

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.

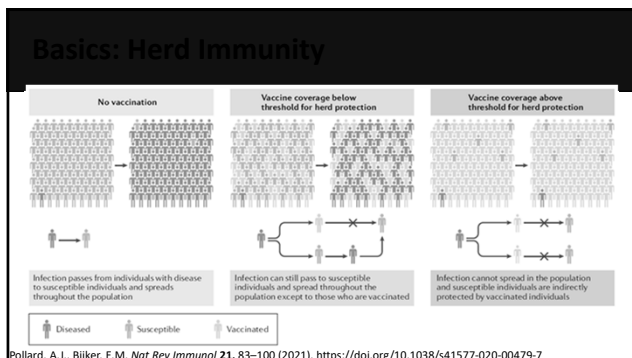
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Basics of Immunology & Vaccines

- **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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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

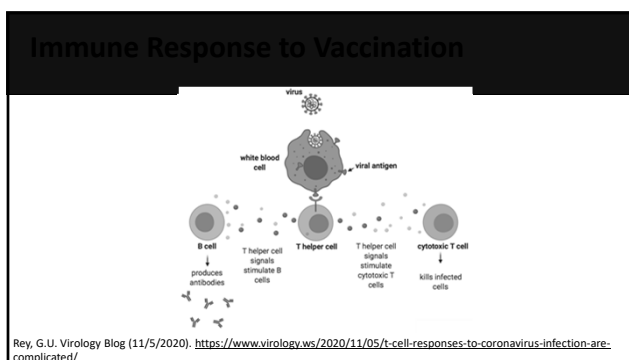
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Immune Response to Vaccination

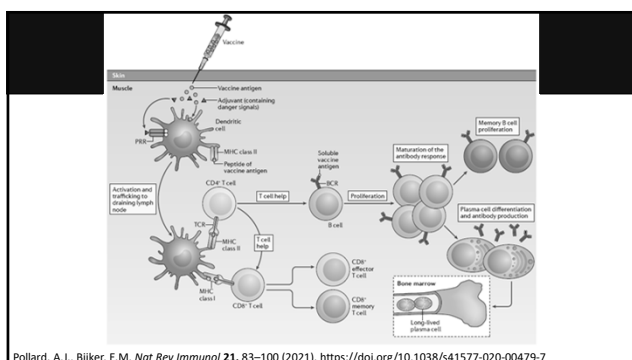
- Dendritic cells** – activation, antigen presentation
- B cells** – antibody production
- T cells** – cellular immunity, immune memory

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

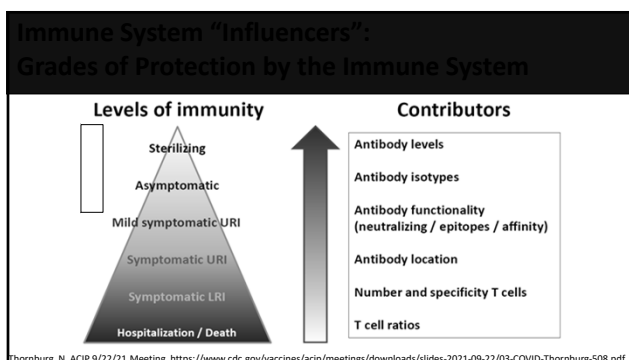
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Contributors to Protection

- **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>

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“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

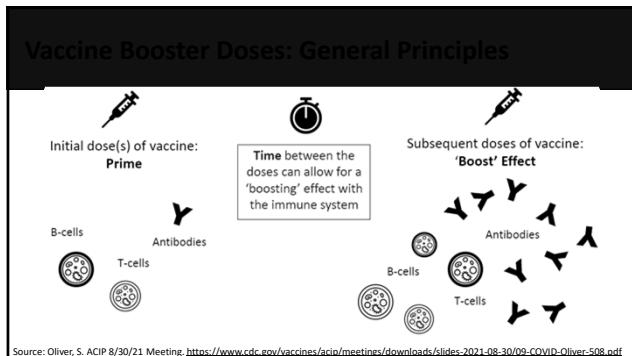
Pollard, A.J., Bijker, E.M. *Nat Rev Immunol* **21**, 83–100 (2021). <https://doi.org/10.1038/s41577-020-00479-7>

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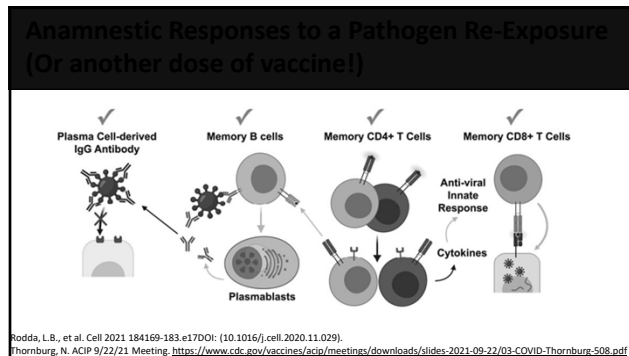
“Suboptimal” Response to an Initial Vaccination Series: Short incubation-period infection

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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- ### 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**)

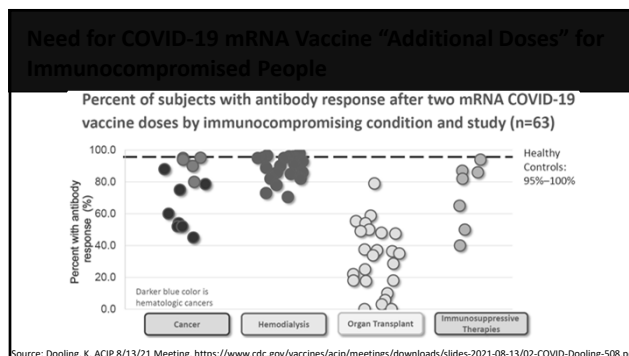
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- ### Vaccine "Boosters" versus "Additional Doses"
- **Boosters:**
 - Response to the **primary series** of the vaccine is **sufficient**
 - Immunity wanes over time:
 - Declining antibody titers
 - Epidemiologic evidence of increased infections and/or 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>

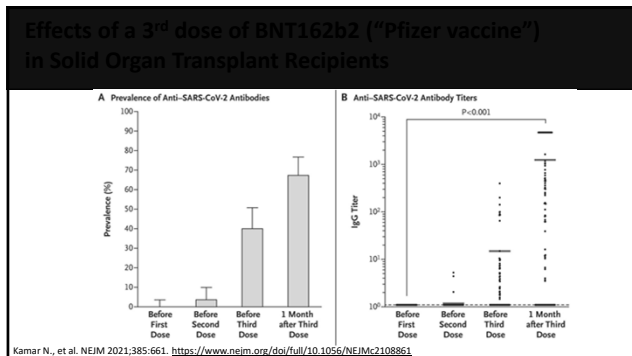
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- ### Factors that can influence Circulating Antibody Response to an Initial Vaccine Series
- Age (e.g., infants, elderly)
 - Immunosuppression (e.g., B cell vs. T cell, inherited vs. acquired vs. drug-induced)
 - Type of vaccine (e.g., live vs. inactivated)
 - 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>

