

Immunization:

“These go to 11” – Vaccine Boosters for the Amplification of Immunity



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Learning Objectives

- At the conclusion of this CPE activity, participants should be able to:
 - 1) Explain how the immune system responds to a booster dose of a vaccine
 - 2) Concisely explain the clinical outcome data supporting administration of COVID-19 3rd doses and/or booster doses
 - 3) Given a specific patient case, determine whether they would qualify for a COVID-19 vaccine booster dose and assign an appropriate product to administer.

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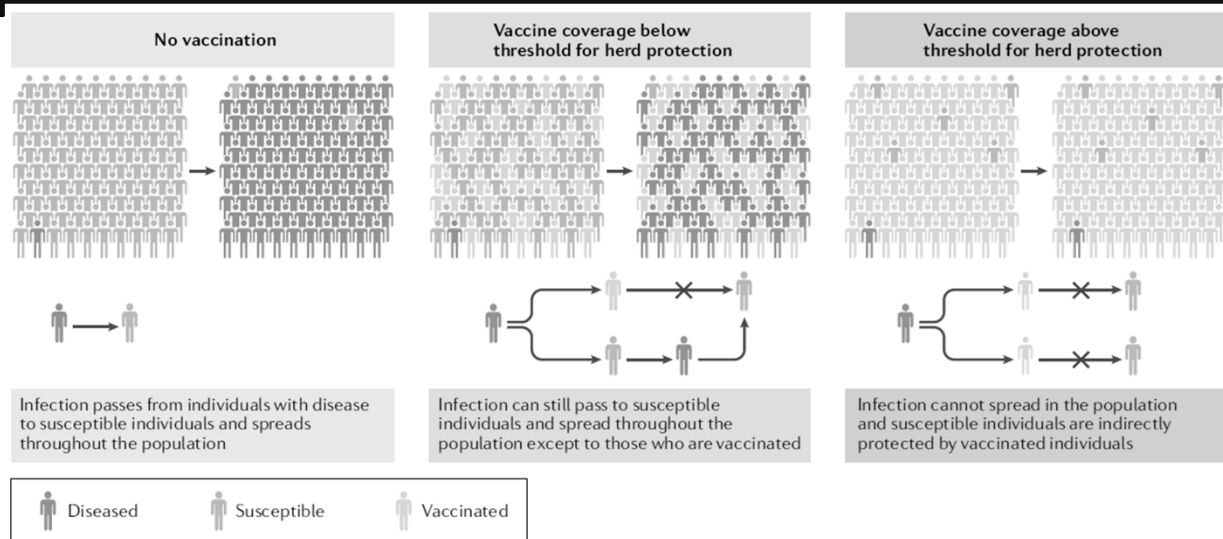
Basics of Immunology & Vaccines

- **Goals for all vaccines:**
 - Protect the individual against disease and/or infection caused by a pathogen during post-vaccination exposure events
 - Prevent onward transmission of the infection (“**herd immunity**”)
- **Usual types of vaccines:**
 - Live (attenuated) or non-live (inactivated)
 - Protein or polysaccharide antigen(s)
- **Newer types of vaccines:**
 - Nucleic acids (RNA, DNA)
 - Viral Vectors

Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

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Basics: Herd Immunity



Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

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Quick Knowledge Check Question!

- Which of the following appears to be **MOST IMPORTANT** for a vaccine's overall effectiveness?
 - Production of circulating antibodies
 - Production of memory T cell cells

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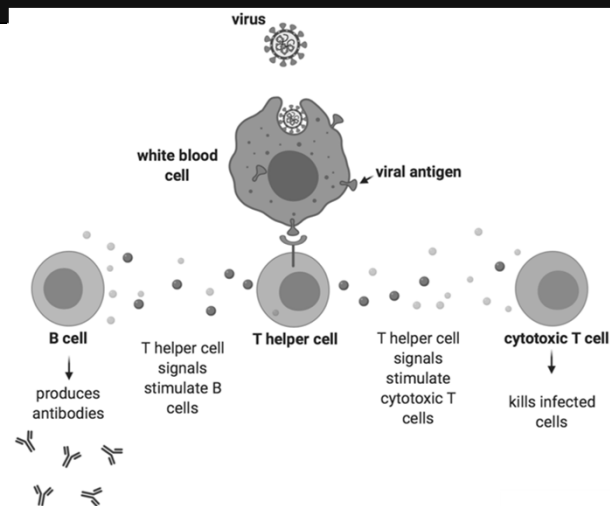
Immune Response to Vaccination

- **Dendritic cells** – activation, antigen presentation
- **B cells** – antibody production
- **T cells** – cellular immunity, immune memory

Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

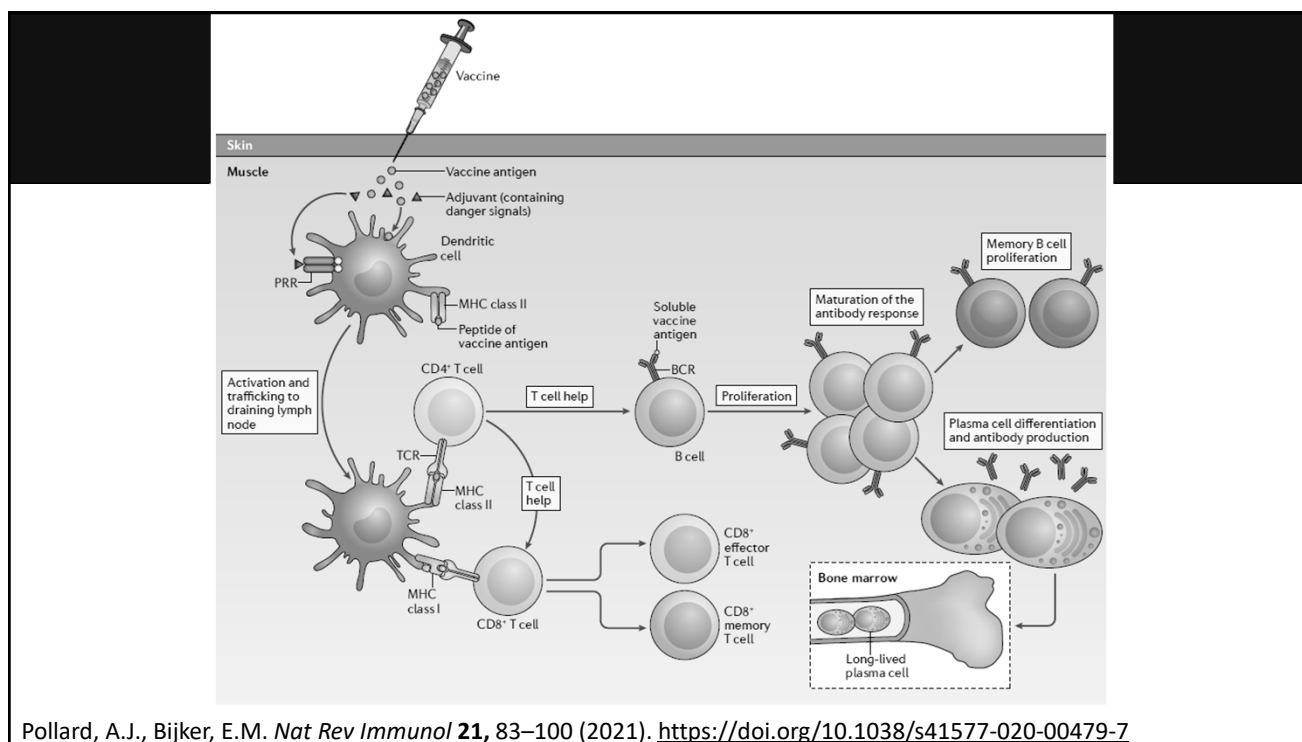
9

Immune Response to Vaccination



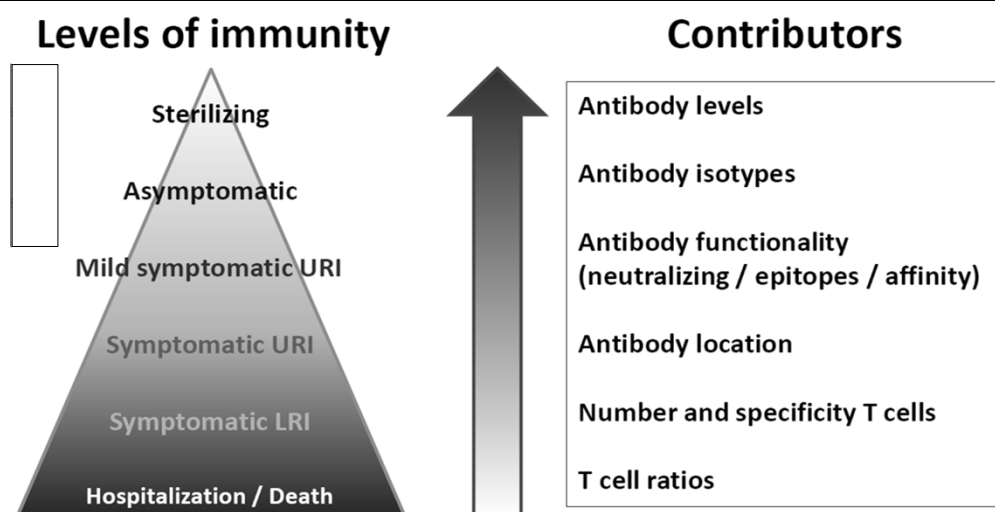
Rey, G.U. *Virology Blog* (11/5/2020). <https://www.virology.ws/2020/11/05/t-cell-responses-to-coronavirus-infection-are-complicated/>

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Immune System “Influencers”: Grades of Protection by the Immune System



Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Contributors to Protection

- **Sterilizing immunity:**
 - driven primarily by antibodies
- **T cell response:**
 - **T helper cells** assist with:
 - Cellular immunity
 - B cell development & antibody production
 - Mucosal surface immunity
 - **Cytotoxic T cells:**
 - Appear to help to prevent progression to **more severe disease**

Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

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Response to Vaccinations: Reasons & Need for “Booster Doses”

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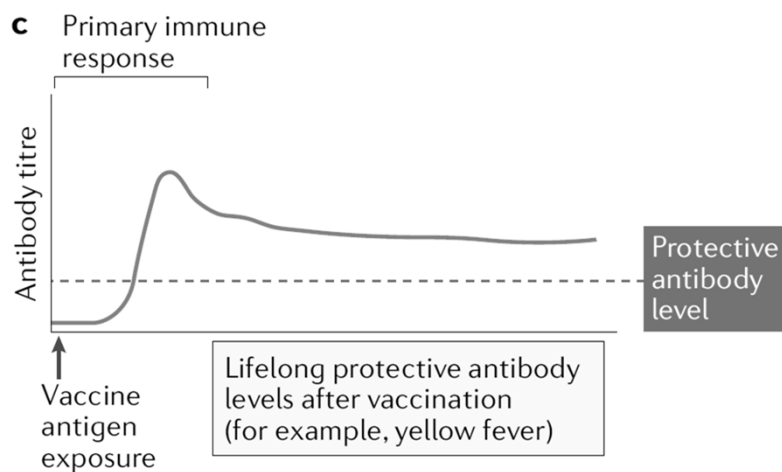
Factors that Influence Duration of Vaccine Efficacy & Need for Booster Doses

- What is my measure of efficacy?
 - Protection from **any infection** vs. **severe/life-threatening infection**?
- What is the **incubation period** of the pathogen's process of infection?
- What are the **circulating antibody** concentrations / elimination half-life?
 - Amount of variation from person to person?
- How long does it take for immune memory / re-activation of antibody production?
 - [Usually ~3-4 days]

Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

15

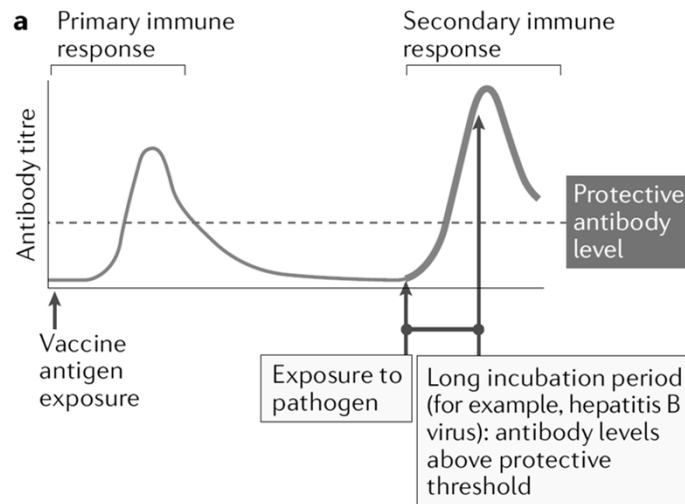
“Optimal” Immune Response to an Initial Vaccination Series



Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

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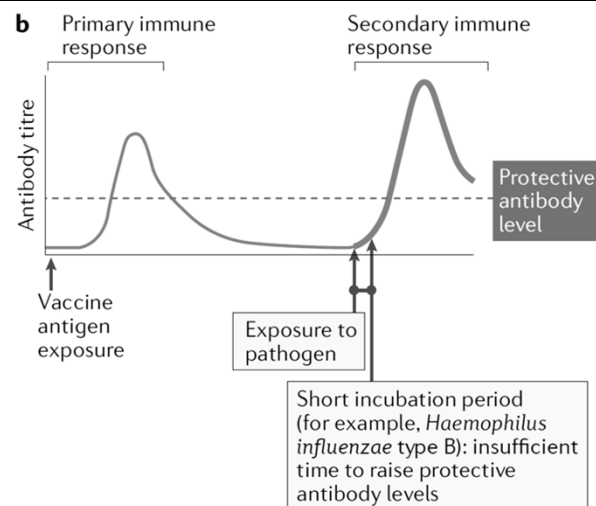
“Adequate” Response to an Initial Vaccination Series: Long incubation-period infection



Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

17

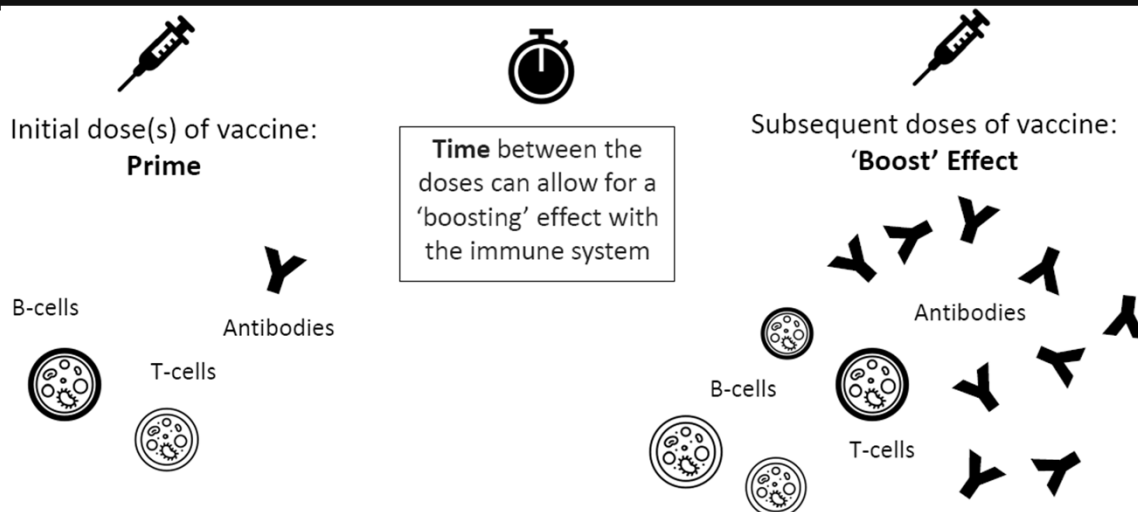
“Suboptimal” Response to an Initial Vaccination Series: Short incubation-period infection



Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

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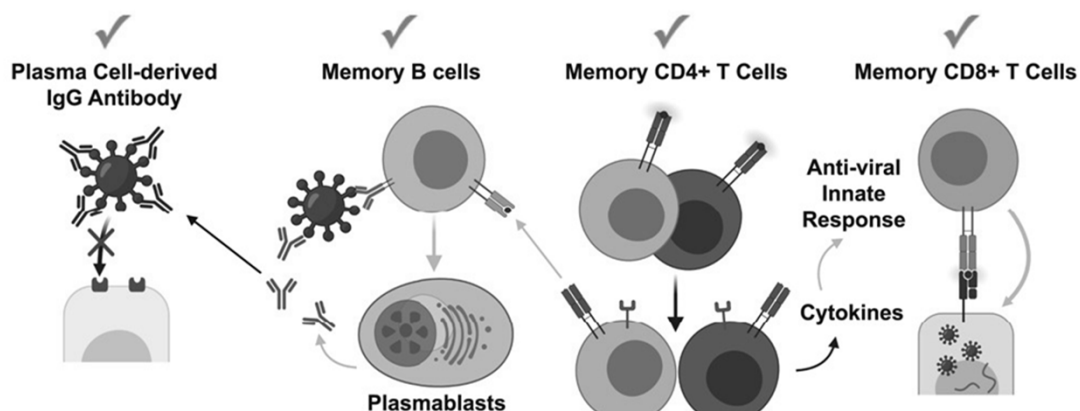
Vaccine Booster Doses: General Principles



Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

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Anamnestic Responses to a Pathogen Re-Exposure (Or another dose of vaccine!)



Rodda, L.B., et al. Cell 2021 184169-183.e17DOI: (10.1016/j.cell.2020.11.029).

Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Factors Driving Need for COVID-19 Vaccine Booster Doses

- Current circulating SARS-CoV-2 viral variant characteristics:
 - “**Relative resistance**” to antibody neutralizing activity
 - Higher/faster/more effective infectivity
- Persons with **suboptimal response** to primary vaccination series
- [Expected] **declines of circulating antibody levels** in persons with **adequate response** to primary vaccination series:
 - People with high exposure risk
 - People with somewhat lower initial response +/- high risk of severe disease
- Suboptimal overall population vaccination rates (**insufficient herd immunity**)

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Vaccine “Boosters” versus “Additional Doses”

- **Boosters:**
 - Response to the **primary series** of the vaccine is **sufficient**
 - Immunity wanes over time:
 - Declining antibody titers
 - Epidemiologic evidence of increased infections and/or severe disease
- **Additional Doses:**
 - Response to the originally-designed **primary series** of the vaccine is **insufficient**
 - Immunity inadequate:
 - Low/unmeasurable antibody titers
 - Epidemiologic evidence of no/limited protection from infections and/or severe disease

Source: Goswami, N. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/03-COVID-Goswami-508.pdf>

22

Factors that can Influence Circulating Antibody Response to an Initial Vaccine Series

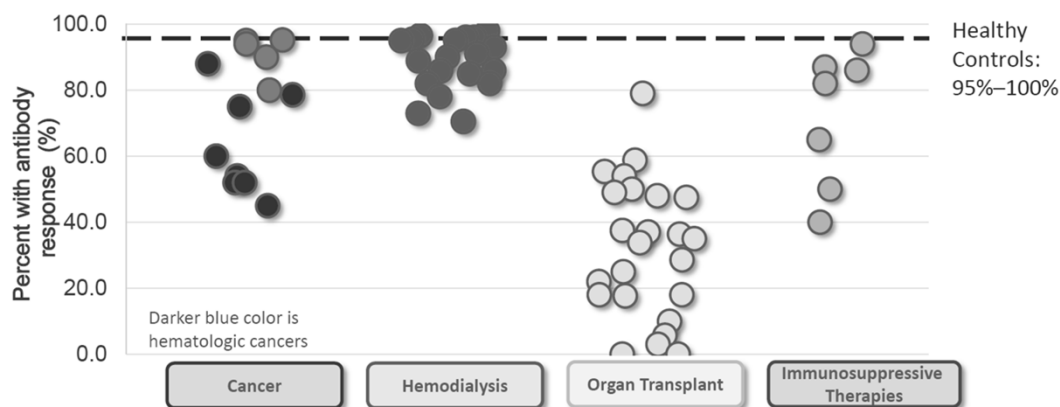
- Age (e.g., infants, elderly)
- Immunosuppression (e.g., B cell vs. T cell, inherited vs. acquired vs. drug-induced)
- Type of vaccine (e.g., live vs. inactive)
- Vaccine dosage, route, administration schedule
- Antibody response to **initial** vaccination(s)

Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

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Need for COVID-19 mRNA Vaccine “Additional Doses” for Immunocompromised People

Percent of subjects with antibody response after two mRNA COVID-19 vaccine doses by immunocompromising condition and study (n=63)

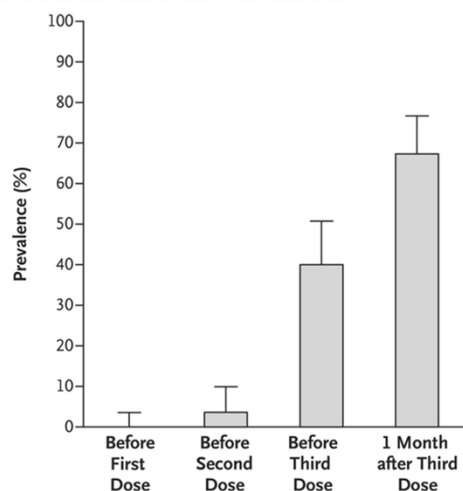


Source: Dooling, K. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/02-COVID-Dooling-508.pdf>

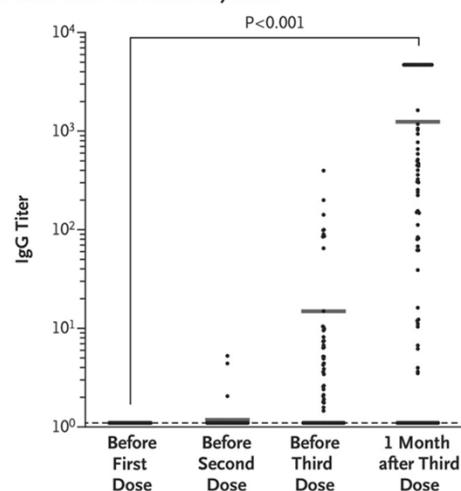
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Effects of a 3rd dose of BNT162b2 (“Pfizer vaccine”) in Solid Organ Transplant Recipients

A Prevalence of Anti-SARS-CoV-2 Antibodies



B Anti-SARS-CoV-2 Antibody Titers

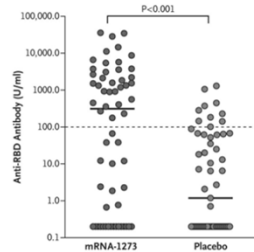


Kamar N., et al. NEJM 2021;385:661. <https://www.nejm.org/doi/full/10.1056/NEJMc2108861>

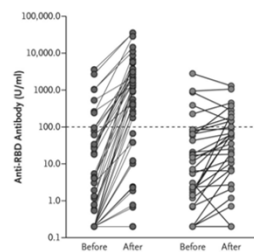
25

Effects of a 3rd dose of mRNA-1273 (“Moderna vaccine”) in Solid Organ Transplant Recipients

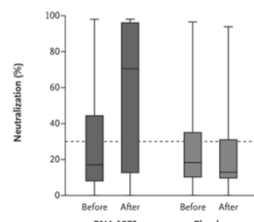
A Anti-RBD Antibodies after Third Dose



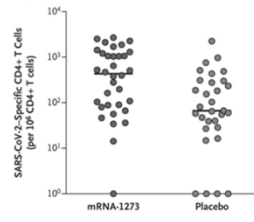
B Anti-RBD Antibodies before and after Third Dose



C Neutralization before and after Third Dose



D Polyfunctional CD4+ T Cells after Third Dose



Hall, V.G., et al. NEJM 2021;385:1244. <https://www.nejm.org/doi/full/10.1056/NEJMc2111462>

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Current Recommendations for “Additional Doses” of mRNA vaccines

- “...people with moderately to severely compromised immune systems [should] receive an additional dose of mRNA COVID-19 vaccine at least 28 days after a second dose...”

