], Barbara J. Flynn [1,9], Anne P. Werner[1,9], Danielle A. Wagner[1], I-Ting Teng[1], Bob C. Lin[1], Christopher Moore[1], Nazaire Jean-Baptiste[1], Robin Carroll[1], Stephanie L. Foster[2], Mit Patel[2], Madison Ellis[2], Venkata-Viswanadh Edara[2], Nahara Vargas Maldonado[2], Mahnaz Minai[3], Lauren McCormick[1],


C
Live virus neutralization
Reciprocal ID50 titer (Log10)
4
3
2
1
0
6
40
41
43
Weeks Post-immunization
D
Lentiviral pseudovirus neutralization
Reciprocal ID50 titer (Log10)
4
3
2
1
0
6
40
41
43
Weeks Post-immunization
Boost:
mRNA-1273
D614G
Delta
Beta
Omicron
mRNA-Omicron
D614G
Delta
Beta
Omicron

When will we need a variant-specific vaccine?

Variant-specific vaccine

- To date, all vaccines have been made against the ancestral strain (WU/2020) that first appeared in Wuhan in 2019.
- But the variant D614G, not WU/2020, was the strain that left China and swept across Asia, Europe, and the United States.
- D614G was subsequently replaced by the more contagious variants alpha, then delta variants, followed by the more immune evasive omicron and BA.2 variants.
- In all cases, protection afforded by vaccines made to protect against the ancestral strain have also protected against severe disease with subsequent variants.

Will we need a yearly COVID-19 vaccine in a manner similar to the influenza vaccine?

Yearly COVID-19 vaccines?

- We get yearly influenza vaccine because natural infection or immunization the previous year doesn't necessarily protect against severe disease the following year.
- Coronaviruses aren't influenza virus. To date, protection against severe disease appears to be holding up for more than one year.
- If a variant emerges that is resistant to protection against severe disease, then we will need a variant-specific vaccine, not a yearly vaccine.

Moving from pandemic to endemic

Moving from pandemic to endemic

- Either natural infection or immunization protects against severe disease, possibly for years.
- Neither natural infection nor immunization protects against mild illness for longer than several months.
- At some point, we are going to have to abandon our current policies of zero tolerance and accept mild disease, much in the same way that we accept mild disease for other winter respiratory viruses.
- Stay home if you're sick. If you can't stay home, wear a mask.

Find us online:

vaccine.chop.edu

Children's Hospital of Philadelphia®

Vaccine Education Center

To ask a question:

Type your question into the Q&A box

Pennsylvania Chapter

American Academy of Pediatrics

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Thank You!

- Instructions on how to claim credit for your participation in today's Let's Talk webinar ***"COVID-19 Boosters: Where from Here?"*** will be emailed to all of today's participants, along with a recording of the session.

- If you have any additional questions or issues, please email info@paaap.org.

- Save the date for PA AAP's annual Advocacy Day in Harrisburg, PA on June 8th, 2022 !

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