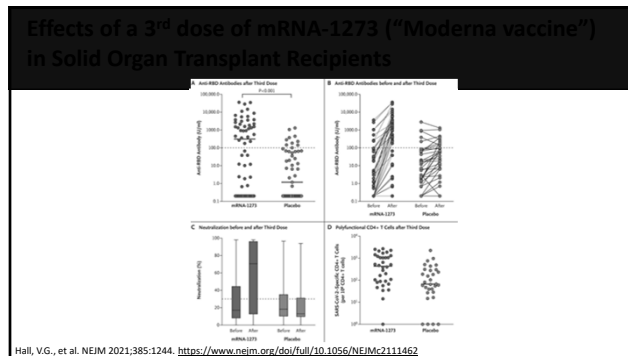
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Current Recommendations for "Additional Doses" of mRNA vaccines

- "...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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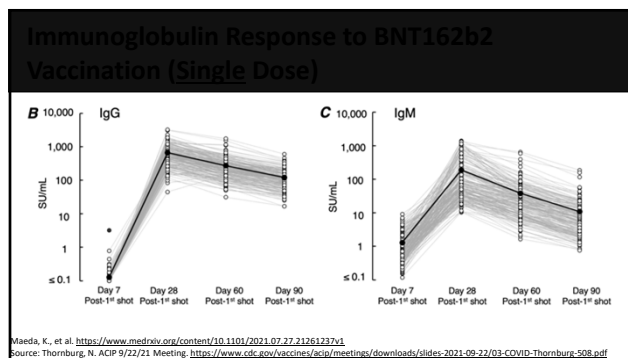
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Immunoglobulin (Antibody) Half-lives

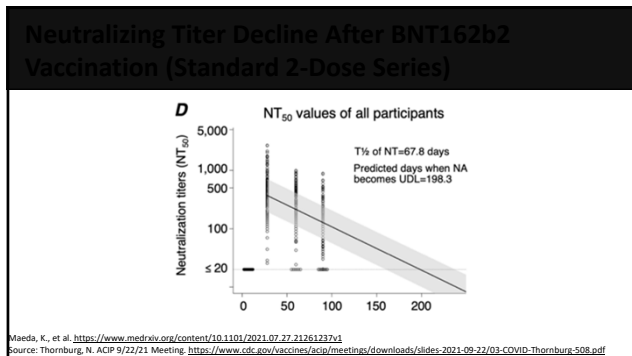
Immunoglobulin	Approximate half-life (days)
IgM	5-6
IgA	5-6
IgG1	21
IgG2	21
IgG3	7
IgG4	21

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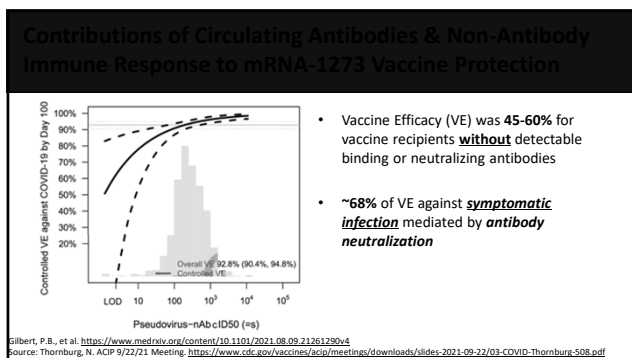
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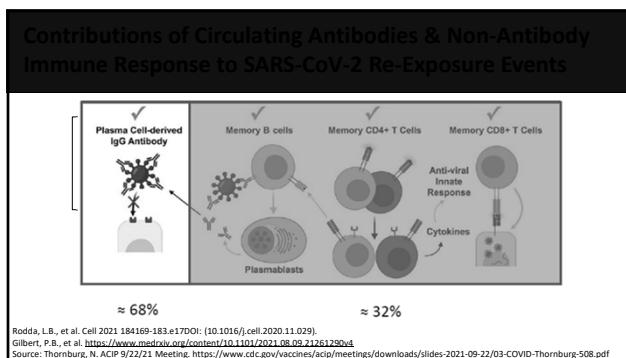
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Data on COVID-19 Vaccines: Antibody Levels and Anamnestic Responses

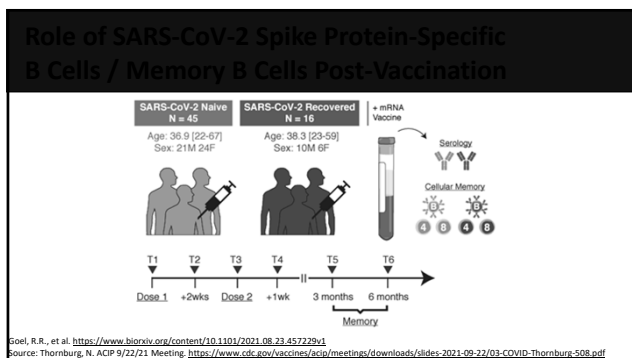
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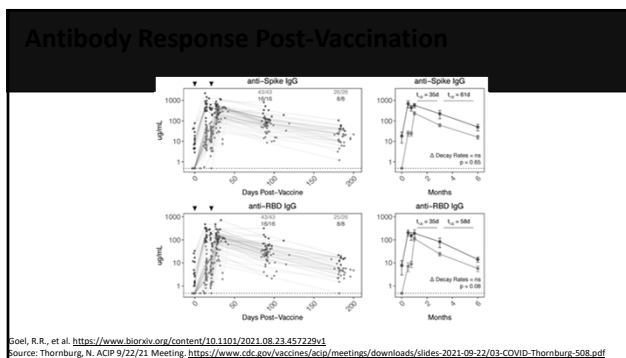
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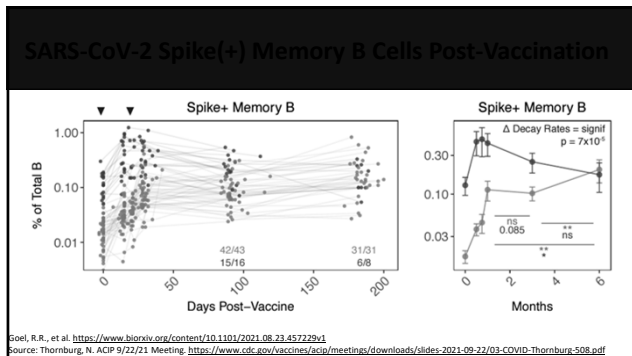
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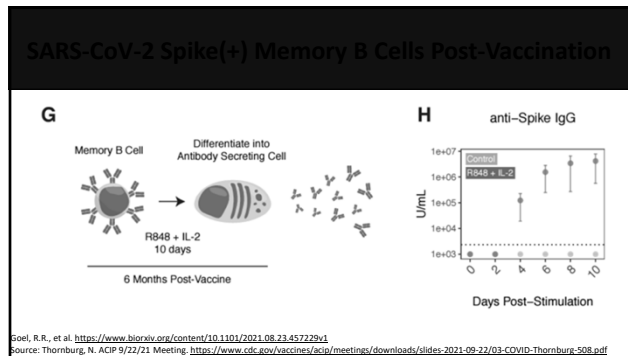
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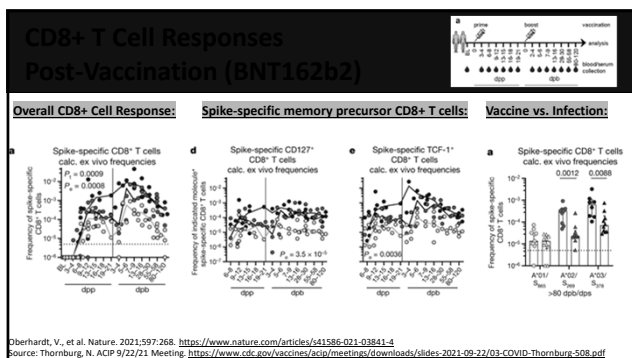
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Quick Knowledge & Learning Check!