Currently, CDC is recommending that moderately to severely immunocompromised people receive an additional dose. This includes people who have

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking medicine to suppress the immune system
- Received a stem cell transplant within the last 2 years or are taking medicine to suppress the immune system
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress your immune response

People should talk to their healthcare provider about their medical condition, and whether getting an additional dose is appropriate for them.

Source: CDC. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html> (Accessed 11/1/21)

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Data on COVID-19 Vaccines: Circulating Antibody Declines & Need for “Booster Doses”



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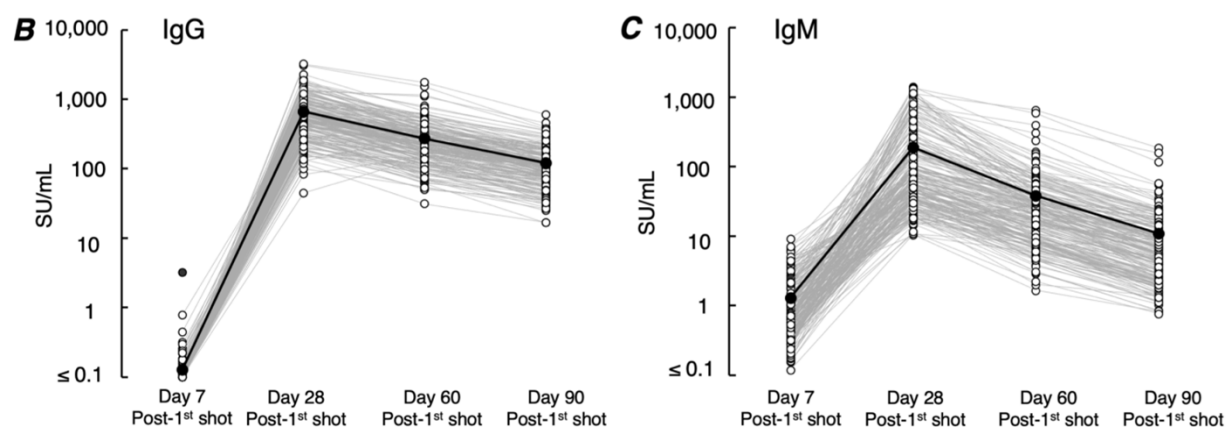
Immunoglobulin (Antibody) Half-lives

| Immunoglobulin | Approximate half-life (days) |
|----------------|------------------------------|
| IgM | 5-6 |
| IgA | 5-6 |
| IgG1 | 21 |
| IgG2 | 21 |
| IgG3 | 7 |
| IgG4 | 21 |

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Immunoglobulin Response to BNT162b2 Vaccination (Single Dose)

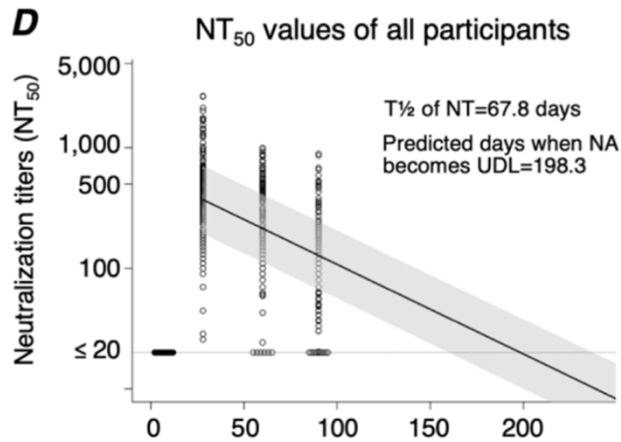


Maeda, K., et al. <https://www.medrxiv.org/content/10.1101/2021.07.27.21261237v1>

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Neutralizing Titer Decline After BNT162b2 Vaccination (Standard 2-Dose Series)



Maeda, K., et al. <https://www.medrxiv.org/content/10.1101/2021.07.27.21261237v1>

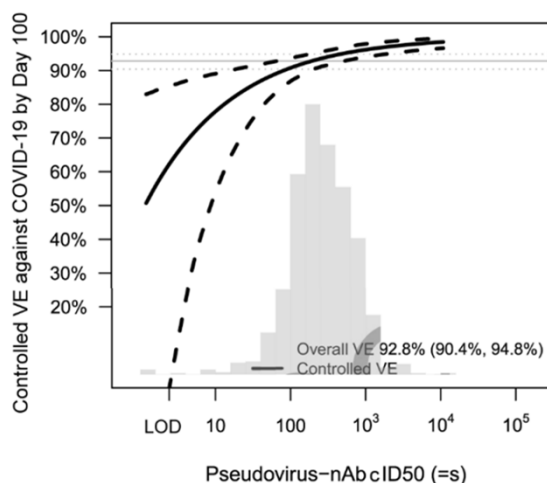
Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Data on COVID-19 Vaccines: Antibody Levels and Anamnestic Responses

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Contributions of Circulating Antibodies & Non-Antibody Immune Response to mRNA-1273 Vaccine Protection



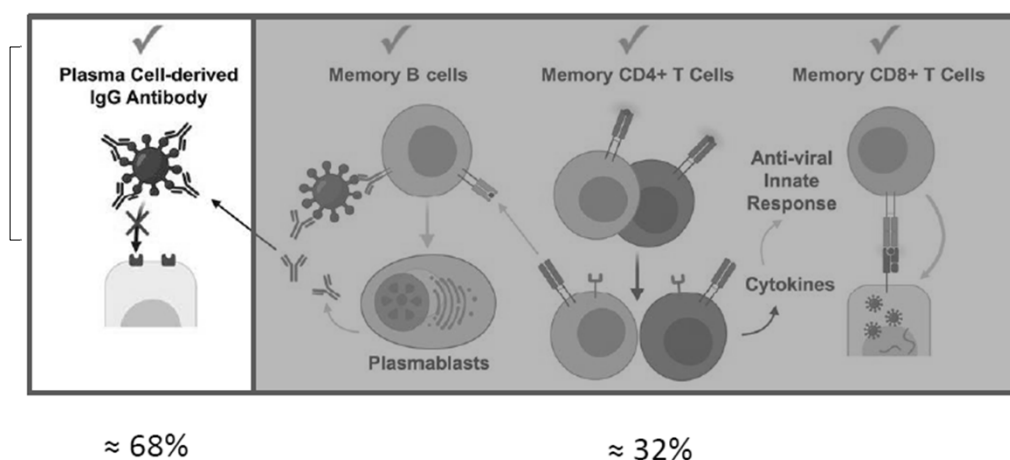
- Vaccine Efficacy (VE) was **45-60%** for vaccine recipients **without** detectable binding or neutralizing antibodies
- ~**68%** of VE against ***symptomatic infection*** mediated by ***antibody neutralization***

Gilbert, P.B., et al. <https://www.medrxiv.org/content/10.1101/2021.08.09.21261290v4>

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Contributions of Circulating Antibodies & Non-Antibody Immune Response to SARS-CoV-2 Re-Exposure Events



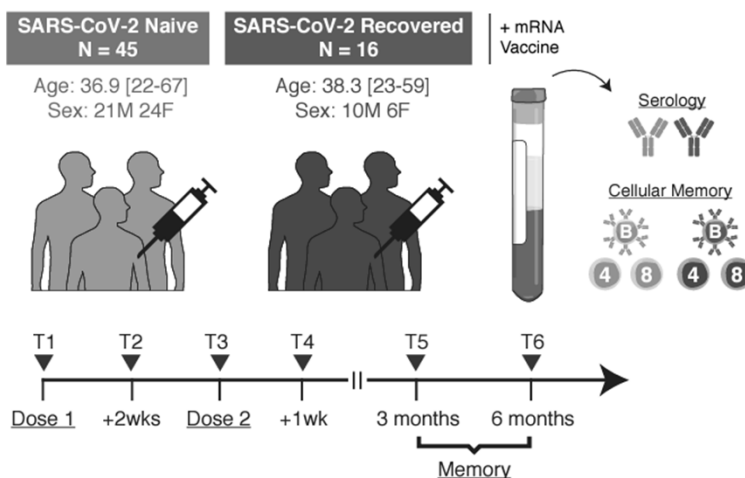
Rodda, L.B., et al. Cell 2021 184169-183.e17DOI: (10.1016/j.cell.2020.11.029).

Gilbert, P.B., et al. <https://www.medrxiv.org/content/10.1101/2021.08.09.21261290v4>

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Role of SARS-CoV-2 Spike Protein-Specific B Cells / Memory B Cells Post-Vaccination

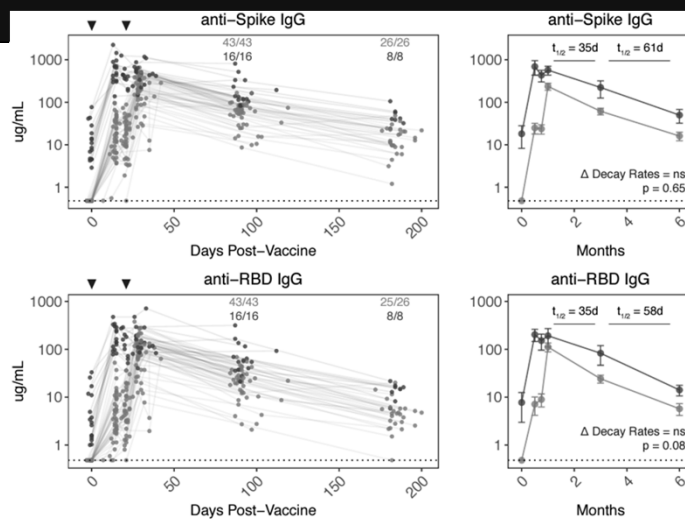


Goel, R.R., et al. <https://www.biorxiv.org/content/10.1101/2021.08.23.457229v1>

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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Antibody Response Post-Vaccination

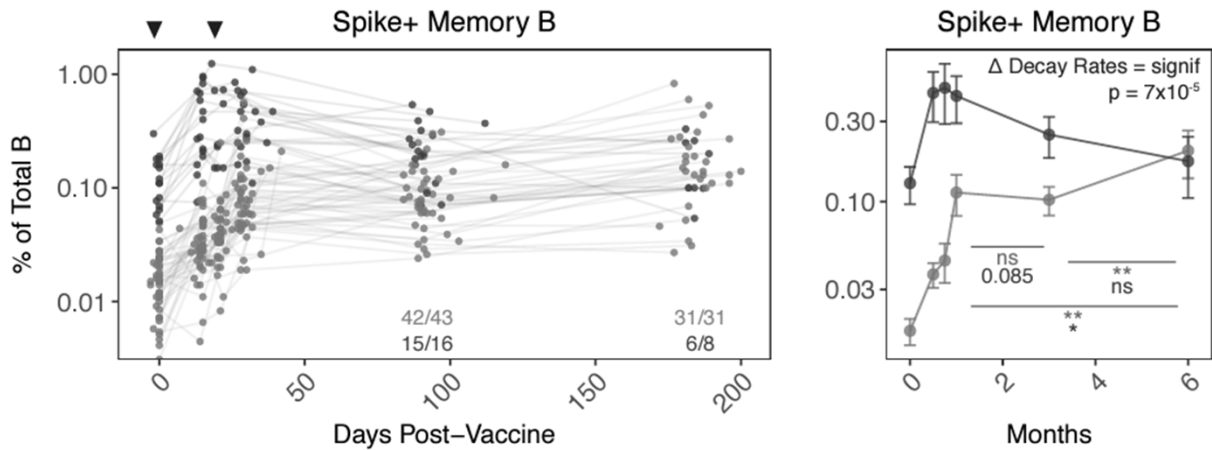


Goel, R.R., et al. <https://www.biorxiv.org/content/10.1101/2021.08.23.457229v1>

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

36

SARS-CoV-2 Spike(+) Memory B Cells Post-Vaccination

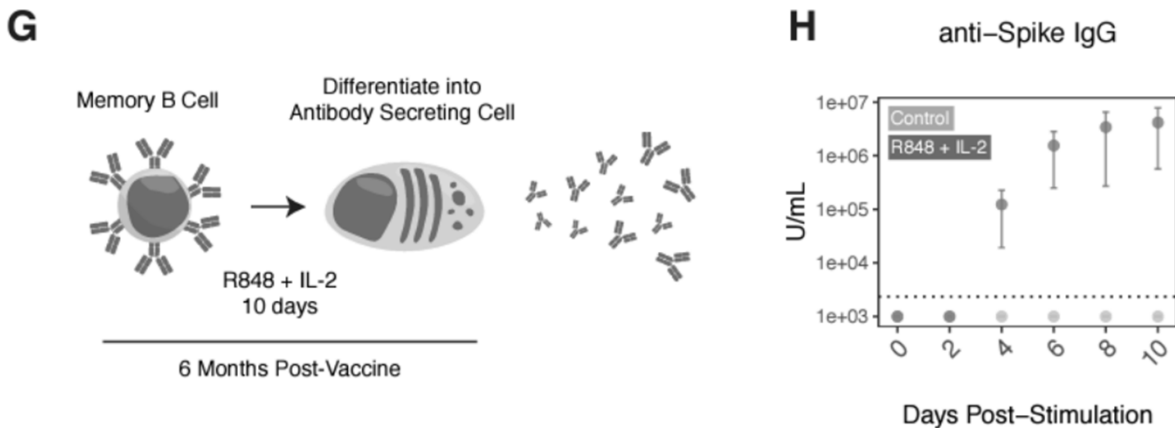


Goel, R.R., et al. <https://www.biorxiv.org/content/10.1101/2021.08.23.457229v1>

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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SARS-CoV-2 Spike(+) Memory B Cells Post-Vaccination

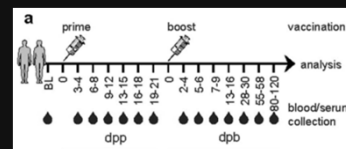


Goel, R.R., et al. <https://www.biorxiv.org/content/10.1101/2021.08.23.457229v1>

Source: Thornburg, N. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/03-COVID-Thornburg-508.pdf>

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CD8+ T Cell Responses Post-Vaccination (BNT162b2)

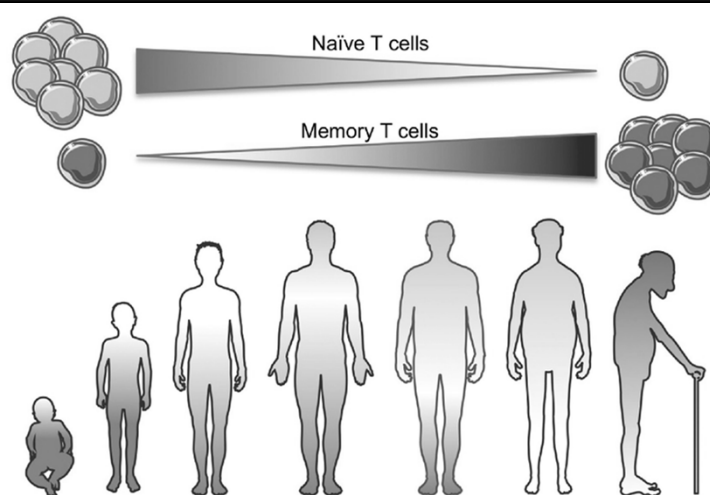


Impact of Patient Age on COVID-19 Vaccine Response to Primary Series



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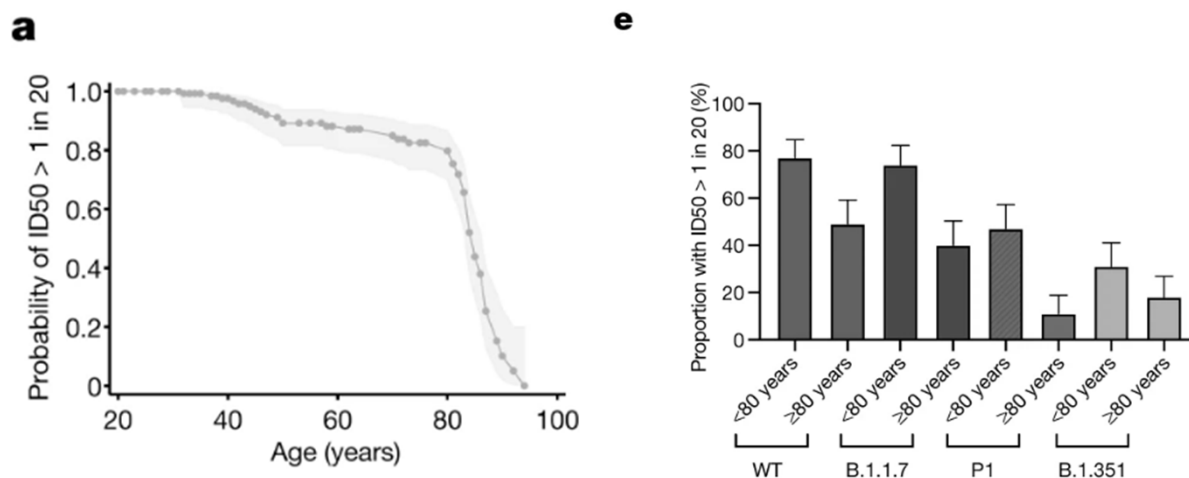
T Cell Changes with Age



Candia, P., et al. Trends Immuno. 2021;42(1):18. <https://doi.org/10.1016/j.it.2020.11.002>

42

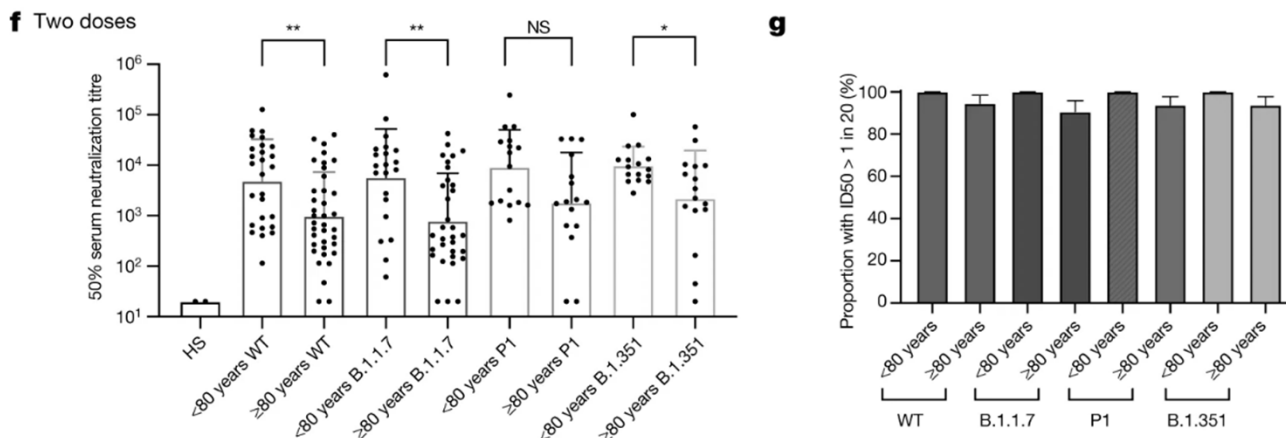
Response to BNT162b2 Stratified by Age: 1st Dose



Collier, D.A., et al. Nature 2021;596:417. <https://www.nature.com/articles/s41586-021-03739-1>

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Response to BNT162b2 Stratified by Age: 2nd Dose



Collier, D.A., et al. Nature 2021;596:417. <https://www.nature.com/articles/s41586-021-03739-1>

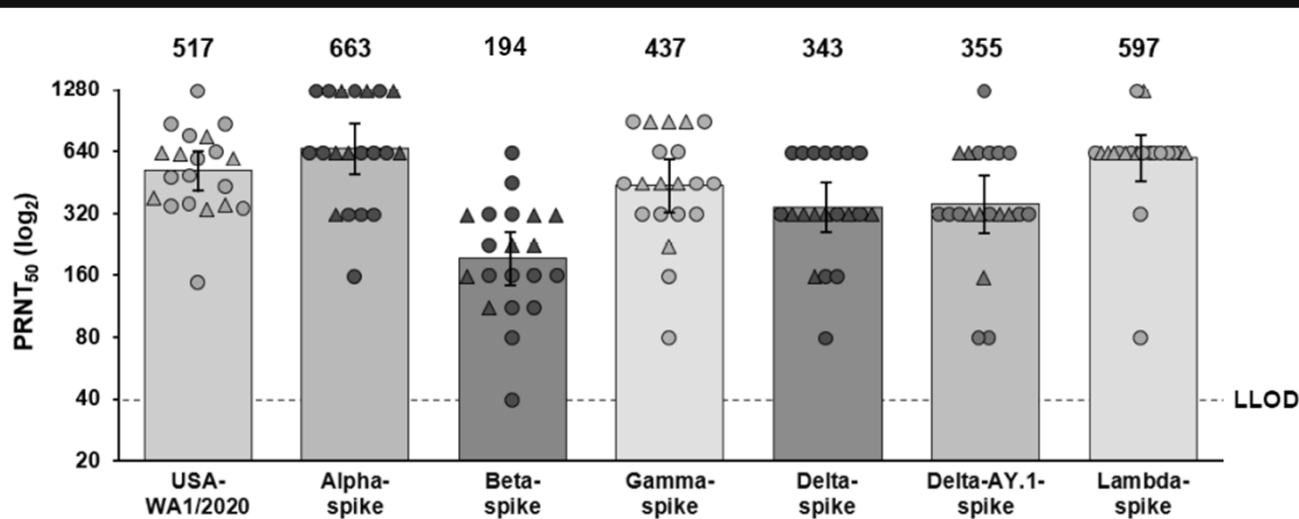
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Data on COVID-19 Vaccines: Impact of SARS-CoV-2 Variants on Antibody Neutralizing Activity & Need for “Booster Doses”



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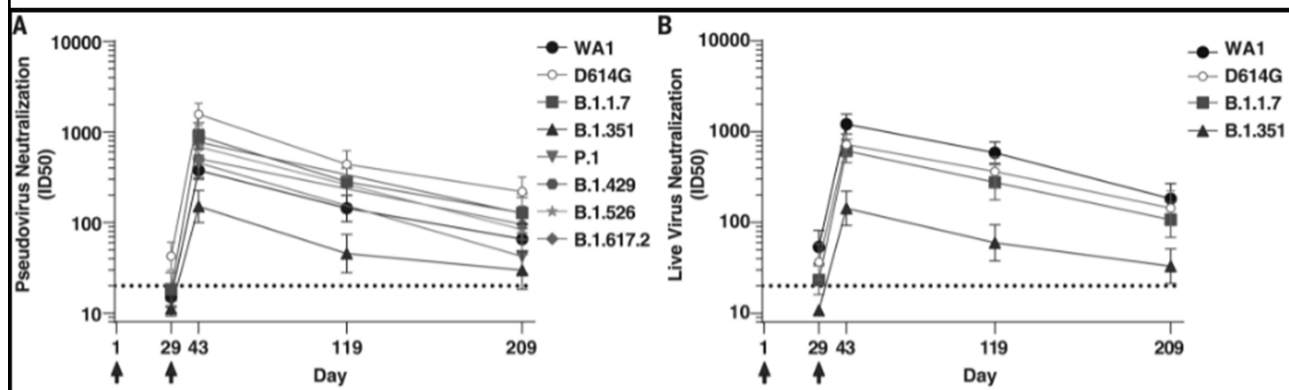
Neutralizing activity of sera from BNT162b2-vaccinated people vs. various SARS-CoV-2 Variants