- A 50 year old female (she/her) comes to your pharmacy. You know her well, as she frequently gets prescriptions for a variety of medications, including immunosuppressants (She had a kidney transplant approximately 5 years ago).
- You note that she completed her 2-dose primary series of Comirnaty ("Pfizer" vaccine) approximately 2 months ago.
- She has not gotten any additional vaccinations of any kind since that time.

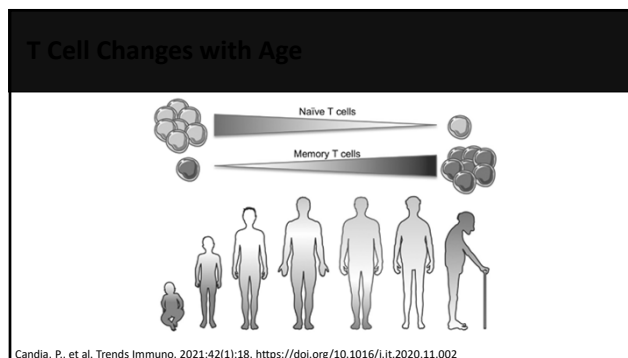
QUESTION: Should she receive a 3rd dose of COVID-19 Vaccine **at this time**?

- Yes
- No

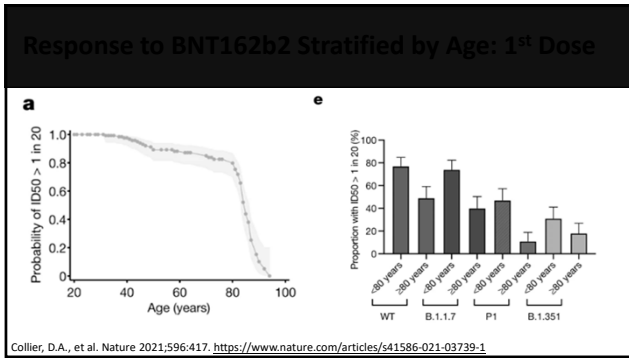
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Impact of Patient Age on COVID-19 Vaccine Response to Primary Series

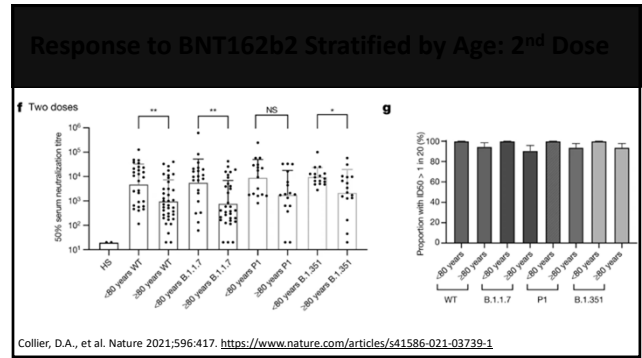
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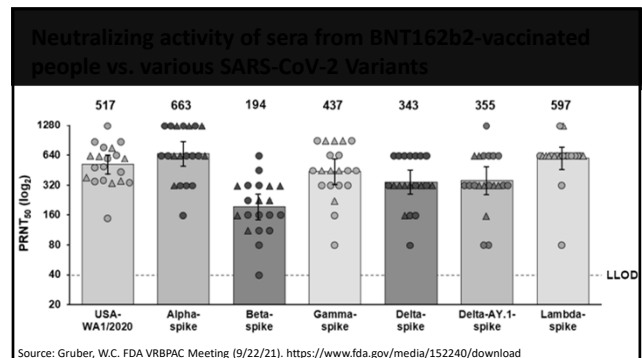


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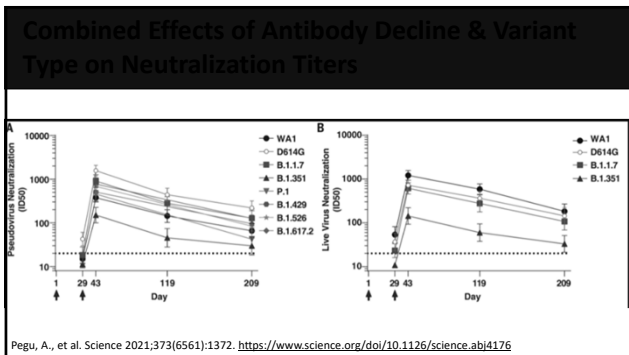
Data on COVID-19 Vaccines: Impact of SARS-CoV-2 Variants on Antibody Neutralizing Activity & Need for “Booster Doses”

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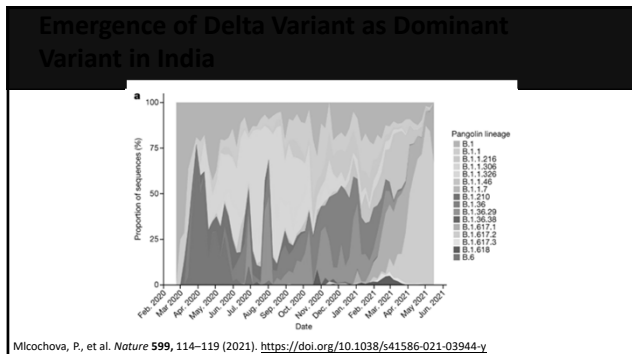