Source: Gruber, W.C. FDA VRBPAC Meeting (9/22/21). <https://www.fda.gov/media/152240/download>

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Combined Effects of Antibody Decline & Variant Type on Neutralization Titers



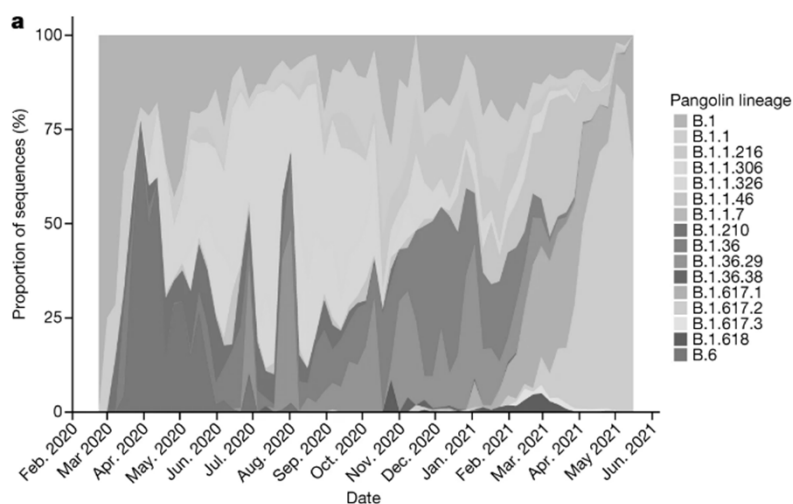
Pegu, A., et al. Science 2021;373(6561):1372. <https://www.science.org/doi/10.1126/science.abj4176>

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**Delta Variant:
What's the Big Deal???**

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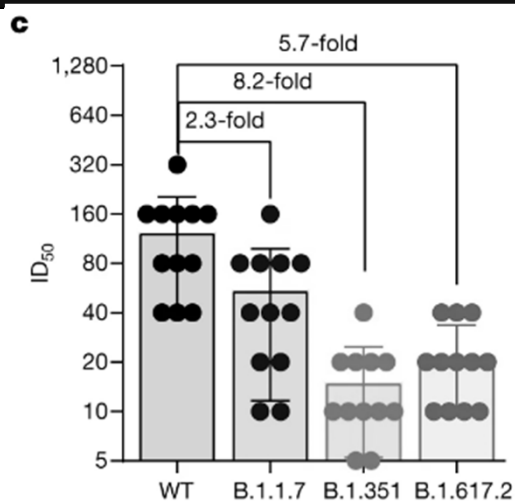
Emergence of Delta Variant as Dominant Variant in India



Mrcochova, P., et al. *Nature* **599**, 114–119 (2021). <https://doi.org/10.1038/s41586-021-03944-y>

49

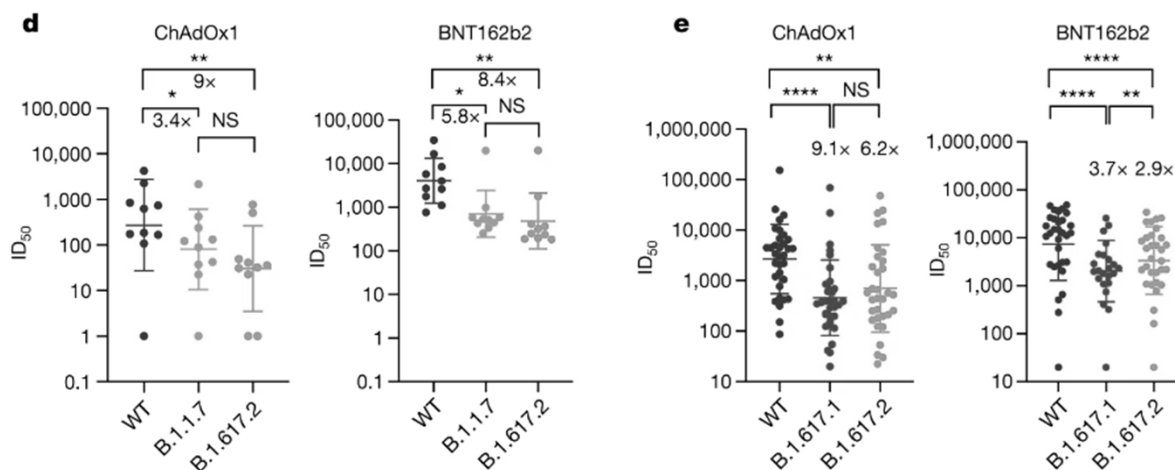
Neutralizing Capacity of Convalescent Serum vs. Delta Variant



Mrcochova, P., et al. *Nature* **599**, 114–119 (2021). <https://doi.org/10.1038/s41586-021-03944-y>

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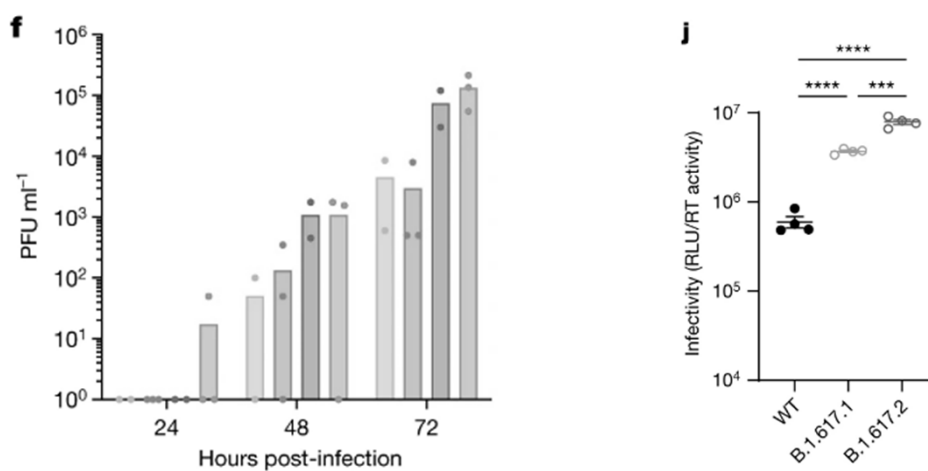
Neutralizing Capacity of ChAdOx1 (“Astra-Zeneca Vaccine”) & BNT162b2 vs. Delta Variant



Mrcochova, P., et al. *Nature* **599**, 114–119 (2021). <https://doi.org/10.1038/s41586-021-03944-y>

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Delta Variant: Ability to Infect & Replicate in Human Cells



Mrcochova, P., et al. *Nature* **599**, 114–119 (2021). <https://doi.org/10.1038/s41586-021-03944-y>

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Delta Variant: Viral Loads for Breakthrough Infections (Israel)

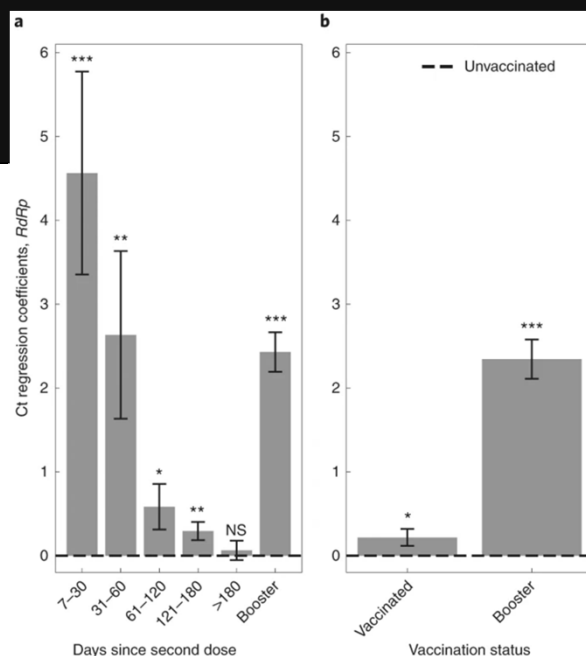
- Evaluated **Delta variant-caused breakthrough infections** (BTIs) in adults ≥ 20 y.o. in Israel (6/28/21 – 9/9/21):
 - 3,100 infections in unvaccinated people
 - 12,934 BTIs of two-dose-vaccinated (BNT162b2)
 - 519 BTIs of booster-vaccinated individuals
- Used **PCR cycle threshold value ("Ct" value)** to estimate viral load
 - Higher cycle threshold = lower viral load
 - 1 Ct unit difference is approximately **2x** difference in viral load

Levine-Tiefenbrun, M., et al. *Nat Med* (2021). <https://doi.org/10.1038/s41591-021-01575-4>

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Delta Variant: Viral Loads for Breakthrough Infections

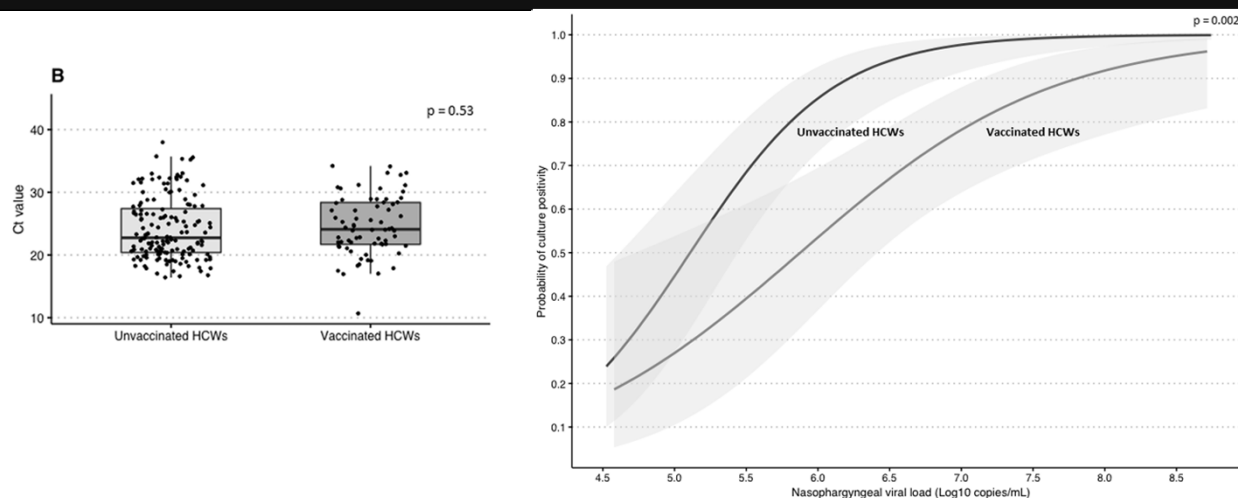
- Similar results stratifying by:
 - Age < or > 50 y.o.
 - Hospitalized vs. non-hospitalized
 - Starting 14d post-vaccination



Levine-Tiefenbrun, M., et al. *Nat Med* (2021). <https://doi.org/10.1038/s41591-021-01575-4>

54

All Ct Values are NOT created equal: Infectivity of Vaccinated vs. Unvaccinated Persons with “Breakthrough” COVID-19 Infections



Shamier, M.C., et al. <https://www.medrxiv.org/content/10.1101/2021.08.20.21262158v1>

55

Quick Knowledge & Learning Check!

- Which of the following statements about the **SARS-CoV-2 Delta Variant** and/or **COVID Vaccines** is **FALSE**?
 - a) Vaccine-induced serum neutralizing activity is decreased vs. the Delta variant (compared to original SARS-CoV-2 virus)
 - b) The Delta variant appears to cause more rapid infections with higher replication (compared to original SARS-CoV-2 virus)
 - c) Breakthrough infections in vaccinated persons have higher viral loads versus unvaccinated persons
 - d) Vaccinated people with breakthrough infections appear to be less infective than unvaccinated people

56

Let's Put it All Together:

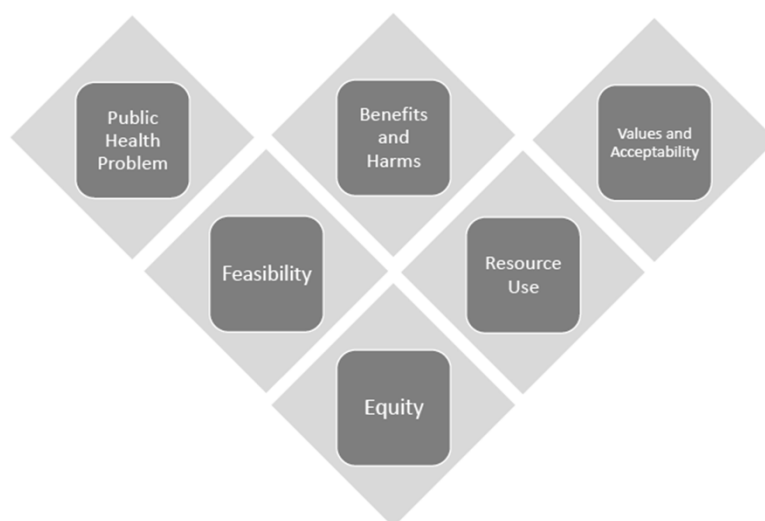
Pandemic / Public Health Implications of COVID-19 Vaccine Booster Doses



57

COVID-19 Vaccine Booster Doses: ACIP Working Group

Evidence to Recommendations (EtR) Framework



Source: Oliver, S. ACIP 11/19/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/06-COVID-Oliver-508.pdf>

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COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address

Do we need them?

Do they work?

Public
Health
Problem

Benefits
and
Harms

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

59

COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address

Public
Health
Problem

Benefits
and
Harms

Is vaccine effectiveness (VE)
waning over time?

Is VE **reduced** for the **Delta**
variant?

Does the data vary by
sub-population?

Are booster doses of COVID-19 vaccines
safe and **immunogenic**?

Will booster doses of COVID-19 vaccines
reduce COVID-19 **incidence, hospitalization**
and/or **mortality**?

Do booster doses **improve VE** against the
Delta variant?

12

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

60

COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address



Public
Health
Problem

Is vaccine effectiveness (VE) waning over time?

Is VE at **6-8 months** similar to what was noted at **2 months** after vaccination?

How does this data vary by **severity** of disease?

What data on **waning VE** would identify a need for **booster dose** of COVID-19 vaccines?

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

61

COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address



Public
Health
Problem

Is VE **reduced** for the **Delta variant**?

How does this vary by **severity** of disease?

How would this information impact VE for **future variants**?

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

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Need for COVID-19 Vaccine Booster Doses: Impacts of the Delta Variant

Recent U.S. Publications

Public
Health
Problem

| Author | Publication (Date) | Population | Outcomes | Time Assessed |
|------------------|--------------------|---|---|----------------------|
| Tenforde et al. | MMWR (8/18/21) | Multi-state network of hospitalized adults | Hospitalization | March – July 2021 |
| Rosenberg et al. | MMWR (8/18/21) | Adult residents of NY | Documented infection Hospitalization | May – July 2021 |
| Nanduri et al. | MMWR (8/18/21) | Nursing home residents | Documented infection | March – July 2021 |
| Fowlkes et al. | MMWR (8/25/21) | Healthcare workers and first responders in six states | Documented infection | Dec 2020 – July 2021 |
| Puranik et al. | Preprint (8/9/21) | Adults within the Mayo Clinic health system | Documented infection Hospitalization | February – July 2021 |

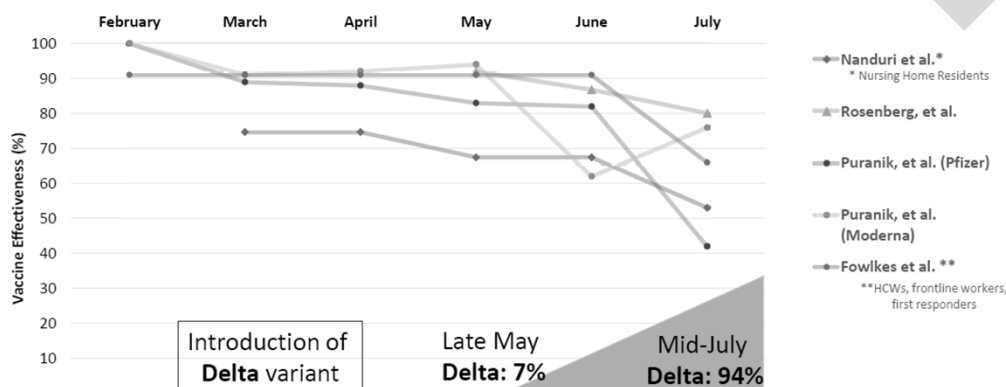
Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

63

Need for COVID-19 Vaccine Booster Doses: Trends in Vaccine Effectiveness vs. Infection

Booster doses of COVID-19 vaccines: Vaccine effectiveness against infection

Public
Health
Problem

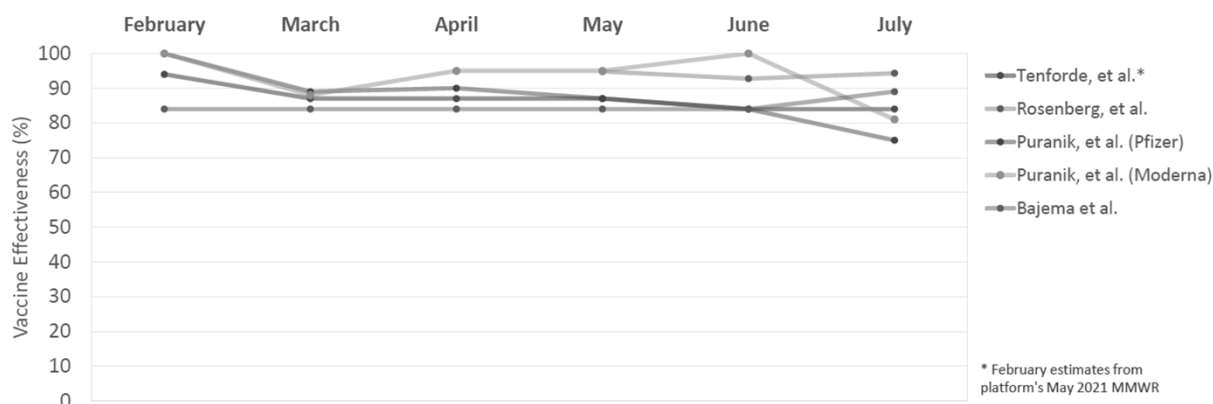


Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

64

Need for COVID-19 Vaccine Booster Doses: Trends in Vaccine Effectiveness vs. Hospitalization

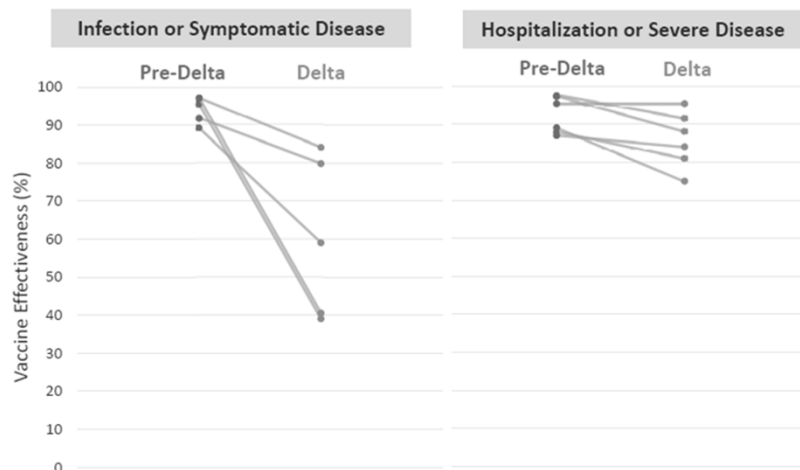
Vaccine effectiveness against hospitalization by month
Adults ≥18 years of age



Source: Dooling, K. ACIP 10/21/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/11-COVID-Dooling-508.pdf>

65

Need for COVID-19 Vaccine Booster Doses: Trends in Vaccine Effectiveness Pre-Delta vs. Delta



In studies comparing the 'Pre-Delta' and 'Delta' periods:

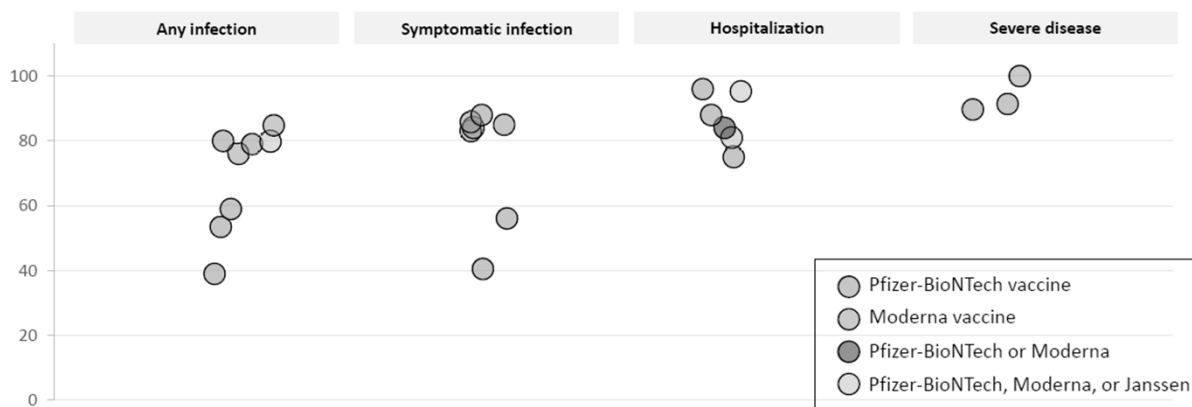
- Pre-Delta vaccine effectiveness estimates high (**87% or higher**)
- Since the introduction of the Delta variant (varies by region)
 - VE against **infection** ranges from 39–84%
 - VE against **hospitalization** ranges from 75–95%

Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

66

Need for COVID-19 Vaccine Booster Doses: Trends in Vaccine Effectiveness Post-Delta

Summary of vaccine effectiveness estimates since introduction of the Delta variant



Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

67

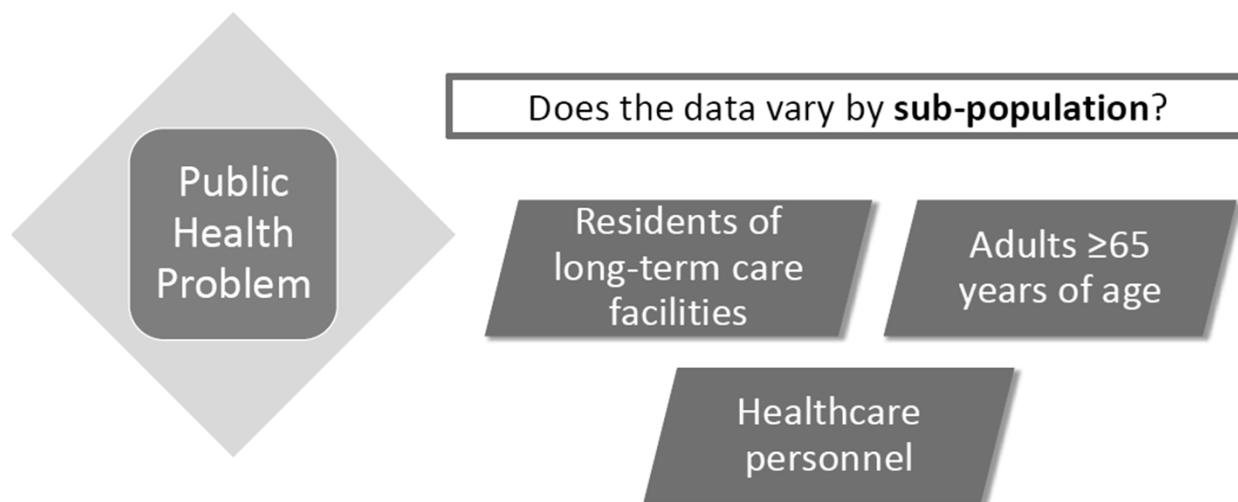
Quick Knowledge & Learning Check!

- **TRUE or FALSE:** People who have **no detectable serum antibody response** to the COVID-19 vaccines still appear to have **~50% protection from COVID-19 infection** as compared to unvaccinated people.

- a) True
- b) False

68

COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address



Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

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Need for COVID-19 Vaccine Booster Doses: Vaccine Efficacy in Important Sub-Populations

LTCF residents, adults ≥65 years of age

- Vaccinated in early phase of COVID-19 vaccine roll-out
- Needed special considerations for other vaccines (boosters, higher-dose vaccines)

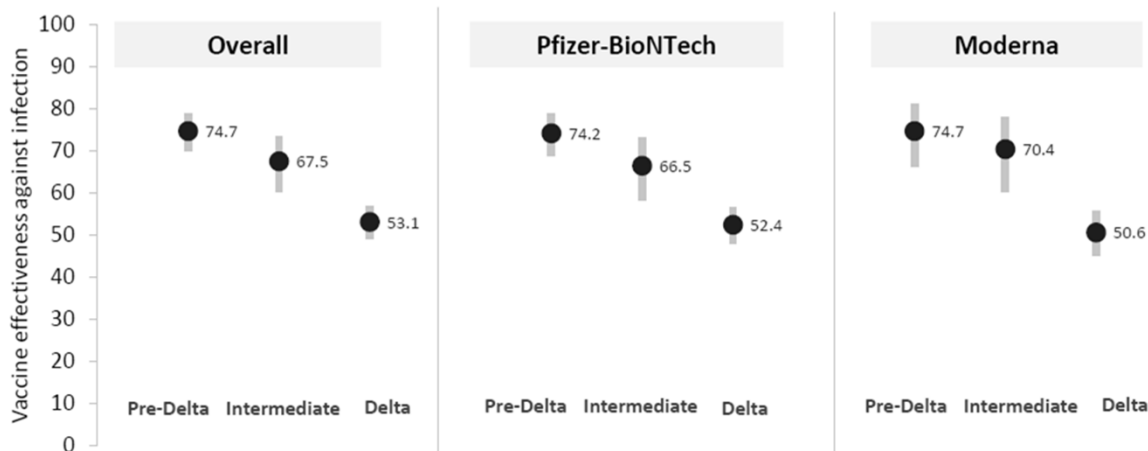
Healthcare personnel

- Vaccinated in early phase of COVID-19 vaccine roll-out
- Continued exposure to SARS-CoV-2
- Additional considerations include continuity of healthcare systems
 - May have need to prevent asymptomatic or mild infections in healthcare personnel

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

70

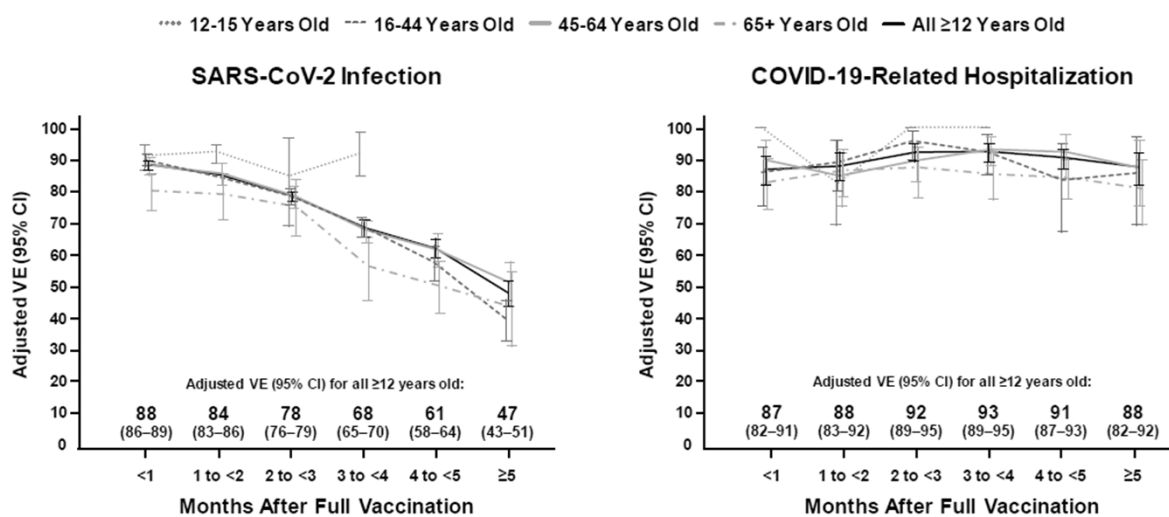
Need for COVID-19 Vaccine Booster Doses: Vaccine Efficacy in Long-Term Care Facility Residents



Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

71

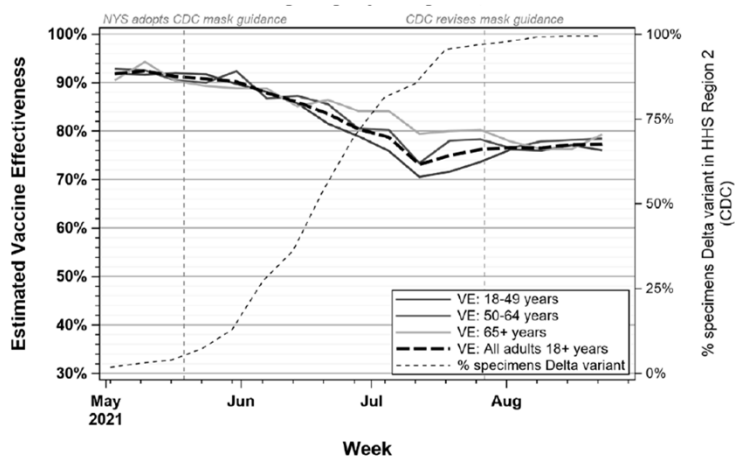
Data on BNT162b2 Vaccine Effectiveness by Age (Kaiser Permanente Southern California)



Source: Gruber, W.C. FDA VRBPAC Meeting (9/22/21). <https://www.fda.gov/media/152240/download>

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Data on COVID-19 Vaccine Effectiveness in NY State: Laboratory-Confirmed Infections

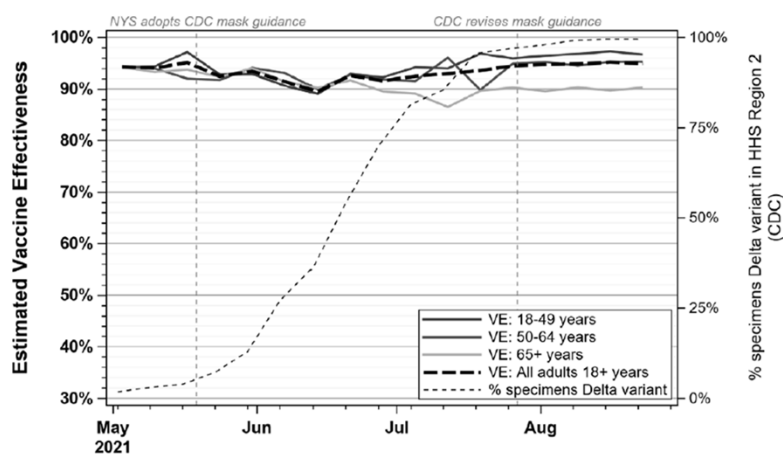


Age-adjusted VE against new COVID-19 infections declined from 92% (May 3–9) to 73% (July 12–18), when Delta reached 85%. Then, decline ceased, with plateau around 77%.

Rosenberg, E.S., et al. MMWR 2021;70(37):1306. https://www.cdc.gov/mmwr/volumes/70/wr/mm7037a7.htm?s_cid=mm7037a7_w
Source: Link-Gelles, R. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/04-COVID-Link-Gelles-508.pdf>

73

Data on COVID-19 Vaccine Effectiveness in NY State: Hospitalizations/Severe Disease



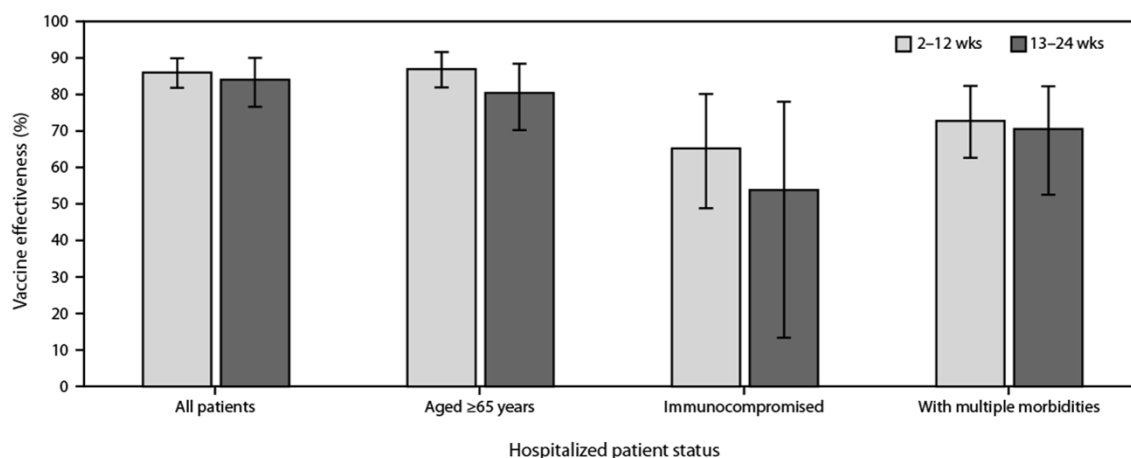
Age-adjusted VE against new COVID-19 hospitalizations remained stable at 90%–95%.

Rosenberg, E.S., et al. MMWR 2021;70(37):1306. https://www.cdc.gov/mmwr/volumes/70/wr/mm7037a7.htm?s_cid=mm7037a7_w
Source: Link-Gelles, R. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/04-COVID-Link-Gelles-508.pdf>

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Need for COVID-19 Vaccine Booster Doses: Hospitalization by Interval Since Vaccination

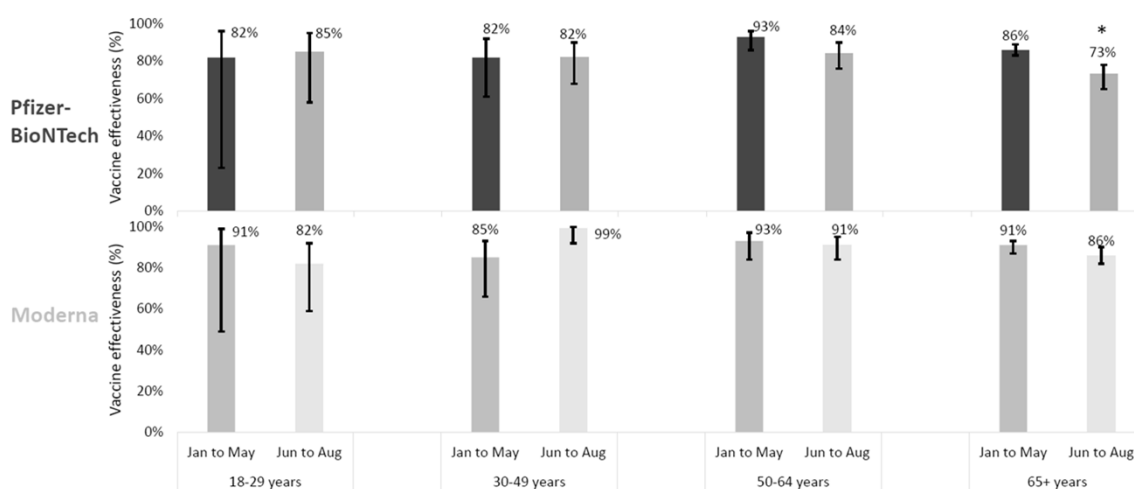
FIGURE 2. Sustained vaccine effectiveness* against COVID-19 among hospitalized adults, by patient status^{1,§} and interval since vaccination — 21 medical centers in 18 states,[¶] March–July 2021



Tenforde, et al. MMWR. <https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm>

75

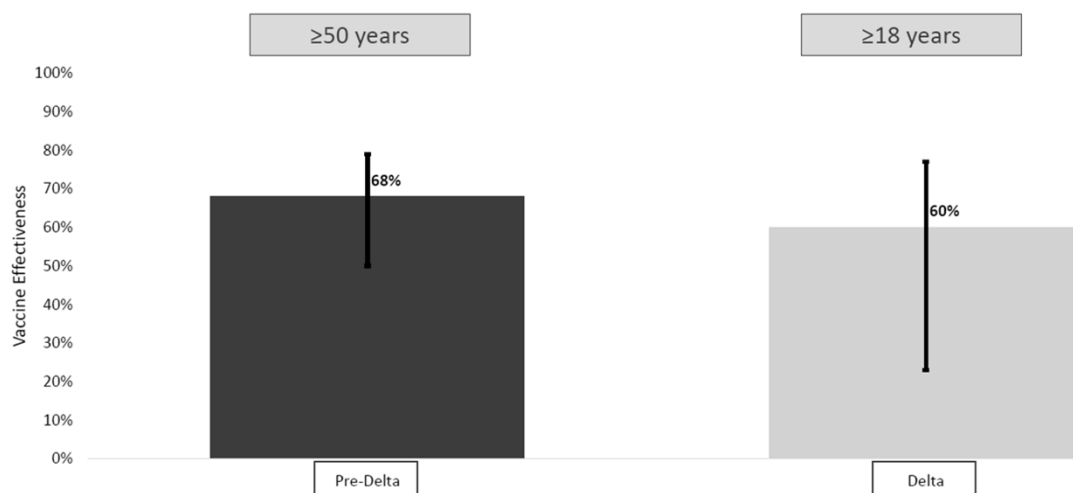
COVID-19 Efficacy for mRNA Vaccines: Hospitalizations



Source: Link-Gelles, R. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/04-COVID-Link-Gelles-508.pdf>

76

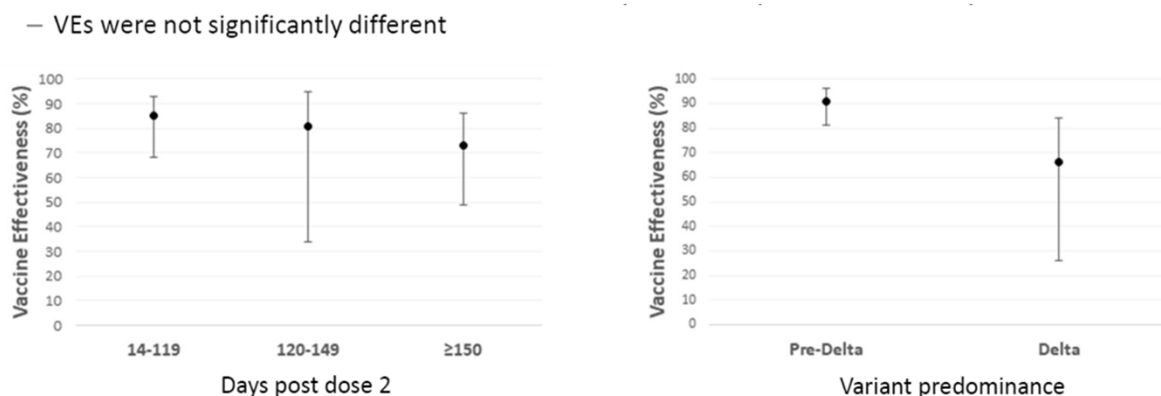
COVID-19 Efficacy for J&J/Janssen Vaccine: Hospitalizations



Source: Link-Gelles, R. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/04-COVID-Link-Gelles-508.pdf>

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Need for COVID-19 Vaccine Booster Doses: Vaccine Efficacy in Frontline Workers



Data from HEROES-RECOVER Cohort

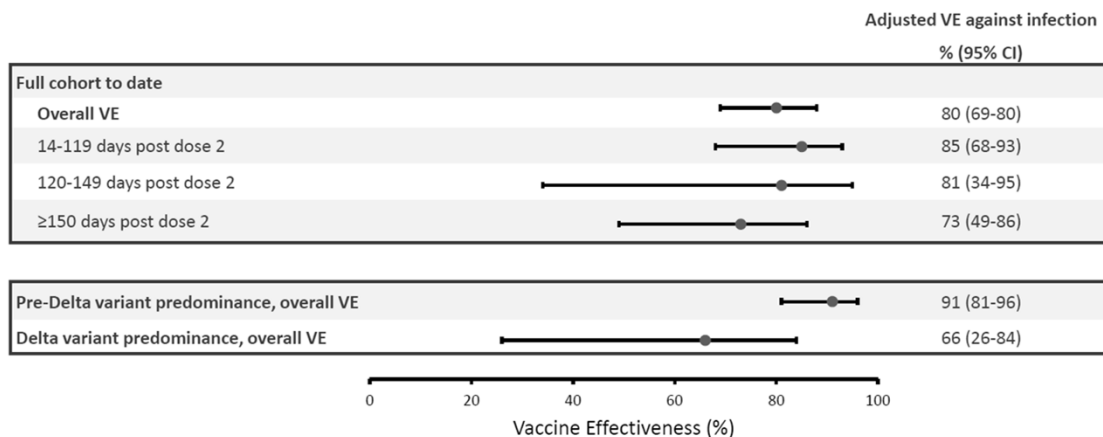
Fowlkes A., et al. https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e4.htm?s_cid=mm7034e4_w

Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

78

COVID-19 Vaccine Booster Doses: Vaccine Efficacy in Frontline Workers (HEROES-RECOVER)

- VE for prevention of asymptomatic & symptomatic infections



Fowlkes, A., et al. MMWR 2021;70(34):1167. <https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e4.htm>

Source: Link-Gelles, R. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/04-COVID-Link-Gelles-508.pdf>

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Quick Knowledge & Learning Check!

- **TRUE or FALSE:** For persons who have only received their primary series of COVID-19 mRNA vaccine, protection from severe COVID-19 disease (i.e., hospitalization due to COVID-19 infection) currently appears to be lower for Pfizer vs. Moderna vaccine recipients.
 - a) True
 - b) False

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COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address

Are booster doses of COVID-19 vaccines **safe** and **immunogenic**?

Do COVID-19 vaccines provide a **boost** in neutralizing antibody response?

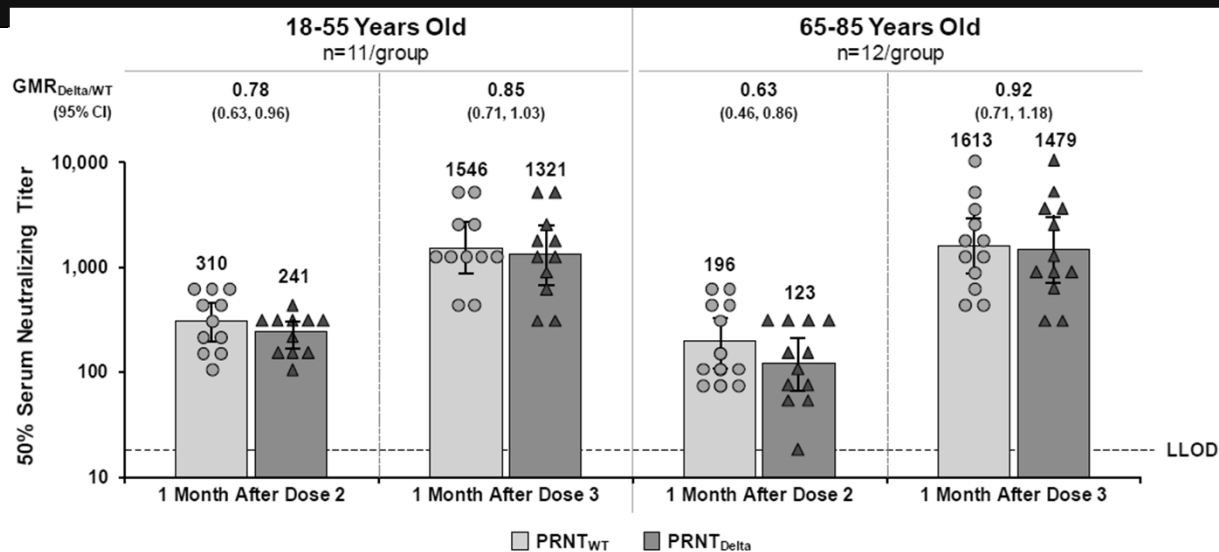
How do neutralizing antibodies correlate to **clinical protection** from COVID-19?