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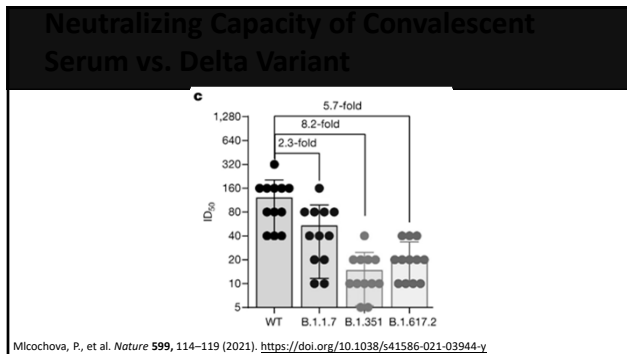
Delta Variant: What’s the Big Deal???

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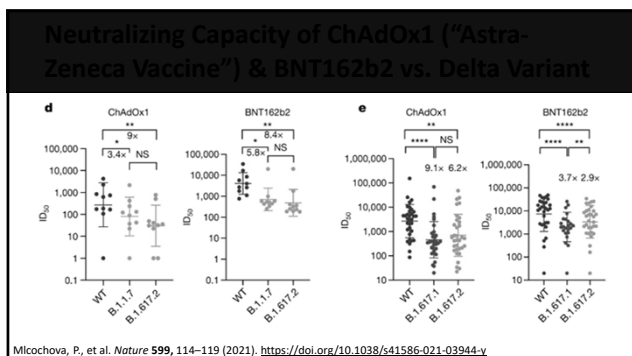
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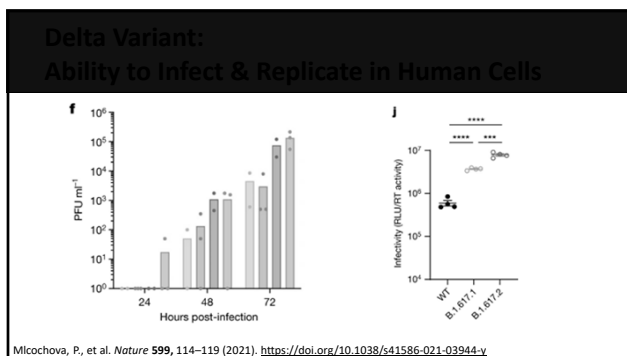
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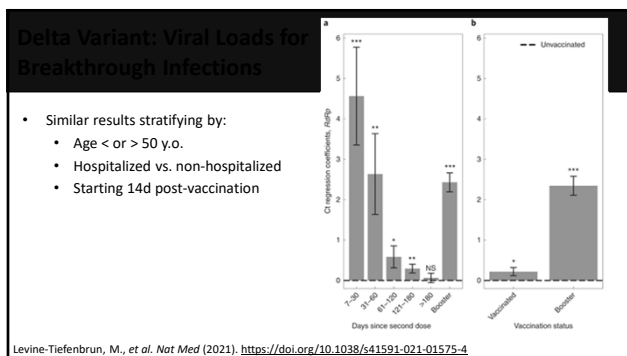
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Delta Variant: Viral Loads for Breakthrough Infections (Israel)

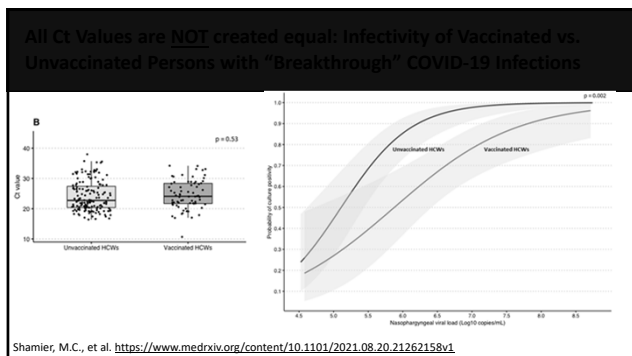
- Evaluated **Delta variant-caused breakthrough infections (BTIs)** in adults ≥ 20 y.o. in Israel (6/28/21 – 9/9/21):
 - 3,100 infections in unvaccinated people
 - 12,934 BTIs of two-dose-vaccinated (BNT162b2)
 - 519 BTIs of booster-vaccinated individuals
- Used **PCR cycle threshold value (“Ct” value)** 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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Quick Knowledge & Learning Check!

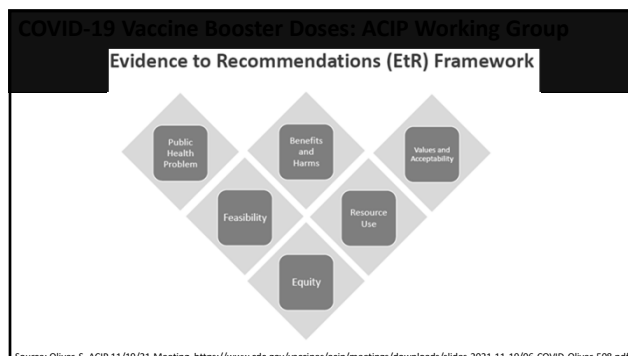
- Which of the following statements about the SARS-CoV-2 Delta Variant and/or COVID Vaccines is **FALSE**?
 - Vaccine-induced serum neutralizing activity is decreased vs. the Delta variant (compared to original SARS-CoV-2 virus)
 - The Delta variant appears to cause more rapid infections with higher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

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Let's Put it All Together:

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

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

Do we need them? Do they work?

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 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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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>

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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

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>

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

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

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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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>

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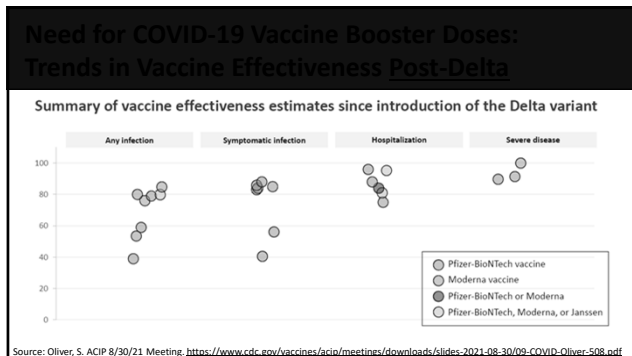
Need for COVID-19 Vaccine Booster Doses: Trends in Vaccine Effectiveness Pre-Delta vs. Delta

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>

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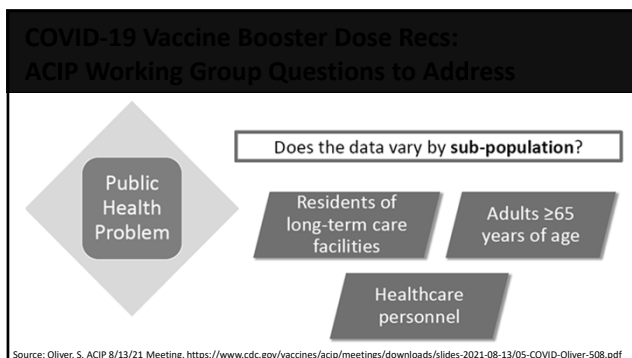


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Quick Knowledge & Learning Check!

- **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

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

LTCF residents, adults ≥65 years of age

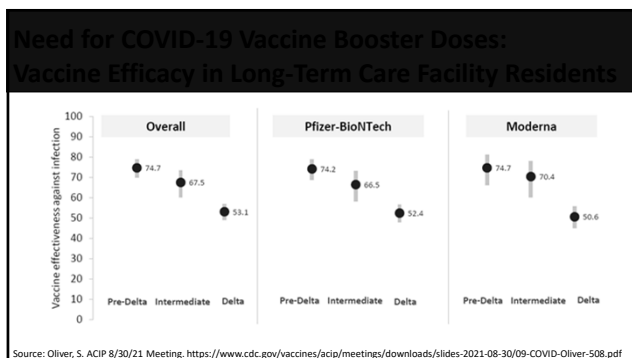
- Vaccinated in early phase of COVID-19 vaccine roll-out
- Needed special considerations for other vaccines (boosters, higher-dose vaccines)

Healthcare personnel

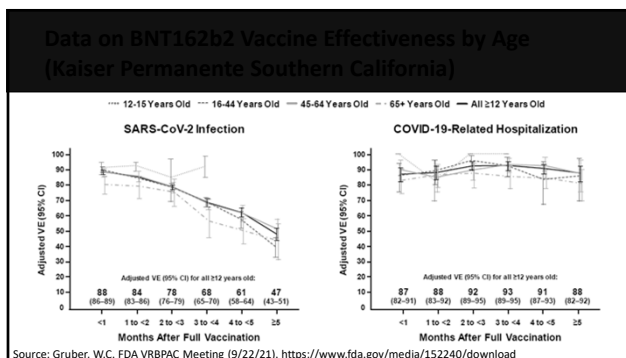
- Vaccinated in early phase of COVID-19 vaccine roll-out
- Continued exposure to SARS-CoV-2
- Additional considerations include continuity of healthcare systems
 - May have need to prevent asymptomatic or mild infections in healthcare personnel

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>

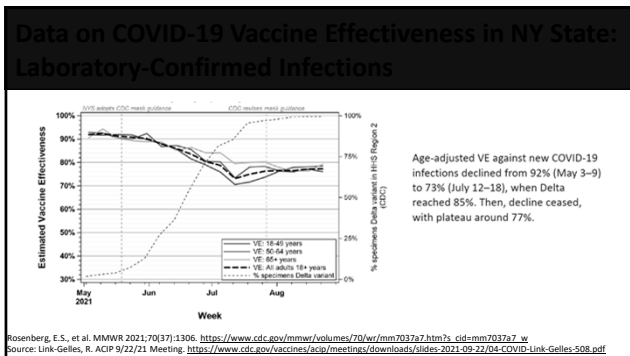
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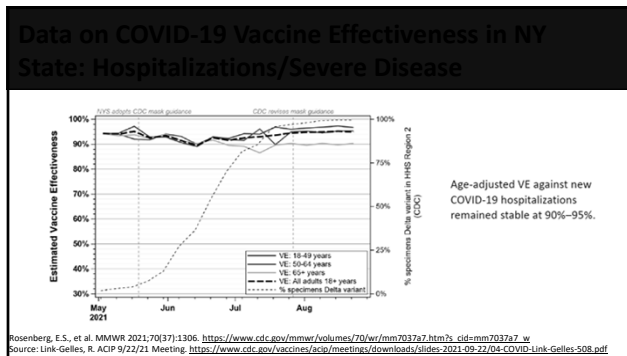
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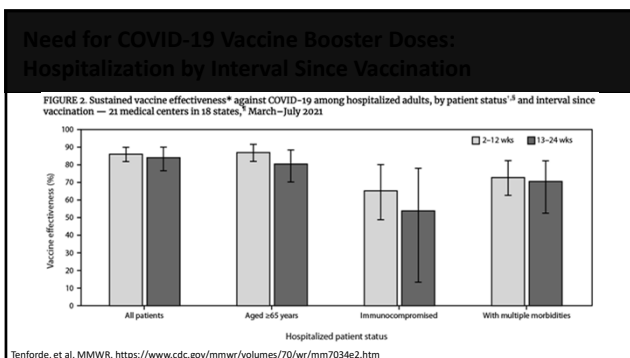
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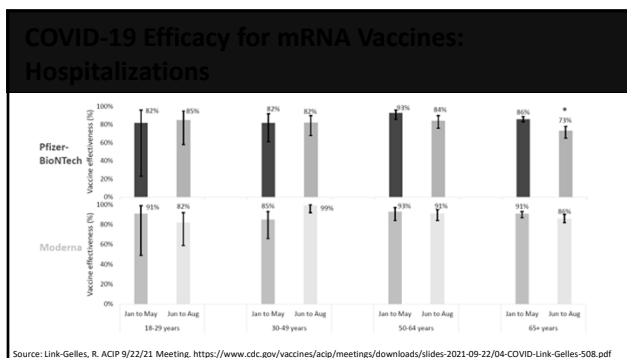
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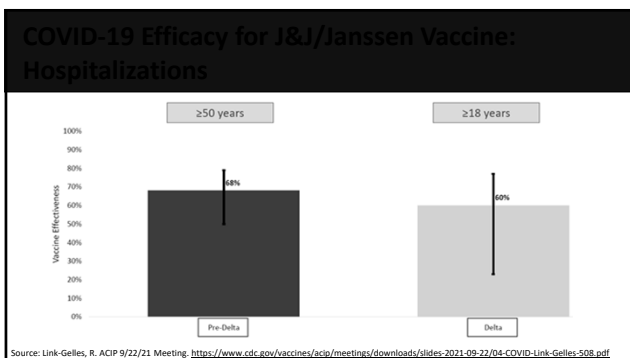
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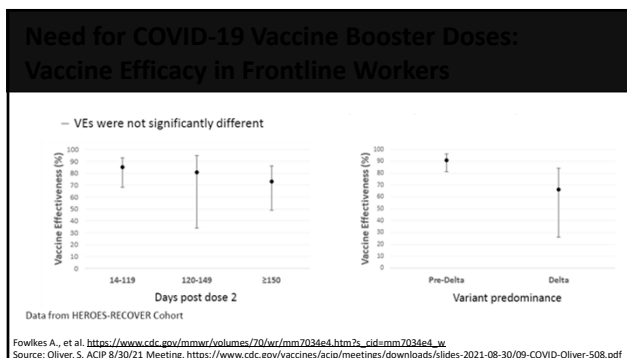
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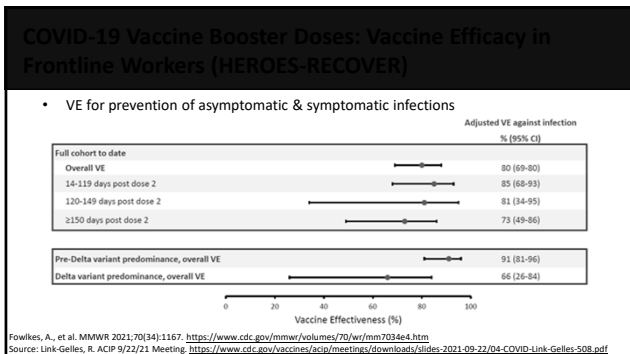
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Quick Knowledge & Learning Check!