Benefits
and
Harms

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

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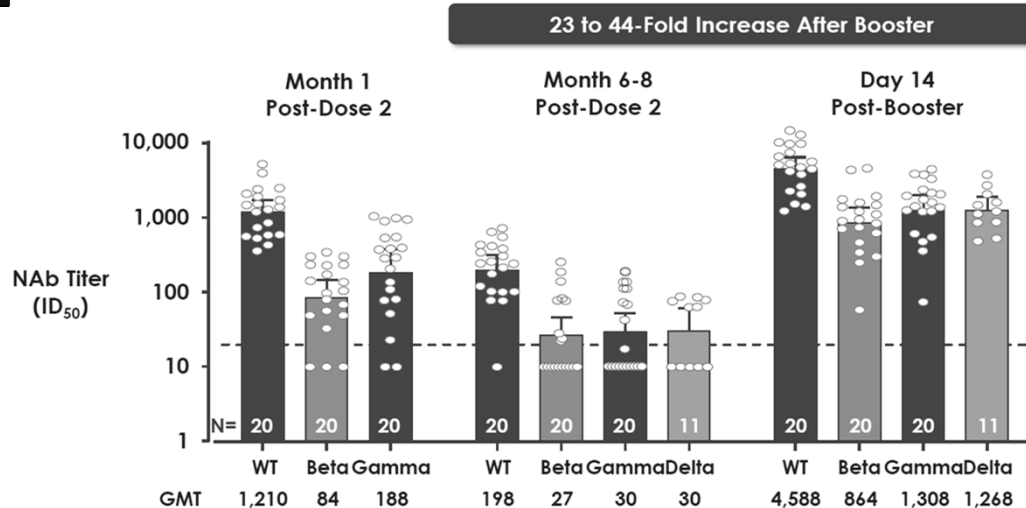
Neutralizing activity of sera from BNT162b2-vaccinated people: Effects of Booster Dose



Source: Gruber, W.C. FDA VRBPAC Meeting (9/17/21). <https://www.fda.gov/media/152240/download>

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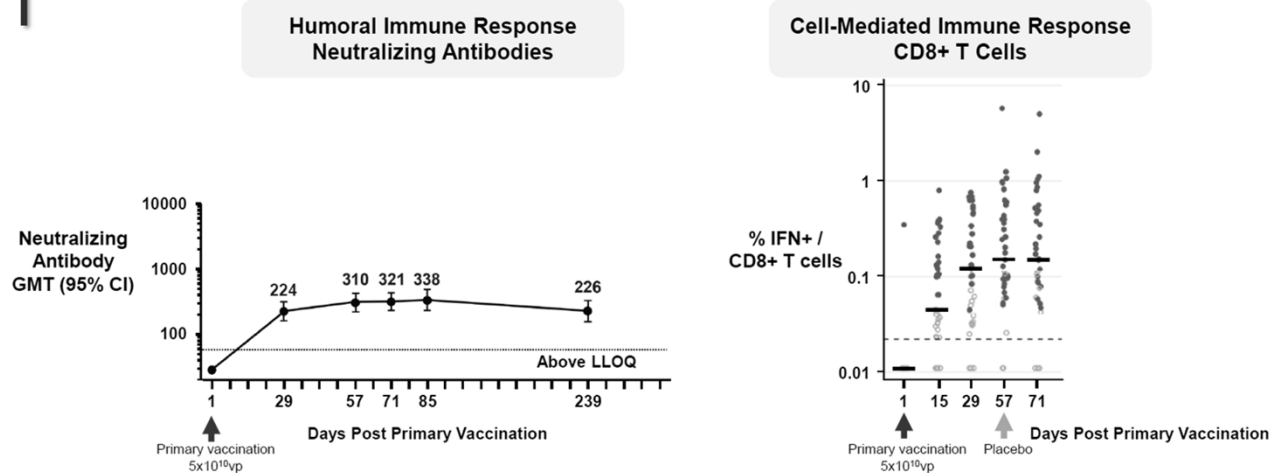
Neutralizing activity of sera from mRNA-1273-vaccinated people: Effects of Booster Dose



Source: Miller, J. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/02-COVID-Miller-508.pdf>

83

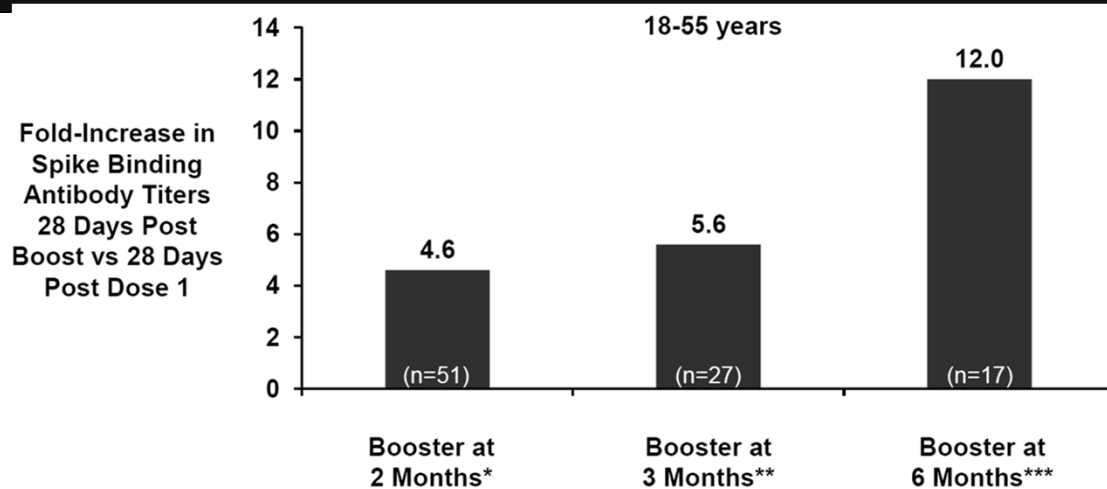
Neutralizing Antibody Titers from Ad26.COV2-single-vaccinated people



Source: Heaton, P. & Douoguih, M. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/03-COVID-Heaton-Douoguih-508.pdf>

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Spike Binding Antibody Titers from Ad26.COV2-vaccinated people: Effects of Timing of Booster Dose



Source: Heaton, P. & Douoguih, M. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/03-COVID-Heaton-Douoguih-508.pdf>

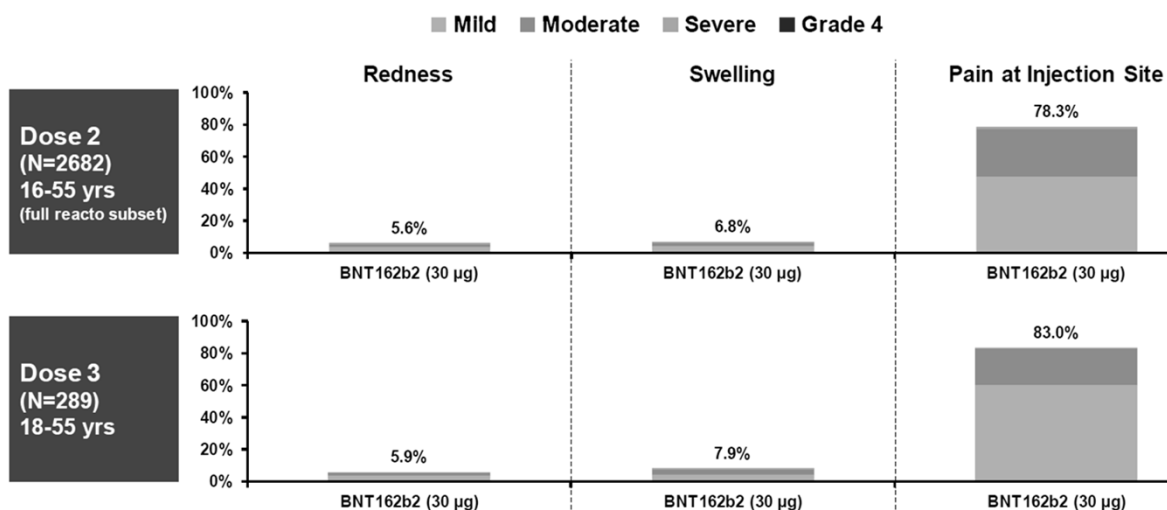
85

Quick Knowledge & Learning Check!

- **TRUE or FALSE:** The emergence of the Delta variant has resulted in **significant declines** in vaccine-associated protection from **severe COVID-19 disease** (hospitalization due to COVID-19 infection).
- a) True
- b) False

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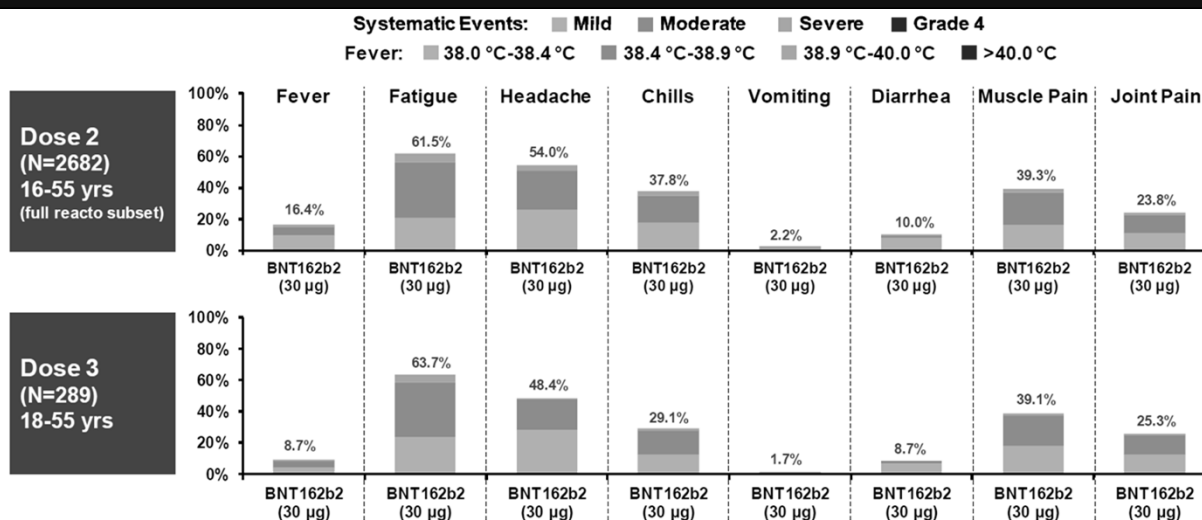
COVID-19 Vaccine Booster Doses: Safety Considerations – Local Reactions – BNT162b2



Source: Gruber, W.C. FDA VRBPAC Meeting (9/17/21). <https://www.fda.gov/media/152240/download>

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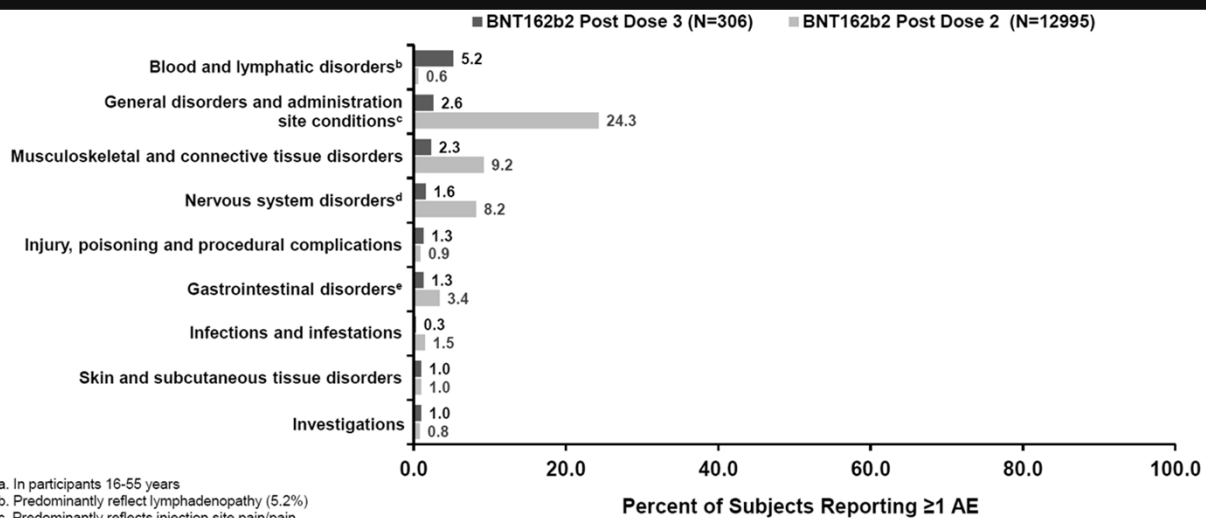
COVID-19 Vaccine Booster Doses: Safety Considerations – Systemic Events – BNT162b2



Source: Gruber, W.C. FDA VRBPAC Meeting (9/17/21). <https://www.fda.gov/media/152240/download>

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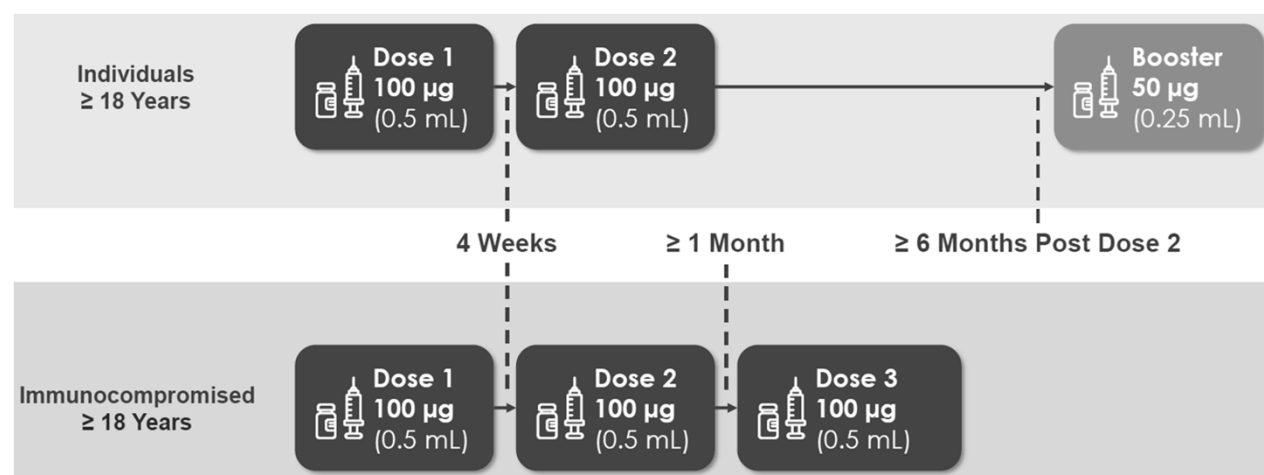
COVID-19 Vaccine Booster Doses: Safety Considerations – Adverse Effects 1 month post-dose – BNT162b2



Source: Gruber, W.C. FDA VRBPAC Meeting (9/17/21). <https://www.fda.gov/media/152240/download>

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COVID-19 Vaccine Booster Doses: Safety Considerations – mRNA-1273



Source: Miller, J. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/02-COVID-Miller-508.pdf>

90

COVID-19 Vaccine Booster Doses: Safety Considerations mRNA-1273

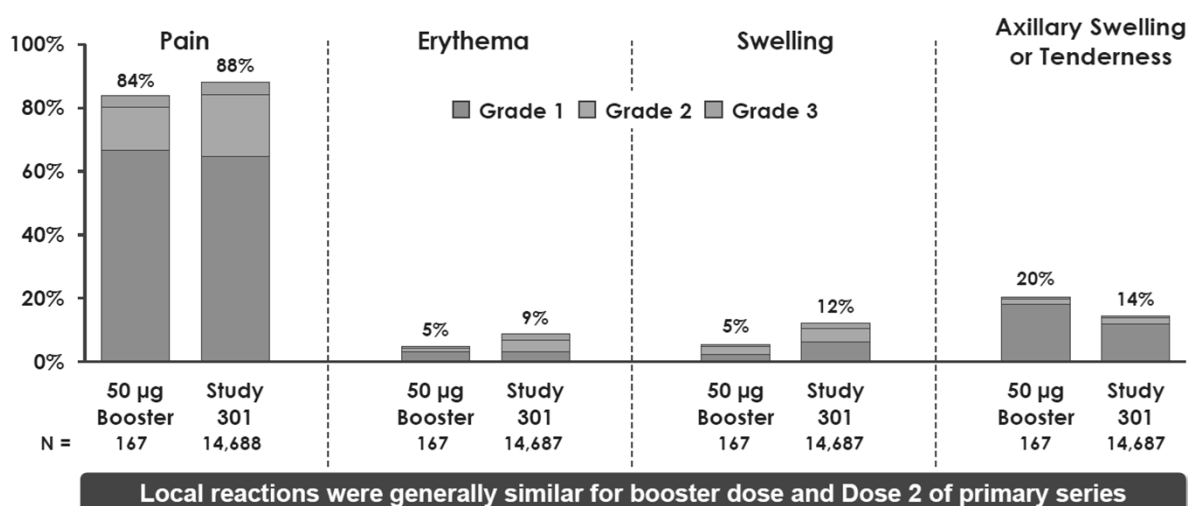
- **Lower Booster Dose Rationale:**

- Use lowest dose for optimal effect
- Lower dose needed for reactivation of immune memory (anamnestic response)
- Lower dose = more vaccine dose supplies

Source: Miller, J. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/02-COVID-Miller-508.pdf>

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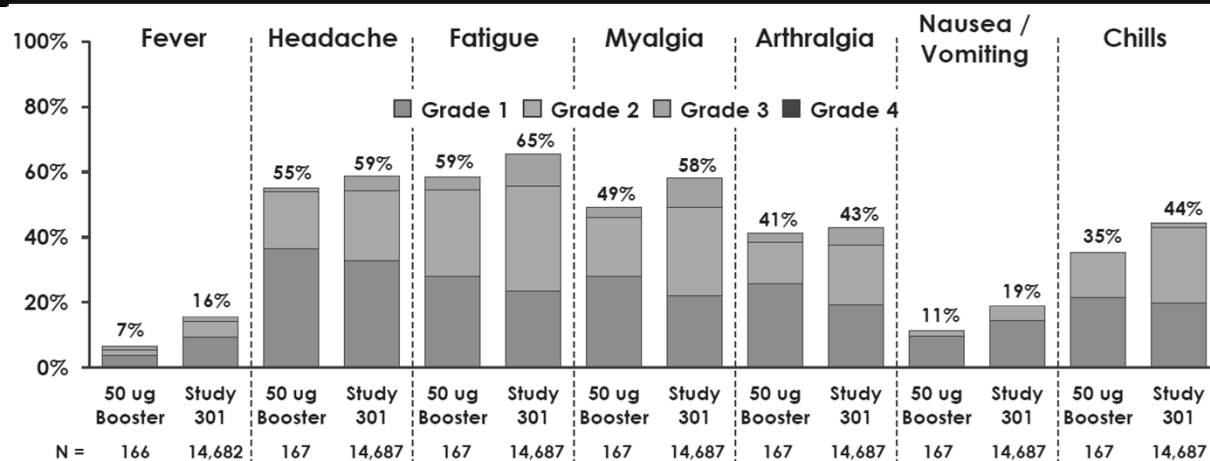
COVID-19 Vaccine Booster Doses: Safety Considerations – Local Reactions – mRNA-1273



Source: Miller, J. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/02-COVID-Miller-508.pdf>

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COVID-19 Vaccine Booster Doses: Safety Considerations – Systemic Reactions – mRNA-1273

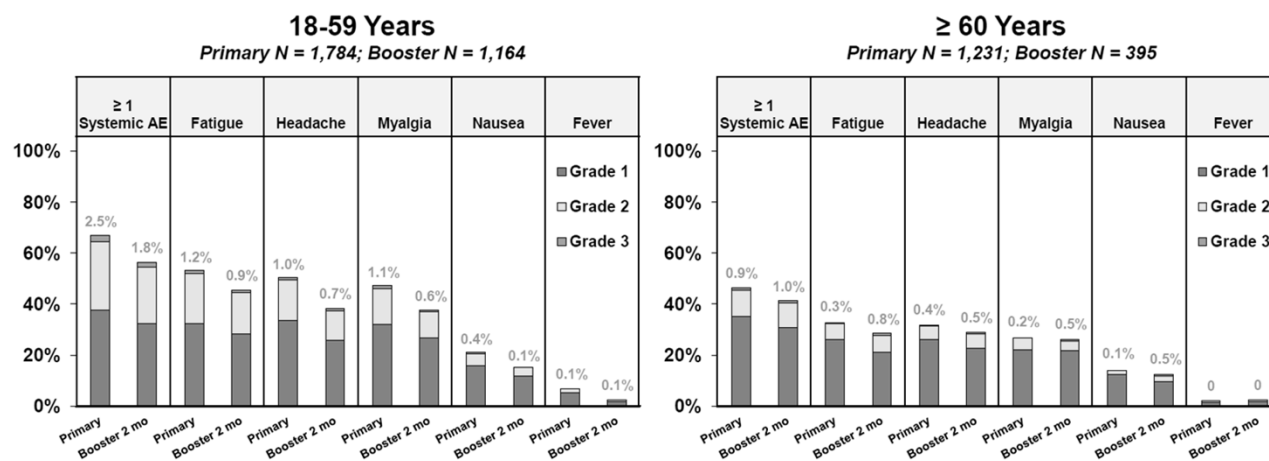


Systemic reactions were generally similar after booster dose compared to Dose 2 of primary series

Source: Miller, J. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/02-COVID-Miller-508.pdf>

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COVID-19 Vaccine Booster Doses: Safety Considerations – Systemic Reactions – Ad26.COV2.S – 2 month Booster



Source: Heaton, P. & Douoguih, M. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/03-COVID-Heaton-Douoguih-508.pdf>

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COVID-19 Vaccine Booster Doses: Safety Considerations – AEs of Interest – Ad26.COV2.S – All Booster

| Adverse Event of Interest | Within 28 Days of Primary Dose | | Within 28 Days of Booster Dose | |
|-------------------------------------|--------------------------------|-----------------------|--------------------------------|----------------------|
| | Ad26.COV2.S (N=15,705) | Placebo (N=15,588) | Ad26.COV2.S (N=8,646) | Placebo (N=8,043) |
| Embolic and thrombotic events (SMQ) | 2 (< 0.1%) | 6 (0.1%) | 3 (< 0.1%) | 3 (< 0.1%) |
| Convulsions / seizures | 0 | 0 | 0 | 0 |
| Tinnitus | 4 (< 0.1%) | 2 (< 0.1%) | 2 (< 0.1%) | 2 (< 0.1%) |
| Guillain-Barre Syndrome | 0 | 0 | 0 | 0 |
| Facial paralysis | 1 (< 0.1%) | 2 (< 0.1%) | 1 (< 0.1%) | 0 |
| Arthritis | 24 (0.2%) | 12 (0.1%) | 4 (< 0.1%) | 5 (0.1%) |

Source: Heaton, P. & Douoguih, M. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/03-COVID-Heaton-Douoguih-508.pdf>

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COVID-19 Vaccine Booster Doses: Safety Considerations – Myocarditis

Myocarditis in Israel

Reported after Pfizer-BioNTech COVID-19 vaccine, December 2020-October 10, 2021

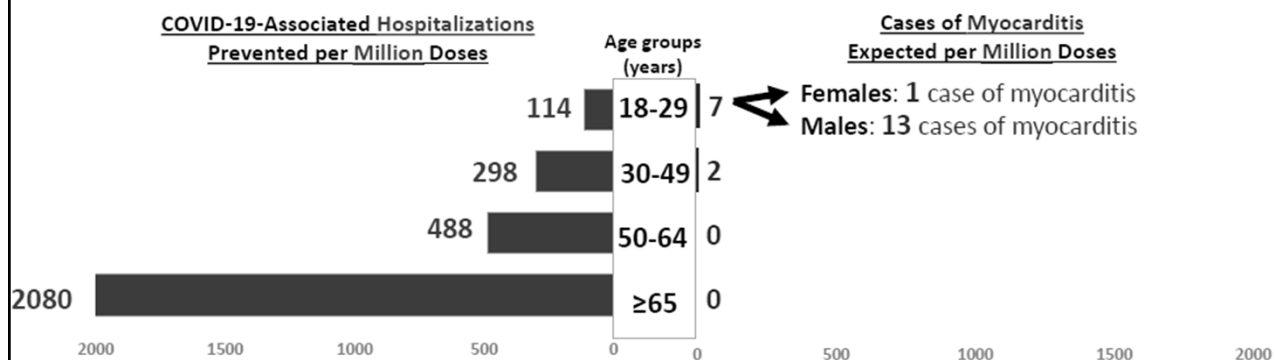
| | Age (years) | Post-dose 1 Rate per 100,000 | Post-dose 2 Rate per 100,000 | Post-dose 3 Rate per 100,000 | Number of 3 rd dose delivered |
|---------|----------------|---------------------------------|---------------------------------|---------------------------------|---|
| Females | 12-15 | 0 | 0.6 | 0 | 279 |
| | 16-19 | 0 | 0.9 | 0 | 97,807 |
| | 20-24 | 0.4 | 2.5 | 0 | 141,910 |
| | 25-29 | 0 | 0.4 | 0 | 130,283 |
| | ≥30 | 0.1 | 0.3 | 0 | 1,542,142 |
| Males | 12-15 | 0.5 | 6.6 | 0 | 292 |
| | 16-19 | 1.2 | 16.1 | 5.2 | 96,238 |
| | 20-24 | 2.2 | 10.3 | 3.6 | 139,015 |
| | 25-29 | 1.2 | 8.4 | 0.7 | 133,650 |
| | ≥30 | 0.5 | 1.7 | 0.4 | 1,448,745 |

Rates of myocarditis after a third dose appear to fall **between** rates seen after **dose 1** and **dose 2**

Source: Oliver, S. ACIP 11/19/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/06-COVID-Oliver-508.pdf>

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COVID-19 Vaccine Booster Doses: Safety Considerations – Myocarditis



Source: Oliver, S. ACIP 11/19/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/06-COVID-Oliver-508.pdf>

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Quick Knowledge & Learning Check!