- 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**?

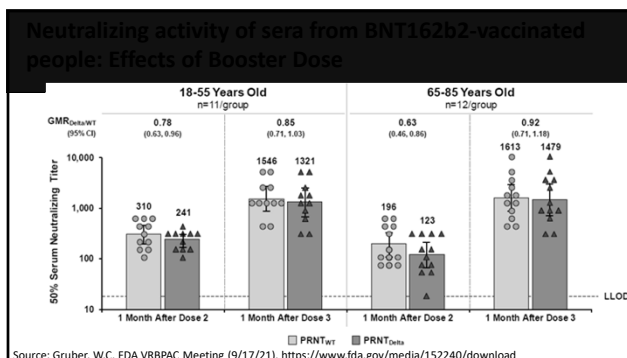
Do COVID-19 vaccines provide a **boost** in neutralizing antibody response?

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

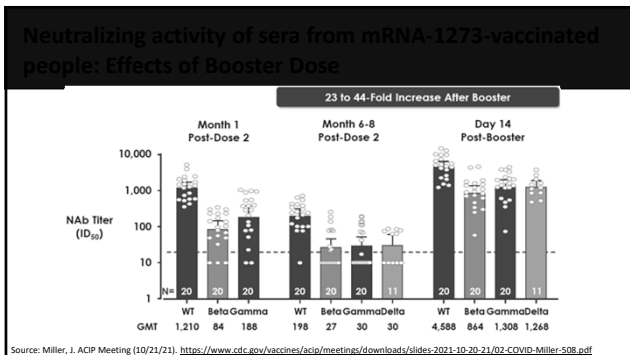
Benefits and Harms

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>

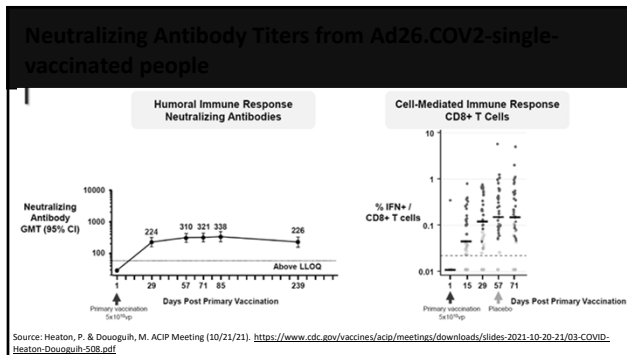
81



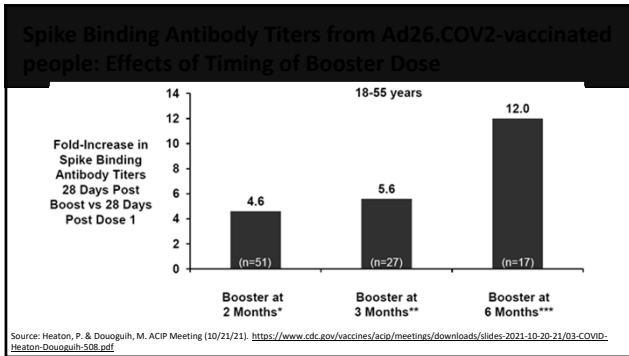
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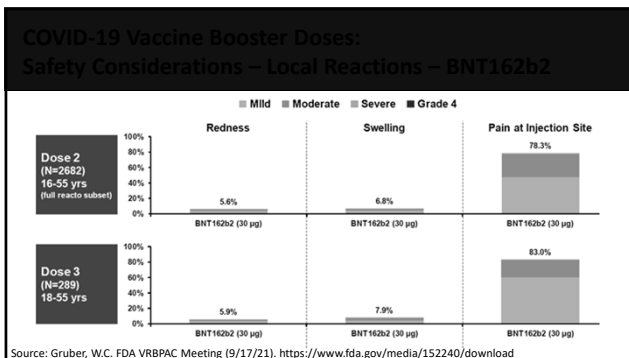
85

Quick Knowledge & Learning Check!

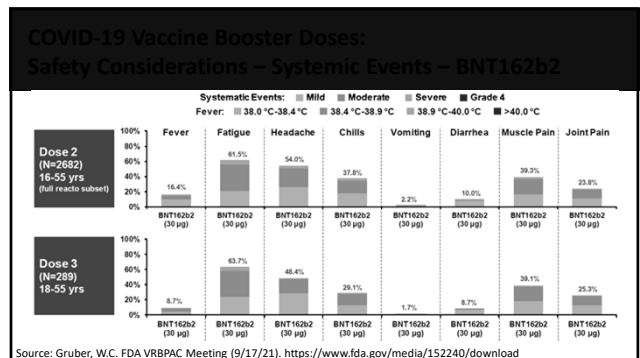
- TRUE or FALSE: The emergence of the Delta variant has resulted in significant declines in vaccine-associated protection from severe COVID-19 disease (hospitalization due to COVID-19 infection).