- Which **ONE** of the following **adverse effects** appears to occur at a **substantially HIGHER** frequency for booster doses of **both mRNA vaccines** (as compared to 2nd doses of the primary series)
 - Fever
 - Lymphadenopathy
 - Nausea / Vomiting

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COVID-19 Vaccines:

**Does what we use for the
primary vaccine
and
boosting vaccine matter?**



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COVID-19 Vaccine Boosters: Homologous vs. Heterologous???

- **"Mix and Match"** research (NIH/NIAID)
- Volunteers completed primary series of COVID vaccine
- ≥ 12 weeks post-primary series
- Primary goals: assess safety, inform public health decisionmaking
 - Safety: No vaccine-related significant adverse effects
 - Solicited adverse effects generally mild, similar to 2nd-dose

Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

100

COVID-19 Vaccine Boosters: Mix & Match?

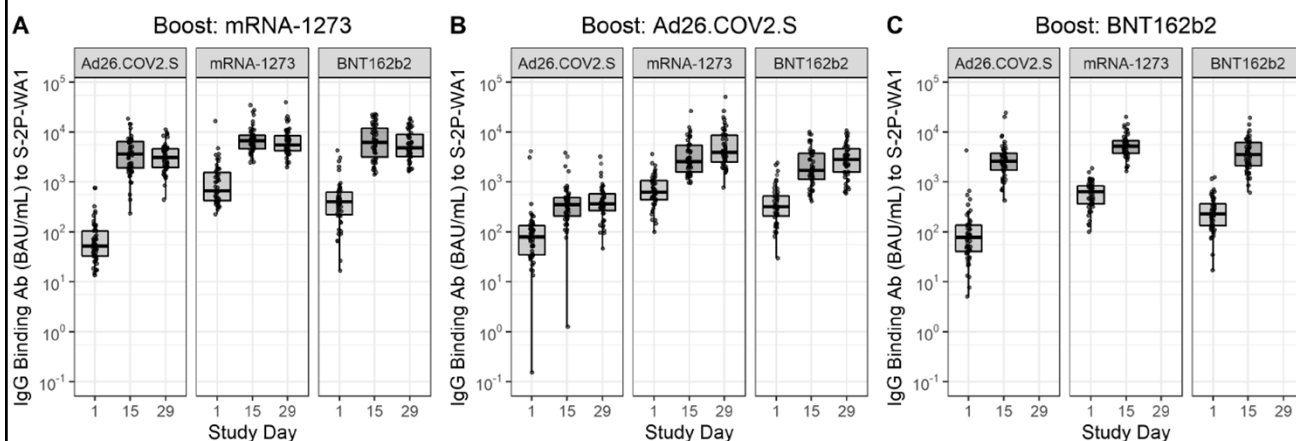
| | Group | Sample Size* | EUA Vaccine | Interval (weeks) | Delayed Booster Vaccination | Strategy Tested |
|---------------------------------|-------|--------------|---|------------------|-----------------------------|-----------------------------------|
| Moderna (100 mcg) | 1 | 50 | Previously dosed Janssen – Ad26.COV2-S | ≥12 | Moderna- mRNA-1273 | Same Strain Heterologous platform |
| | 2 | 50 | Previously dosed Moderna – mRNA-1273 | ≥12 | Moderna- mRNA-1273 | Control - Same Strain & platform |
| | 3 | 50 | Previously dosed Pfizer/BioNTech – BNT162b2 | ≥12 | Moderna- mRNA-1273 | Same Strain Similar platform |
| Janssen (5x10 ¹⁰ vp) | 4 | 50 | Previously dosed Janssen – Ad26.COV2-S | ≥12 | Janssen – Ad26.COV2.S | Control - Same Strain & platform |
| | 5 | 50 | Previously dosed Moderna – mRNA-1273 | ≥12 | Janssen – Ad26.COV2.S | Same Strain Heterologous platform |
| | 6 | 50 | Previously dosed Pfizer/BioNTech – BNT162b2 | ≥12 | Janssen – Ad26.COV2.S | Same Strain Heterologous platform |
| Pfizer (30 mcg) | 7 | 50 | Previously dosed Janssen – Ad26.COV2-S | ≥12 | Pfizer/BioNTech – BNT162b2 | Same Strain Heterologous platform |
| | 8 | 50 | Previously dosed Moderna – mRNA-1273 | ≥12 | Pfizer/BioNTech – BNT162b2 | Same Strain Similar platform |
| | 9 | 50 | Previously dosed Pfizer/BioNTech – BNT162b2 | ≥12 | Pfizer/BioNTech – BNT162b2 | Control - Same Strain & platform |

Study Visits: Days 1, 8 (call), 15, 29, Months 3, 6, 12

Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

101

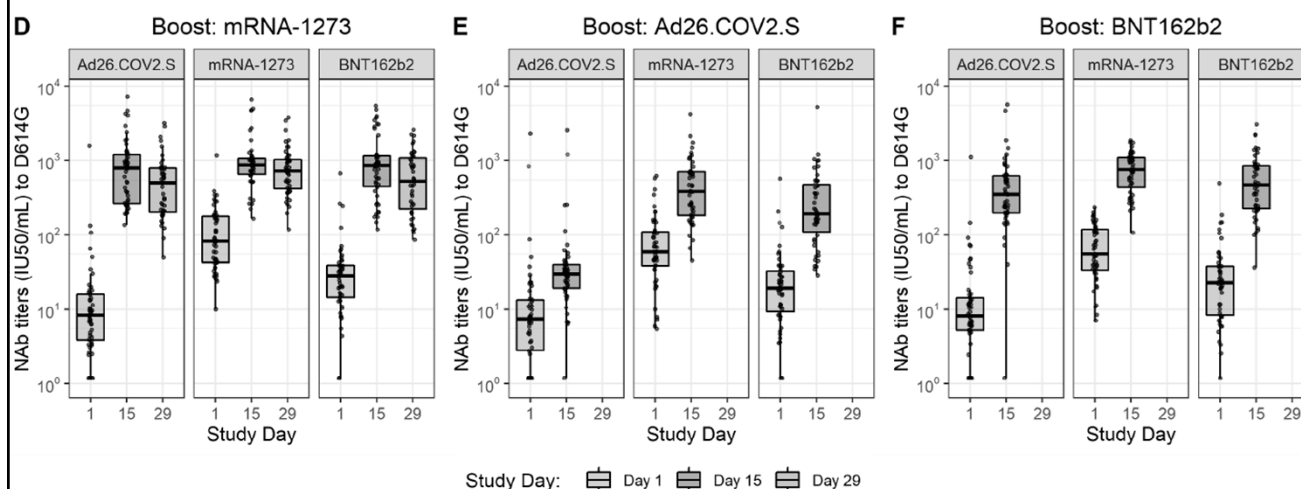
COVID-19 Vaccine Boosters: Mix & Match Study IgG Binding Antibodies



Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

102

COVID-19 Vaccine Boosters: Mix & Match Study Neutralizing Titers

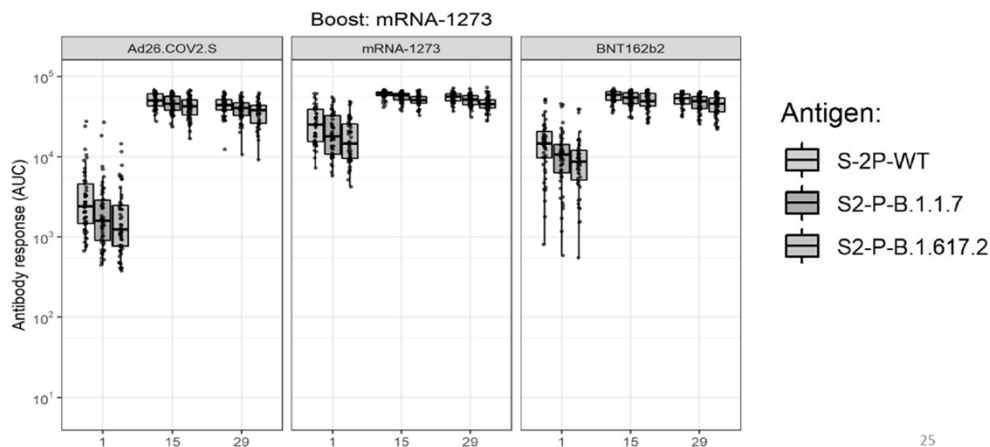


Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

103

COVID-19 Vaccine Boosters: Mix & Match Effects of Variants?

- mRNA-1273 (Moderna) Booster:**

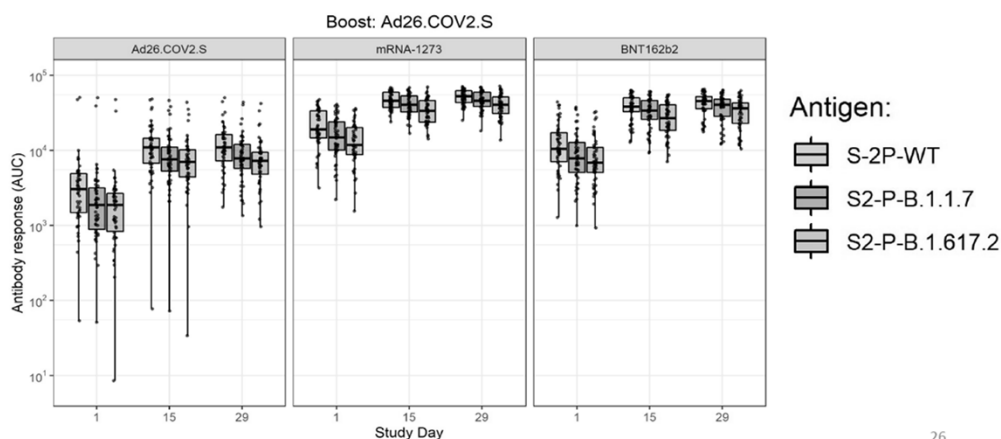


Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

104

COVID-19 Vaccine Boosters: Mix & Match Effects of Variants?

- Ad26.COV2.S (Janssen) Booster:**

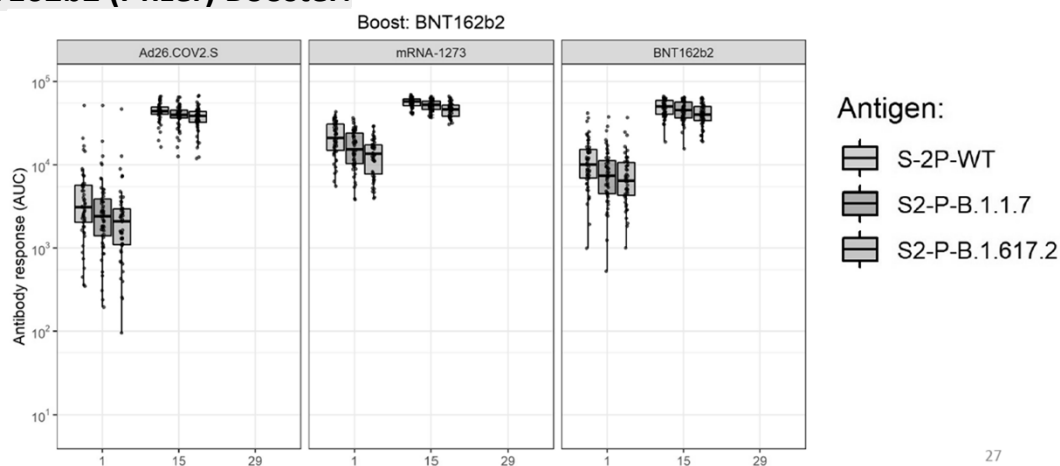


Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

105

COVID-19 Vaccine Boosters: Homologous vs. Heterologous???

- BNT162b2 (Pfizer) Booster:**



Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

106

COVID-19 Vaccine Boosters: Mix & Match

- Heterologous boosting by all 3 vaccines produced increases in antibodies/neutralizing titers
 - **Similar or higher** than homologous boosting
- Boosting by **mRNA vaccines** resulted in **higher antibody titers** during the study period
- Overall, Primary / Boost sequence **did not seem to matter that much**
- **No significant safety concerns**

Source: Lyke, K.E., FDA VRBPAC Meeting (10/15/21). <https://www.fda.gov/media/153128/download>

107

COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address

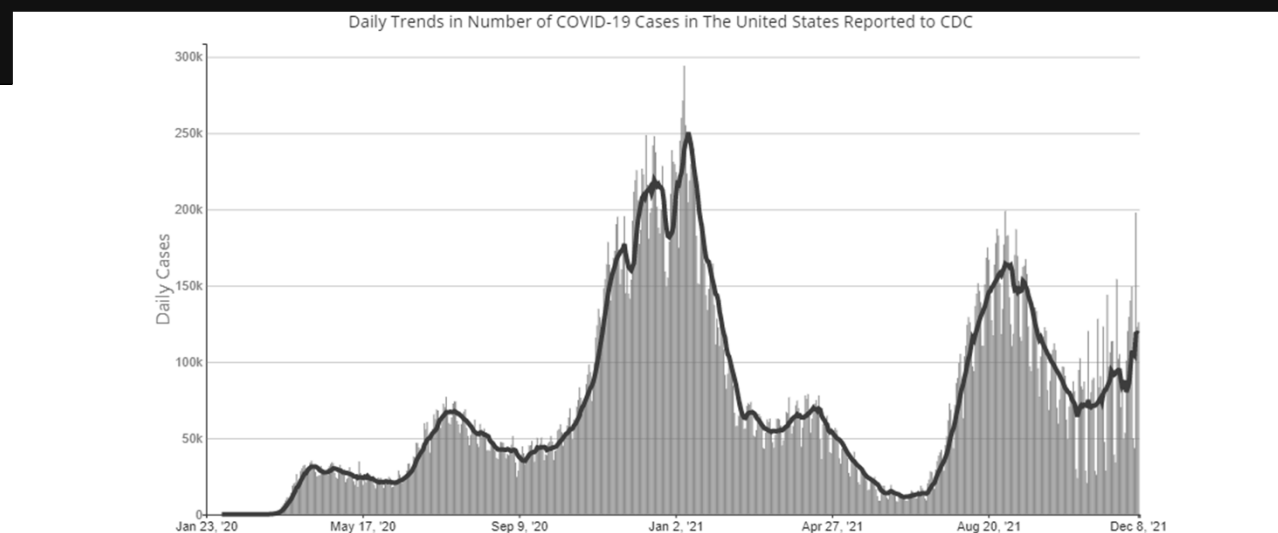
Will booster doses of COVID-19 vaccines reduce COVID-19 **incidence**, **hospitalization** and/or **mortality**?

Benefits
and
Harms

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

108

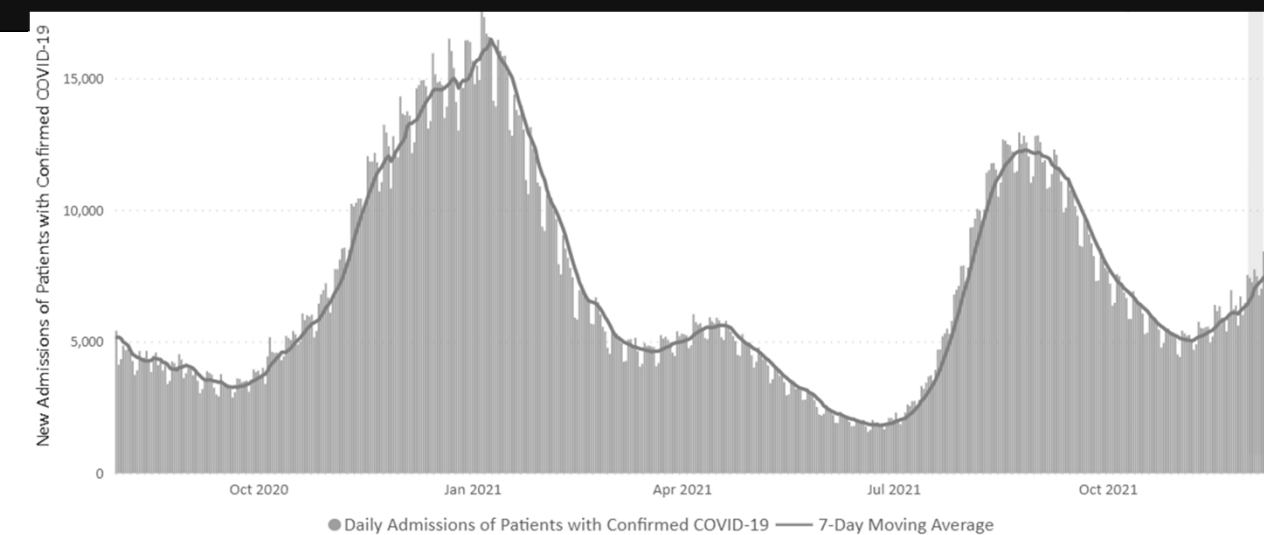
Trends in COVID-19 Cases in the United States (12/8/21)



https://covid.cdc.gov/covid-data-tracker/#trends_dailycases (Accessed 12/9/21)

109

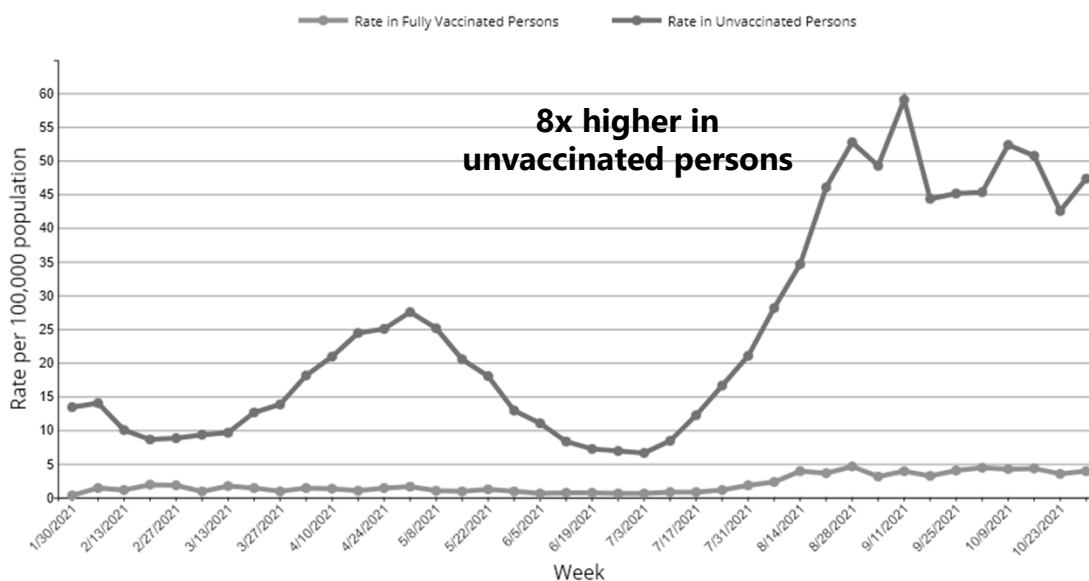
Trends in COVID-19 Hospitalizations (United States, 12/7/21)



<https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions> (Accessed 12/9/21)

110

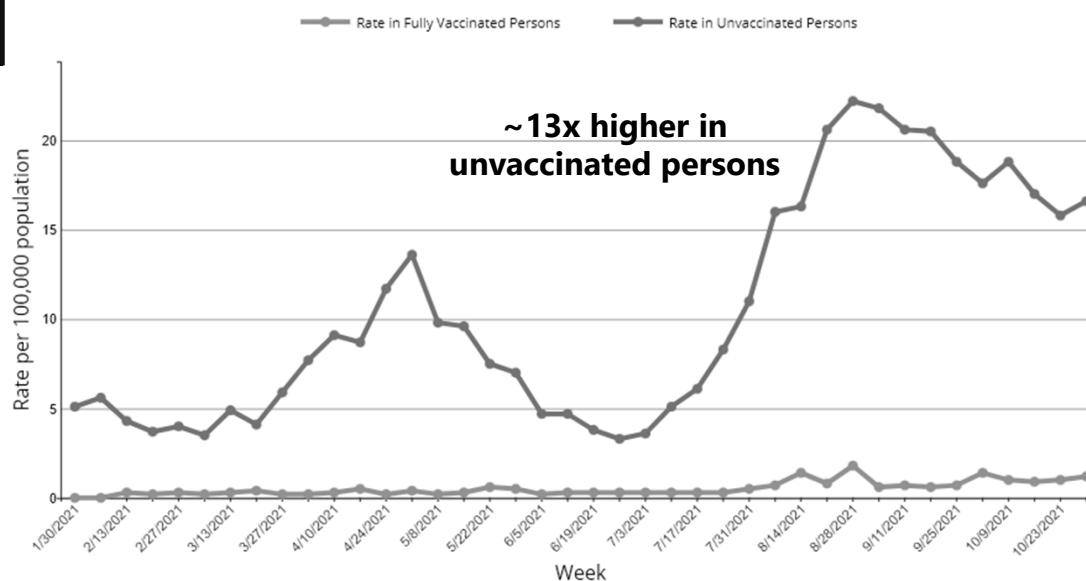
Age-Adjusted Rates of COVID-19-Associated Hospitalizations by Vaccine Status in Adults Aged ≥ 18 Years, January–October 2021



<https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination>

111

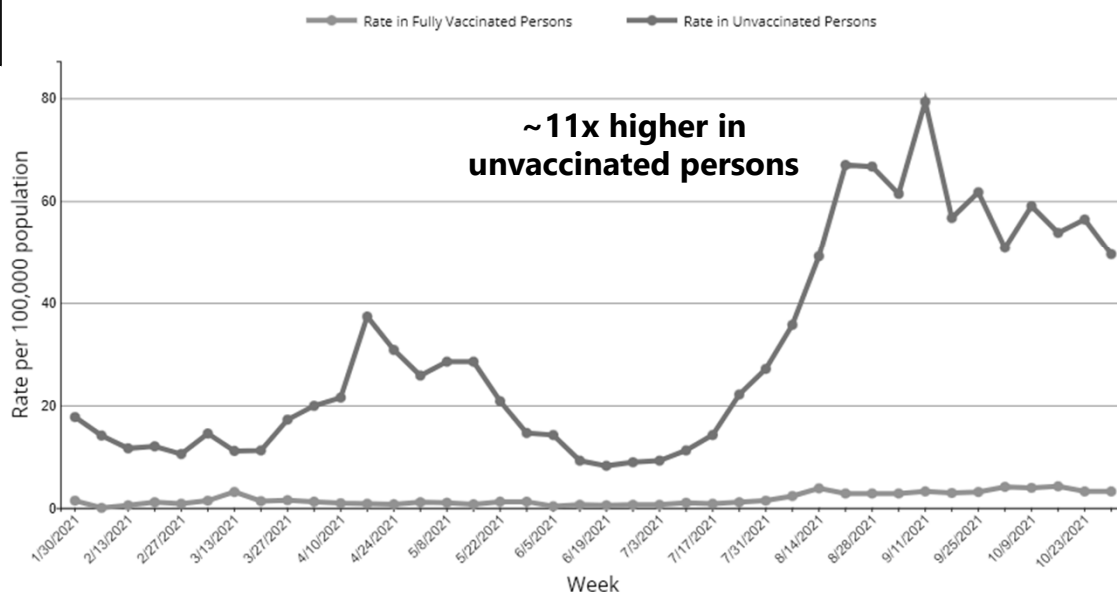
Rates of COVID-19-Associated Hospitalizations by Vaccine Status in Adults Aged 18–49 Years, January–October 2021