a) True
b) False

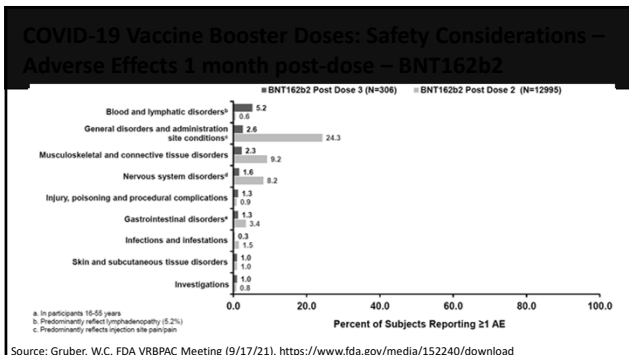
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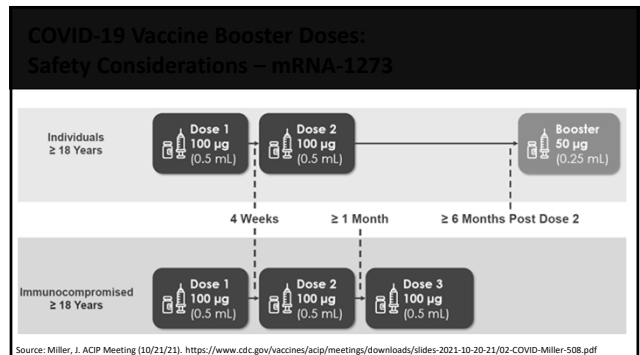
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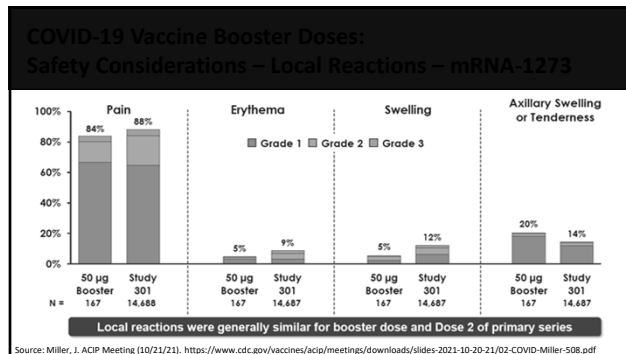
90

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

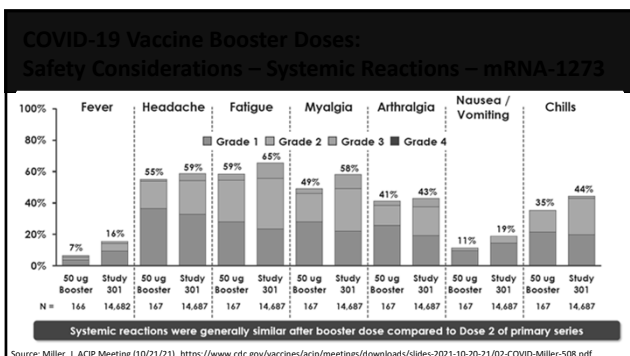
- Lower Booster Dose Rationale:**
 - Use lowest dose for optimal effect
 - Lower dose needed for reactivation of immune memory (anamnestic response)
 - Lower dose = more vaccine dose supplies

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>

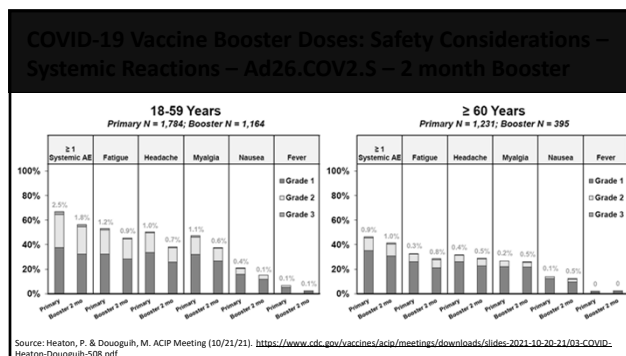
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COVID-19 Vaccine Booster Doses: Safety Considerations – AEs of Interest – Ad26.COVID.2.S – All Booster

Adverse Event of Interest	Within 28 Days of Primary Dose		Within 28 Days of Booster Dose	
	Ad26.COVID.2.S (N=15,705)	Placebo (N=15,588)	Ad26.COVID.2.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. & Douguilh, M. ACIP Meeting (10/21/21). <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/03-COVID-Heaton-Douguilh-508.pdf>

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COVID-19 Vaccine Booster Doses: Safety Considerations – Myocarditis

Myocarditis in Israel

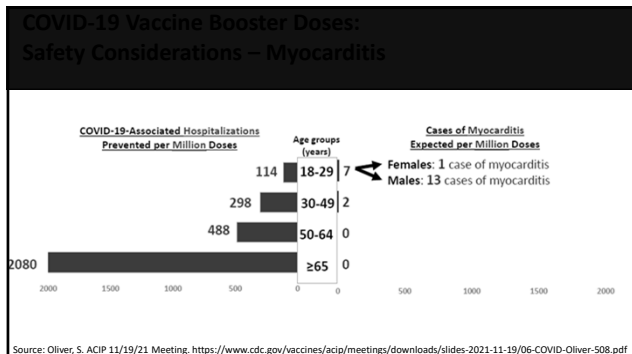
Reported after Pfizer-BioNTech COVID-19 vaccine, December 2020-October 10, 2021

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	279
	16-19	0	0.9	97,807
	20-24	0.4	2.5	141,910
	25-29	0	0.4	130,283
	≥30	0.1	0.3	1,542,142
Males	12-15	0.5	6.6	292
	16-19	1.2	16.1	96,238
	20-24	2.2	10.3	139,015
	25-29	1.2	8.4	133,650
	≥30	0.5	1.7	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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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>

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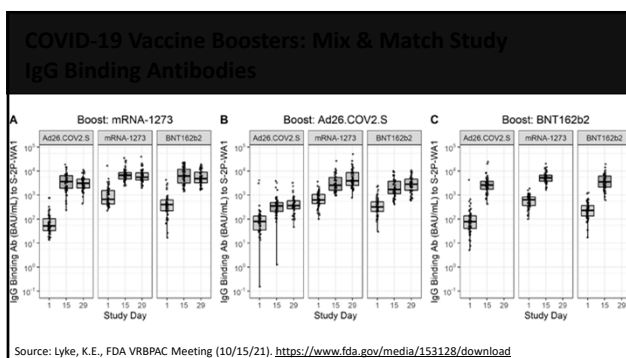
COVID-19 Vaccine Boosters: Mix & Match?