<https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination>

112

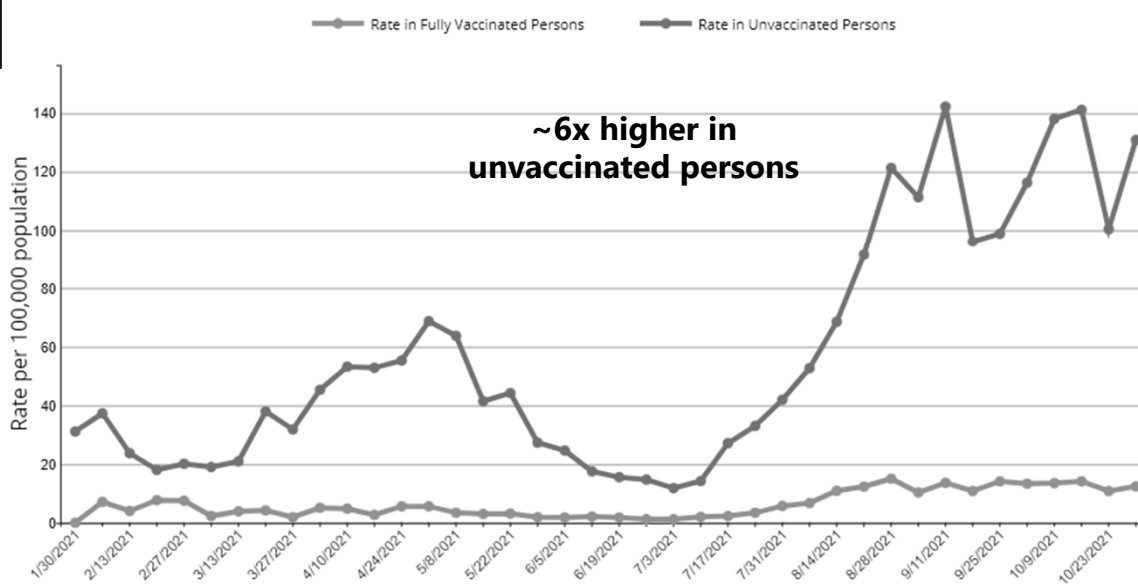
Rates of COVID-19-Associated Hospitalizations by Vaccine Status in Adults Aged 50–64 Years, January–October 2021



<https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination>

113

Rates of COVID-19-Associated Hospitalizations by Vaccine Status in Adults Aged 65+ Years, January–October 2021

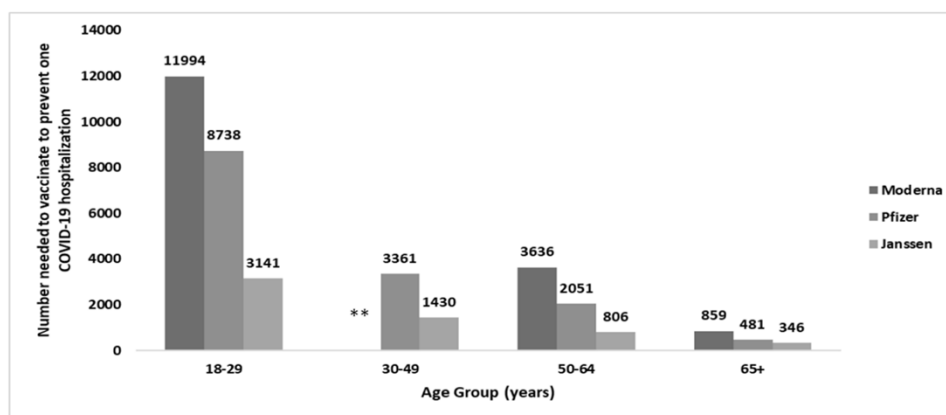


<https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination>

114

COVID-19 Vaccine Booster Doses: ACIP Model Estimations for Benefits by Age Group

Number of people needed to vaccinate with a booster dose
to prevent one hospitalization over 6 months



** Not estimable due to pre-booster efficacy estimated at >95%

Source: Dooling, K. ACIP 10/21/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/11-COVID-Dooling-508.pdf>

115

COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address

Do boosters **improve** VE against the
Delta variant and other variants of
concern?

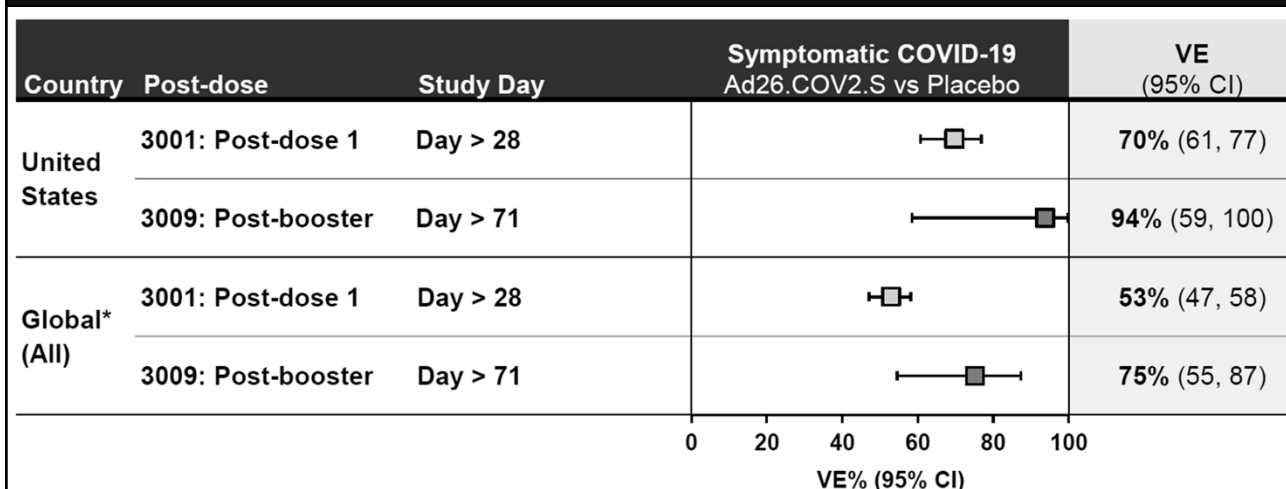
How can we use this data to inform VE
for **future variants**?

Benefits
and
Harms

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

116

Clinical Outcome Data from Ad26.COVID-2-vaccinated people: Effects of Booster Dose



Source: Heaton, P. & Douoguih, M. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/03-COVID-Heaton-Douoguih-508.pdf>

117

Clinical Outcome Data for COVID-19 Vaccine Boosters: Israel - BNT162b2 Vaccine

- Data from Clalit Health Services (>50% of Israeli healthcare coverage)
- Persons who received 3rd dose of BNT162b2 (7/30/21 - 9/23/21) matched to COVID-19-uninfected controls who completed 2-dose primary series (\geq 5mo. Before study)
- HCWs, LTCF residents, Immunocompromised, & homebound persons excluded
- **Primary outcome:**
 - COVID-19 – related hospital admission, severe disease, death

Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

118

Clinical Outcome Data for COVID-19 Vaccine Boosters: Israel - BNT162b2 Vaccine

- **Results / Outcomes:**
 - ~728,000 persons in each study group
 - Median follow-up time: 13d (IQR 6-21) after the 1st week
 - Median age 52 (37-68), ~53% at least 1 RF for severe COVID-19

- **Primary Outcomes:**

| | Vaccinated with two doses | | Vaccinated with three doses | | 1-risk ratio (95% CI) | Risk difference per 100 000 individuals (95% CI) |
|-----------------------|---------------------------|------------------------------|-----------------------------|------------------------------|-----------------------|--|
| | Events | Risk per 100 000 individuals | Events | Risk per 100 000 individuals | | |
| Admission to hospital | 231 | 220.8 | 29 | 14.4 | 93% (88-97) | 206.4 (146.1-275.1) |
| Severe disease | 157 | 158.9 | 17 | 12.9 | 92% (82-97) | 145.9 (93.1-207.7) |
| Death | 44 | 31.9 | 7 | 6.1 | 81% (59-97) | 25.8 (13.0-38.5) |

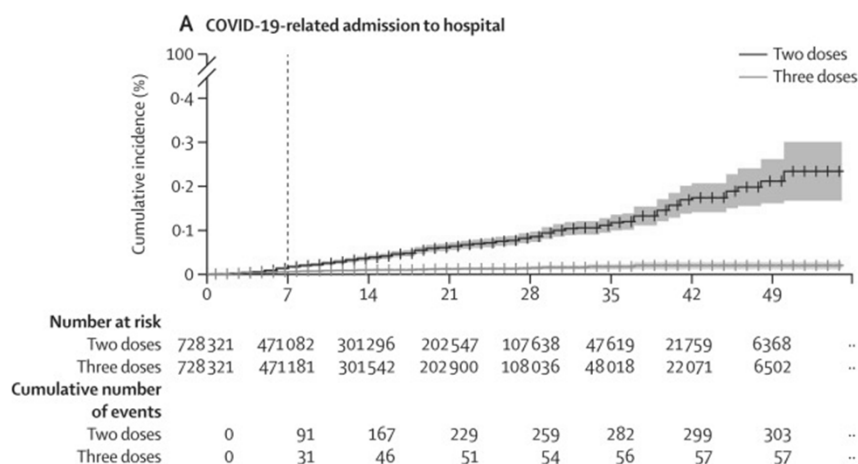
Estimates were obtained using the Kaplan-Meier estimator starting from day 7 after receipt of the third dose, in those who received it.

Table 2: Effectiveness of the third vaccine dose versus two vaccine doses of the BNT162b2 mRNA COVID-19 vaccine

Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

119

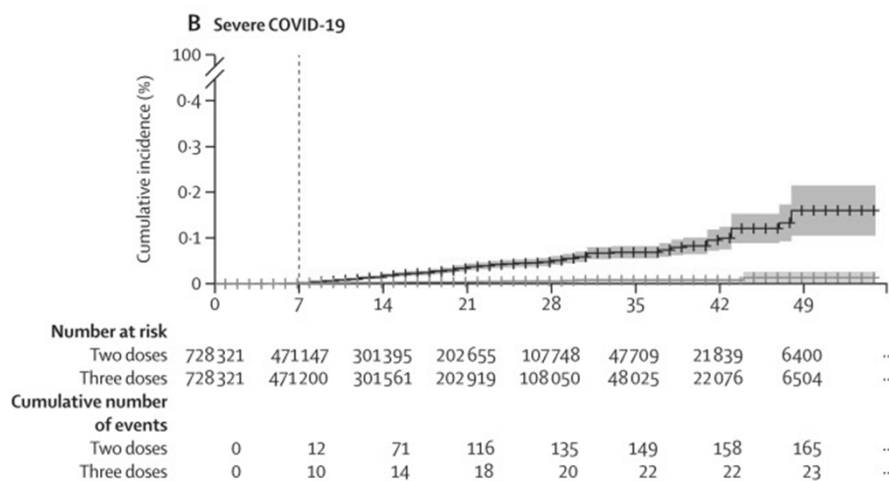
Clinical Outcome Data for COVID-19 Vaccine Boosters: Israel - BNT162b2 Vaccine



Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

120

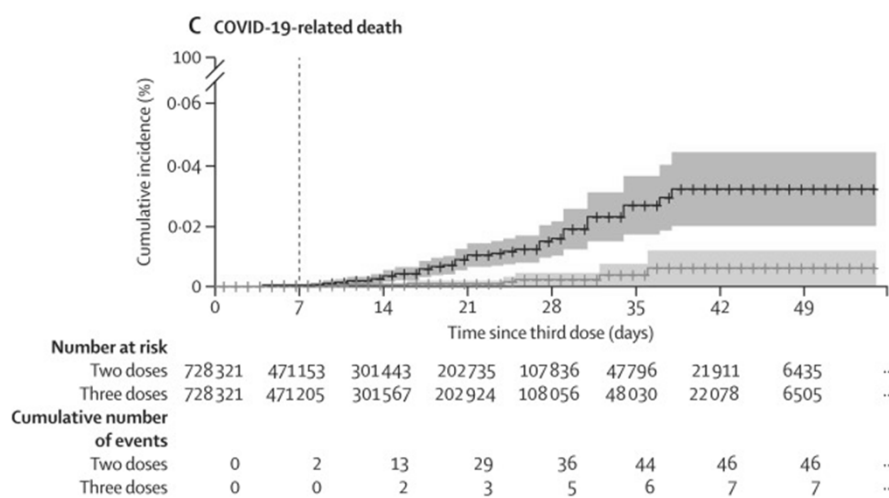
Clinical Outcome Data for COVID-19 Vaccine Boosters: Israel - BNT162b2 Vaccine



Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

121

Clinical Outcome Data for COVID-19 Vaccine Boosters: Israel - BNT162b2 Vaccine



Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

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Effects of COVID-19 Vaccine Boosters on Mortality: Israel - BNT162b2 Vaccine

- Additional Data from Clalit Health Services
- Persons ≥ 50 y.o. who received 3rd dose of BNT162b2 (8/6/21 - 9/29/21) matched to COVID-19-uninfected controls (who only received 2-dose primary series)
 - Boosted persons crossed over into group >7 days post-dose
- Immunocompromised persons excluded
- Primary outcome:
 - COVID-19 – related death

Arbel L., et al. NEJM (12/8/21). <https://doi.org/10.1056/NEJMoa2115624>

123

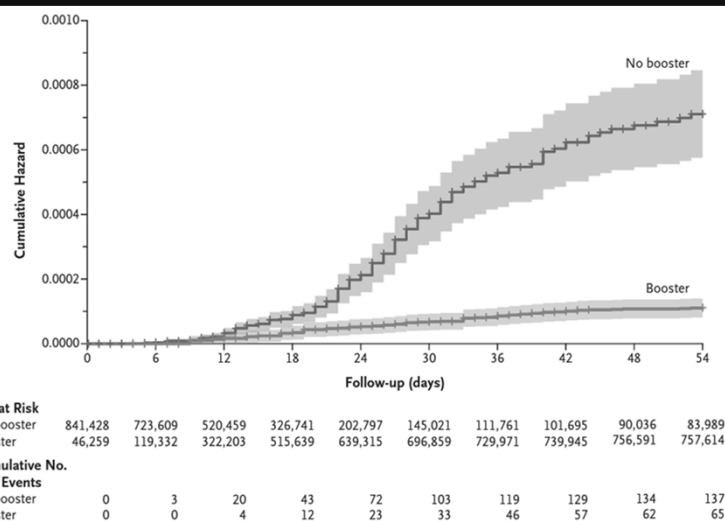
Effects of COVID-19 Vaccine Boosters on Mortality: Israel - BNT162b2 Vaccine

- **Results / Outcomes:**
 - ~843,000 persons included; 60% were ≥ 65 y.o.
 - ~30%+ had diabetes, hypertension, and/or obesity
 - ~2 month follow-up; during time of \uparrow incidence and \downarrow social-distancing restrictions
 -
- **Primary/Secondary Outcomes:**
 - \downarrow deaths observed regardless of age
 - Adjusted hazard ratio for SARS-CoV-2 infection in the booster group = 0.17 (95% CI, 0.16 to 0.18; $P < 0.001$)

Arbel L., et al. NEJM (12/8/21). <https://doi.org/10.1056/NEJMoa2115624>

124

Effects of COVID-19 Vaccine Boosters on Mortality: Israel - BNT162b2 Vaccine



Arbel L., et al. NEJM (12/8/21). <https://doi.org/10.1056/NEJMoa2115624>

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**But What About OMICRON
????????????**

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HEALTH • COVID-19

Scientists recommend COVID booster shots after 4 studies show vaccines may be less effective against the Omicron variant

BY SOPHIE MELLOR
December 8, 2021 10:22 AM EST



The Telegraph @Telegraph
Omicron significantly reduces Covid antibodies generated by Pfizer vaccine, study finds

Read more: telegraph.co.uk/news/2021/12/08/...

CORONAVIRUS

Omicron significantly reduces Covid antibodies generated by Pfizer vaccine, study finds

telegraph.co.uk
Omicron reduces antibodies generated by Pfizer vaccine, study finds

<https://twitter.com/Telegraph/status/1468493647247294465> (Accessed 12/9/21)
<https://fortune.com/2021/12/08/scientists-recommend-covid-boosters-studies-2-shot-vaccine/> (Accessed 12/9/21)

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BNT162b2 Activity vs. Omicron Variant

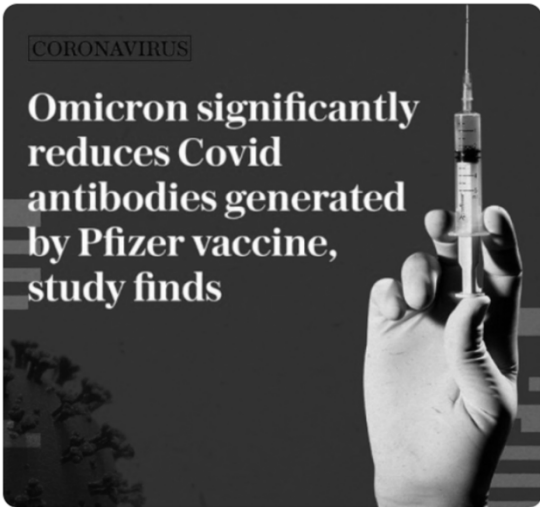
- Preliminary **laboratory** studies:
 - Sera from persons who received **2 doses** had **~25-fold ↓** in neutralization titers
 - Sera from persons who received **booster doses** neutralizes Omicron “... *to levels that are comparable to those observed for the wild-type SARS-CoV-2 spike protein after two doses*”
 - **Doesn't quantify impact on T-cell response
 - Should still be good, ~80% of epitopes preserved
 - CD8+ T-cell populations also increased by 3rd dose

<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant> (Accessed 12/9/21)

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Paul Sax @PaulSaxMD

Well, not really, but we get what you're saying
[telegraph.co.uk/news/2021/12/0...](https://www.telegraph.co.uk/news/2021/12/0...)



CORONAVIRUS

Omicron significantly reduces Covid antibodies generated by Pfizer vaccine, study finds

BK Titanji #ILookLikeAScientist @Boghuma

✳️ We cannot compare virus neutralization studies from different labs head-to-head.
 ✳️ We cannot extrapolate vaccine effectiveness in the population from in-vitro neutralization assays.

They don't tell a full story. Current data indicates vaccines/boosters will work vs #omicron.

6:50 AM · Dec 9, 2021 · Twitter for Android

<https://twitter.com/PaulSaxMD/status/1468653052752121859> (Accessed 12/9/21)
<https://twitter.com/Boghuma/status/1468910990234468358> (Accessed 12/9/21)

129

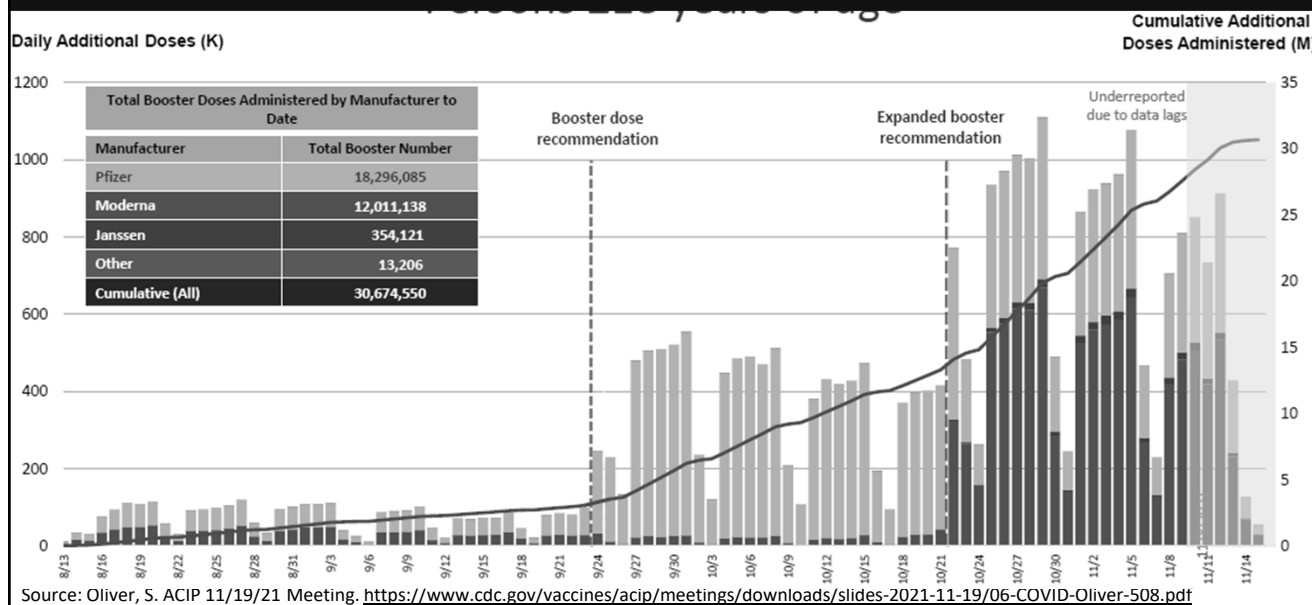
COVID-19 Vaccine Booster Doses: Nov. 2021 ACIP Working Group/CDC Recommendations

- **Top priority** should be **continued vaccination** of **unvaccinated individuals**
- Balance of benefits and risks **varies by age**
 - Older adults have the clearest benefit/risk balance
 - Myocarditis data after booster doses reassuring to date, continue to closely monitor
 - Increases in COVID-19 cases may also impact benefit/risk balance
- **Goals of COVID-19 vaccines:**
 - Primary goal: Prevention of **severe disease**
 - Secondary goals:
 - Maintaining workforce and healthcare capacity
 - Reduce infection and transmission
 - Unknown impact of COVID-19 vaccine booster dose on prevention of transmission. However, even reduction in transmission may be important around winter and holidays

Source: Oliver, S. ACIP 11/19/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/06-COVID-Oliver-508.pdf>

130

COVID-19 Vaccine Booster Doses: Roll-Out Through Mid-November 2021



131

Updated COVID-19 Booster Recommendations (CDC/ACIP, 10/23/21)

COVID-19 vaccine booster dose in persons who completed an mRNA primary series

Persons who should receive a COVID-19 booster dose

- Aged ≥65 years
- Aged ≥18 years and reside in long-term care settings
- Aged 50-64 years with certain underlying medical conditions

Persons who may receive a COVID-19 booster dose, based on individual benefits and risks

- Aged 18-49 years with certain underlying medical conditions*
- Aged 18-64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting

- Booster dose administered at least 6 months after completion of primary series
- Any FDA-approved or authorized COVID-19 vaccine (Pfizer-BioNTech, Moderna, or Janssen) can be used for booster dose, regardless of vaccine received for primary series

Source: Oliver, S. ACIP 11/19/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/06-COVID-Oliver-508.pdf>

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Updated COVID-19 Booster Recommendations (CDC/ACIP, 10/23/21)

COVID-19 vaccine booster dose in persons who received a Janssen COVID-19 vaccine primary dose

- Persons aged ≥ 18 years who received primary vaccination with Janssen COVID-19 vaccine **should** receive a single COVID-19 vaccine booster dose at least 2 months later
- Any FDA-approved or authorized COVID-19 vaccine (Pfizer-BioNTech, Moderna, or Janssen) can be used for booster dose, regardless of vaccine received for primary series

Source: Oliver, S. ACIP 11/19/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/06-COVID-Oliver-508.pdf>

133

Updated Booster Recommendations (CDC/ACIP, 11/29/21)

Everyone Ages 18 and Older Should Get a Booster Shot

IF YOU RECEIVED

Pfizer-BioNTech or Moderna

Who should get a booster:

Everyone 18 years or older

When to get a booster:

At least 6 months after completing your primary COVID-19 vaccination series.

Which booster should you get?

Any of the COVID-19 vaccines authorized in the United States.

IF YOU RECEIVED

Johnson & Johnson's Janssen

Who should get a booster:

Everyone 18 years or older

When to get a booster:

At least 2 months after completing your primary COVID-19 vaccination.

Which booster should you get?

Any of the COVID-19 vaccines authorized in the United States.

<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html> (Accessed 12/9/21)

134

Quick Knowledge & Learning Check!

- A 75 year old male (he/him) comes to the pharmacy to pick up a prescription. He strikes up a conversation with you and you learn the following:
 - He received a dose of the **Janssen/J&J vaccine** in April 2021
 - He hasn't received any other COVID-19 vaccination since then
 - He is interested in getting a "booster dose" of COVID-19 vaccine
- **Q #1:** Is he currently eligible to receive a booster dose?
 - a) Yes
 - b) No

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Quick Knowledge & Learning Check!

- A 75 year old male (he/him) comes to the pharmacy to pick up a prescription. He strikes up a conversation with you and you learn the following:
 - He received a dose of the **Janssen/J&J vaccine** in April 2021
 - He hasn't received any other COVID-19 vaccination since then
 - He is interested in getting a "booster dose" of COVID-19 vaccine
- **Q #2:** Which would be the most appropriate vaccine booster to administer?
 - a) Janssen/J&J
 - b) Moderna
 - c) Pfizer
 - d) Any of the above...whichever one he prefers

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Summary

- Vaccine Boosters are **NOT** a new concept!!!
- The need for vaccine boosters does not mean “***tHe VaCcINeS dOn’T wOrK***”
- Vaccine efficacy vs. COVID-19 and the “optimal” administration series is a **continually-evolving** research area
 - Apparent now that the mRNA vaccines are best described as “**3-dose series**”
- Data support both **efficacy** and **safety** of COVID-19 boosters
- Need for additional boosters [and/or different boosters]in the future?
 - It depends!!!

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Thank you!!!

- Questions?

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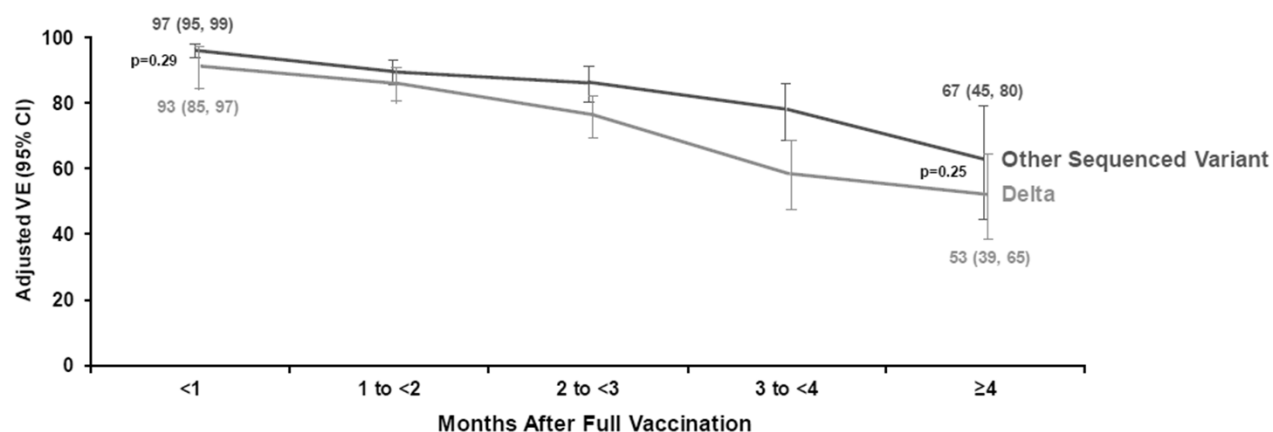
Supplemental & Additional Slides



139

COVID-19 Vaccine Booster Doses: Data on BNT162b2 Vaccine Effectiveness (Kaiser Permanente Southern California)

Adjusted VE Against SARS-CoV-2 Infections, KPSC Members ≥ 12 Years of Age



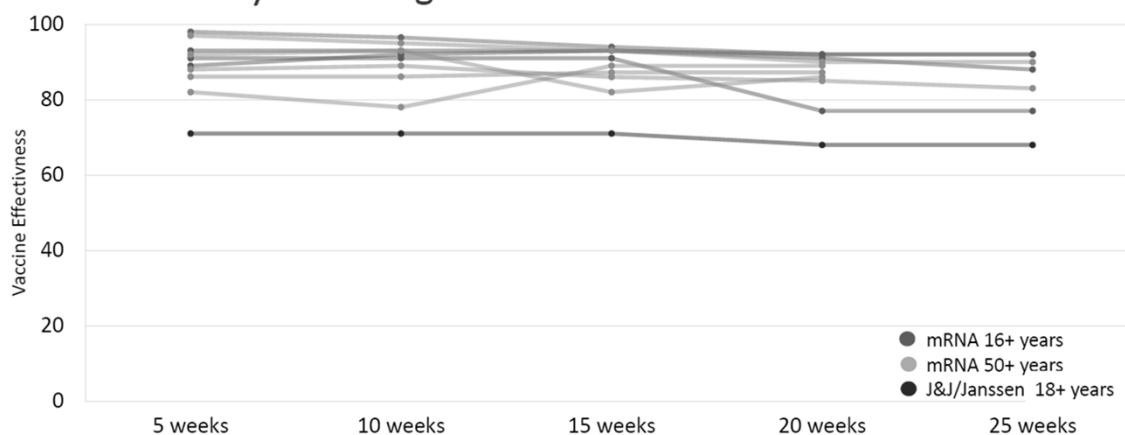
Gruber, W.C. VRBPAC Meeting (9/22/21). <https://www.fda.gov/media/152240/download>

140

COVID-19 Vaccine Booster Doses: Trends in Vaccine Effectiveness vs. Hospitalization

Vaccine effectiveness against hospitalization over time

Adults ≥ 16 years of age

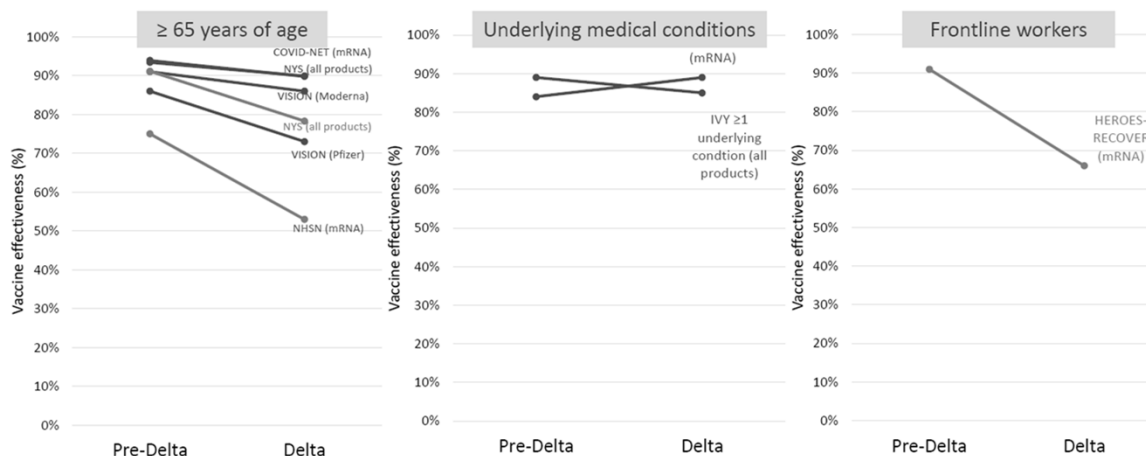


Source: Dooling, K. ACIP 10/21/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/11-COVID-Dooling-508.pdf>

141

Need for COVID-19 Vaccine Booster Doses: Vaccine Efficacy in Important Sub-Populations

Magnitude of vaccine effectiveness (VE) against infection or hospitalization by Delta predominance and study, by risk group

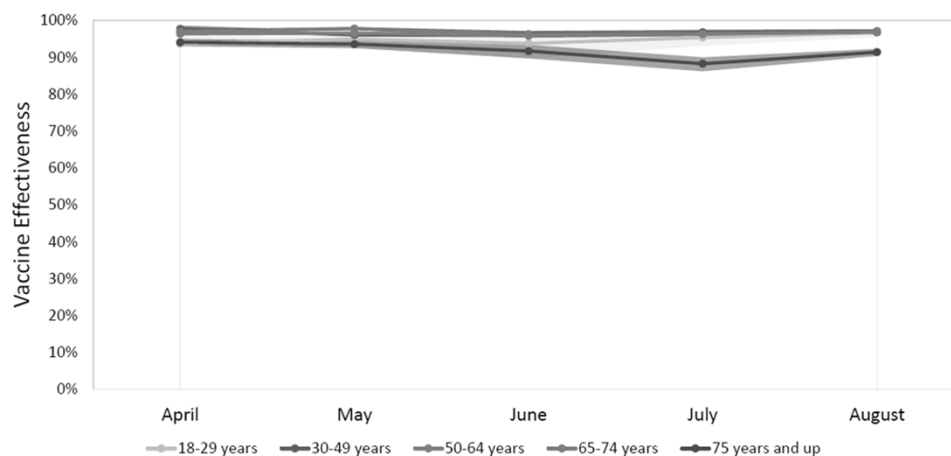


Source: Dooling, K. ACIP 10/21/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/11-COVID-Dooling-508.pdf>

142

Need for COVID-19 Vaccine Booster Doses: Vaccine Efficacy in Important Sub-Populations

- COVID-NET Data:

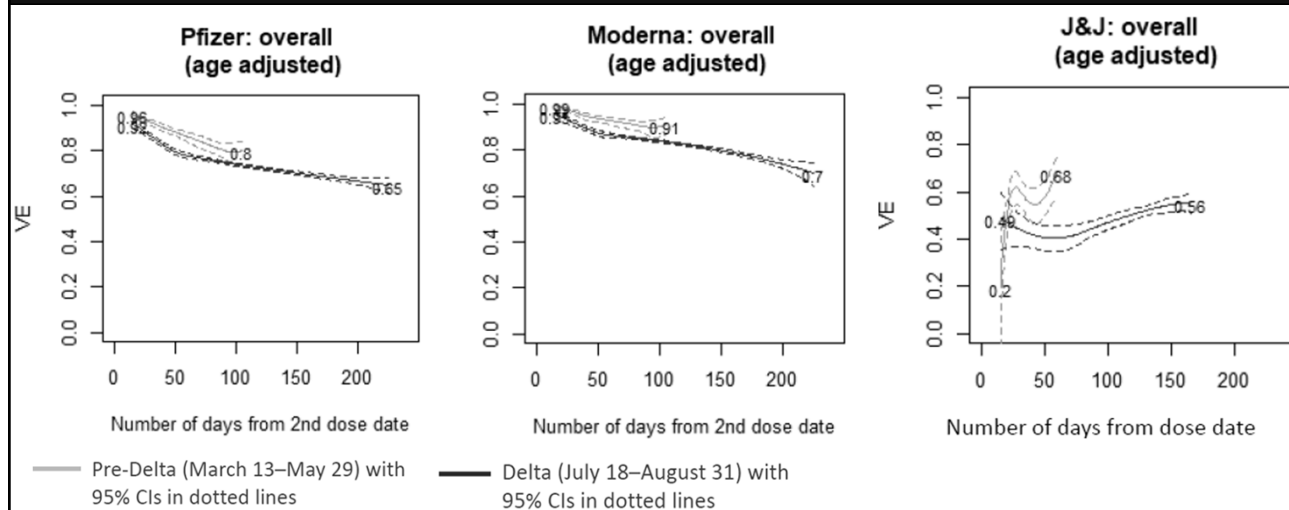


No significant differences in VE by age group or calendar month of hospitalization

Source: Link-Gelles, R. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/04-COVID-Link-Gelles-508.pdf>

143

COVID-19 Vaccine Booster Doses: Vaccine Efficacy vs. Symptomatic Infection (ACIP Working Group)



Source: Link-Gelles, R. ACIP 9/22/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/04-COVID-Link-Gelles->

144

Subgroup Analyses (Hospitalization) for COVID-19 Vaccine Boosters: Israel - Pfizer BNT162b2 Vaccine

| | Total number in analysis (both study groups combined) | Vaccinated with two doses | | Vaccinated with three doses | | 1 – risk ratio (95% CI) | Risk difference per 100 000 individuals (95% CI) |
|---------------------------------|---|---------------------------|------------------------------|-----------------------------|------------------------------|-------------------------|--|
| | | Events | Risk per 100 000 individuals | Events | Risk per 100 000 individuals | | |
| Admissions to hospital | | | | | | | |
| Sex | | | | | | | |
| Male | 458 552 | 140 | 321.6 | 21 | 25.2 | 92% (85 to 97) | 296.4 (177.2 to 443.2) |
| Female | 483 548 | 91 | 132.1 | 8 | 5.0 | 96% (93 to 99) | 127.1 (87.2 to 175.9) |
| Age group, years | | | | | | | |
| 16–39 | 288 072 | 6 | 7.0 | 1 | 2.1 | 70% (–70 to 100) | 4.9 (–2.1 to 12.3) |
| 40–69 | 448 366 | 73 | 104.9 | 10 | 8.1 | 92% (83 to 97) | 96.7 (60.1 to 148.7) |
| ≥70 | 162 958 | 140 | 574.3 | 16 | 41.3 | 93% (87 to 97) | 533.0 (390.1 to 675.3) |
| Number of coexisting conditions | | | | | | | |
| 0 | 462 690 | 14 | 13.4 | 2 | 1.5 | 89% (60 to 100) | 11.9 (4.3 to 22.3) |
| 1–2 | 336 850 | 61 | 111.5 | 7 | 9.7 | 91% (80 to 98) | 101.9 (61.9 to 145.9) |
| ≥3 | 142 560 | 156 | 689.7 | 20 | 56.3 | 92% (87 to 96) | 633.4 (456.4 to 847.7) |

Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

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Subgroup Analyses (Severe Disease) for COVID-19 Vaccine Boosters: Israel - Pfizer BNT162b2 Vaccine

| | Total number in analysis (both study groups combined) | Vaccinated with two doses | | Vaccinated with three doses | | 1 – risk ratio (95% CI) | Risk difference per 100 000 individuals (95% CI) |
|---------------------------------|---|---------------------------|------------------|-----------------------------|------------------|-------------------------|--|
| | | Events | Risk per 100 000 | Events | Risk per 100 000 | | |
| Severe disease | | | | | | | |
| Sex | | | | | | | |
| Male | 458 652 | 103 | 233.0 | 13 | 24.8 | 89% (73 to 98) | 208.2 (109.7 to 343.9) |
| Female | 483 614 | 54 | 93.2 | 4 | 2.8 | 97% (93 to 99) | 90.4 (57.4 to 137.8) |
| Age group, years | | | | | | | |
| 16–39 | 288 086 | 2 | 2.5 | 0 | 0.0 | NA | 2.5 (0.7 to 7.5) |
| 40–69 | 448 410 | 38 | 57.9 | 5 | 3.5 | 94% (85 to 99) | 54.4 (28.0 to 87.6) |
| ≥70 | 163 054 | 108 | 447.5 | 10 | 35.8 | 92% (83 to 98) | 411.7 (285.9 to 548.7) |
| Number of coexisting conditions | | | | | | | |
| 0 | 462 706 | 5 | 3.1 | 0 | 0.0 | NA | 3.1 (0.7 to 6.0) |
| 1–2 | 336 902 | 39 | 82.0 | 2 | 3.2 | 96% (85 to 100) | 78.8 (39.3 to 126.8) |
| ≥3 | 142 658 | 113 | 503.5 | 15 | 51.6 | 90% (80 to 96) | 451.9 (322.3 to 605.2) |

Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

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Clinical Outcome Data for COVID-19 Vaccine Boosters: Israel - Pfizer BNT162b2 Vaccine

- Secondary Outcome

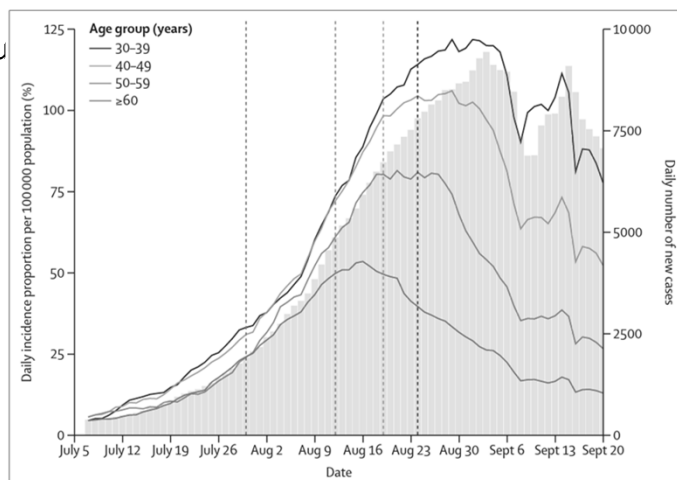


Figure 2: Daily incidence of SARS-CoV-2 infection for different age groups around initiation of third dose vaccination

Barda, N., et al. Lancet (10/29/21). [https://doi.org/10.1016/S0140-6736\(21\)02249-2](https://doi.org/10.1016/S0140-6736(21)02249-2)

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COVID-19 Vaccine Booster Doses: Aug. 2021 ACIP Working Group/CDC Recommendations



- Receipt of **COVID-19 vaccine primary series** will continue to have the largest public health impact
- Decisions for boosters need to focus on prevention of **severe disease, hospitalization and death**
- Important to ensure **global vaccine availability**: new variants could emerge from regions with **low** vaccine coverage and **high** community transmission

Source: Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

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COVID-19 Vaccine Booster Doses: Aug. 2021 ACIP Working Group/CDC Recommendations

- **Top priority** should be **continued vaccination** of **unvaccinated individuals**
 - Planning for delivery of booster doses to vaccinated individuals should not deter outreach for delivery of primary series to unvaccinated individuals
- Priority for booster dose policy:
 - Prevention of **severe disease** in **at-risk populations**
- **Simplicity** and **flexibility** will be important to support equitable and efficient delivery of booster doses

Source: Oliver, S. ACIP 8/30/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf>

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COVID-19 Vaccine Booster Doses: Aug. 2021 ACIP Working Group/CDC Recommendations

- **Neutralizing antibody** data will be important for booster dose discussions, but may not represent the entire immune response to COVID-19 vaccines
 - Cellular immune response can be difficult to measure, but important
 - Commercial antibody testing **not authorized** or **recommended** to evaluate post-vaccination immune response
- Based on available data and timing of vaccine roll-out, initial booster vaccine policy focused on at-risk **adult** populations
 - At-risk populations could include:
 - Adults ≥65 years of age, LTCF residents, healthcare personnel



Oliver, S. ACIP 8/13/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/05-COVID-Oliver-508.pdf>

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COVID-19 Vaccine Booster Doses: Sept. 2021 ACIP Working Group/CDC Recommendations

- **Top priority** should be **continued vaccination** of **unvaccinated individuals**
- Jurisdictions have a variety of vaccination and disease control priorities
 - E.g. COVID-19 cases, delivery of primary COVID-19 vaccines series and influenza vaccines
- Balance of benefits and risks **varies by age**
 - Adults ≥65 years have the clearest benefit/risk
 - Benefit to other age groups incrementally smaller, given high effectiveness maintained from primary series

Goals of booster program:

- Prevention of **severe disease**
- Other considerations are important, such as maintaining workforce and healthcare capacity, prevention of transmission, individual benefit/risk balance

Oliver, S. ACIP 9/23/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-9-23/03-COVID-Oliver.pdf>

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COVID-19 Vaccine Booster Doses: Sept. 2021 Benefits vs. Risks (ACIP Working Group)

Potential Benefits

- May confer reduced risk of severe disease
 - Strongest evidence in older adults
 - Vaccine effectiveness of an mRNA primary series remains high in younger age groups
- May confer reduced risk of SARS-CoV-2 infection
 - Waning of vaccine protection via a combination of time since vaccination and delta variant has been observed in most age groups
 - Infection may be symptomatic or asymptomatic
 - May reduce work absence and preserve capacity of important sectors
 - May reduce transmission of SARS-CoV-2 infection to other at-risk persons

Source: Dooling, K. ACIP 9/23/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-9-23/04-COVID-Dooling.pdf>

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COVID-19 Vaccine Booster Doses: Sept. 2021 Benefits vs. Risks

Potential risks

- Myocarditis and myopericarditis, although very rare, may occur following mRNA vaccination. It is more common in younger age groups, particularly males aged <30 years.
 - Most patients with myocarditis have been hospitalized for short periods, with the majority achieving resolution of acute symptoms
 - The rate of myocarditis following a booster dose is not yet known
- Anaphylaxis, although rare, may occur following mRNA vaccination. The rate of anaphylaxis following a booster dose is not yet known
- Reactogenicity, including transient local and systemic symptoms, are common following mRNA vaccines. The 3rd dose of Pfizer-BioNTech COVID-19 vaccine appears to have similar reactogenicity as the 2nd dose.

Source: Dooling, K.. ACIP 9/23/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-9-23/04-COVID-Dooling.pdf>

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COVID-19 Vaccine Booster Doses: Sept. 2021 Benefits vs. Risks

Consider individual risk of SARS-CoV-2 exposure

- Risk of exposure in occupational, living and transportation settings
- Ability to consistently wear a mask, maintain social distance, and other mitigation measures
- Rates of SAR-CoV-2 infection in the community

Consider individual risk of developing severe COVID-19, if infected

- Underlying medical conditions, particularly if not well controlled

Consider personal characteristics

- Living with or caring for a frail or immunocompromised person
- Consequences of inability to meet personal or occupational obligations due to SARS-CoV-2 infection

Source: Dooling, K.. ACIP 9/23/21 Meeting. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-9-23/04-COVID-Dooling.pdf>

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Summary of Booster Recommendations & Schedule of Administration (CDC/ACIP, 11/29/21)

ADULT COVID-19 VACCINE SCHEDULES & DOSES

Initial COVID-19 Vaccine

Pfizer-BioNTech
(0.3 mL x 2 doses 21 days apart)

≥ 28 days

Additional Dose

Pfizer-BioNTech: 0.3 mL
Mod – severe
immunocompromised

Booster Dose

Can mix & match booster dose in eligible patients following completion of primary vaccination with a different available COVID-19 vaccine

Pfizer-BioNTech: 0.3 mL

≥ 65 yo
≥ 18 yo and reside in long-term care setting
≥ 18 yo w/ underlying medical conditions
≥ 18 yo who work or live in high-risk settings

Moderna
(0.5 mL x 2 doses 28 days apart)

≥ 28 days

Moderna: 0.5 mL
Mod – severe
immunocompromised

BOOSTER

≥ 6 months

Moderna: 0.25 mL

≥ 65 yo
≥ 18 yo and reside in long-term care setting
≥ 18 yo w/ underlying medical conditions
≥ 18 yo who work or live in high-risk settings

Janssen (J&J)
(0.5 mL single dose)

BOOSTER

≥ 2 months

Janssen (J&J): 0.5 mL
≥ 18 yo

Last Update: 10/26/21

Source: Monica Mahoney, Pharm.D. <https://twitter.com/mmPharmD/status/1452997979401560075> [Accessed 12/8/21]