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

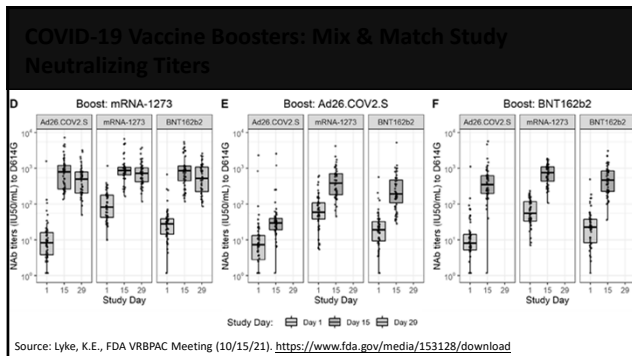
Study Visits: Days 1, 8 (call), 15, 29, Months 3, 6, 12

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

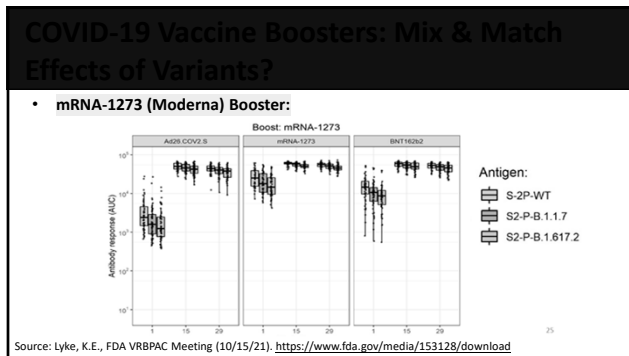
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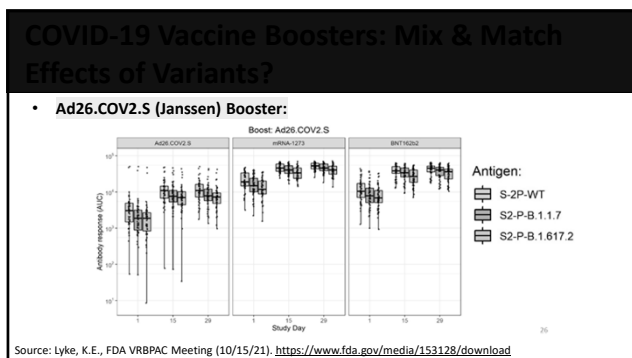
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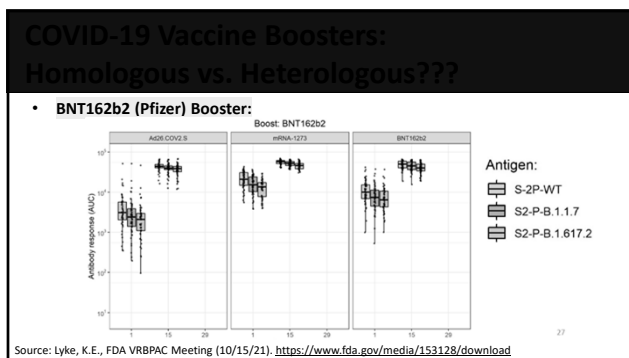
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COVID-19 Vaccine Boosters: Mix & Match

- 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>

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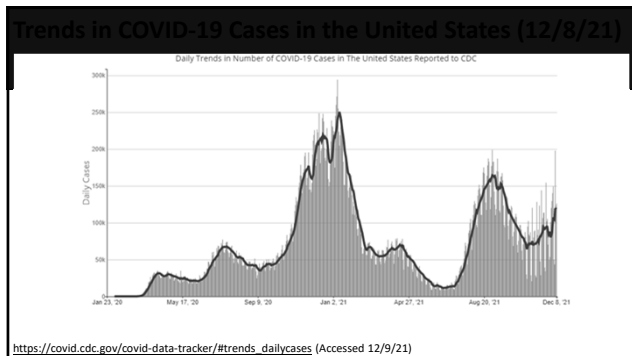
COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address

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

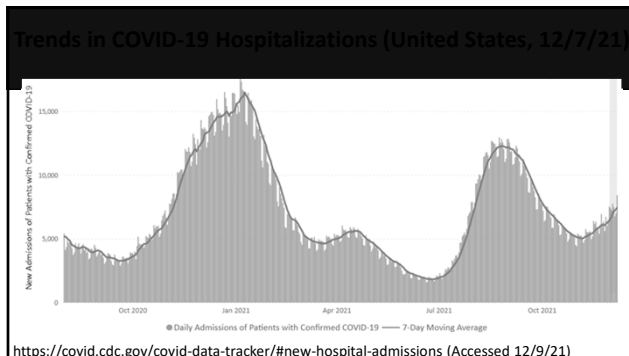
Benefits and Harms

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>

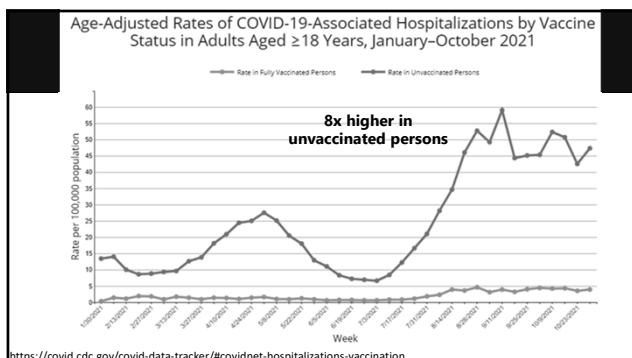
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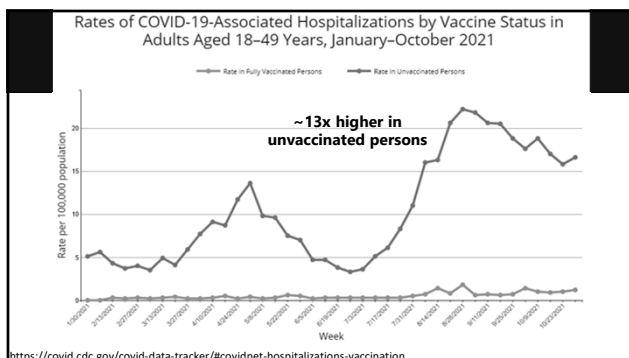
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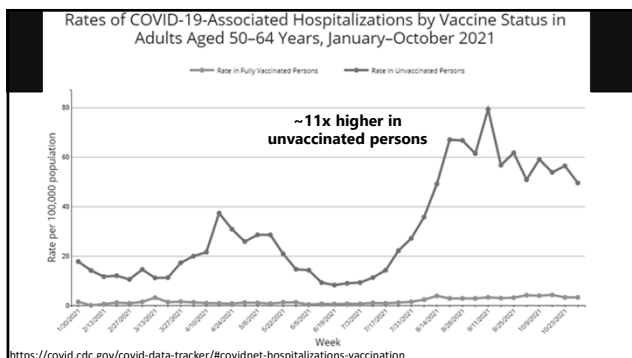
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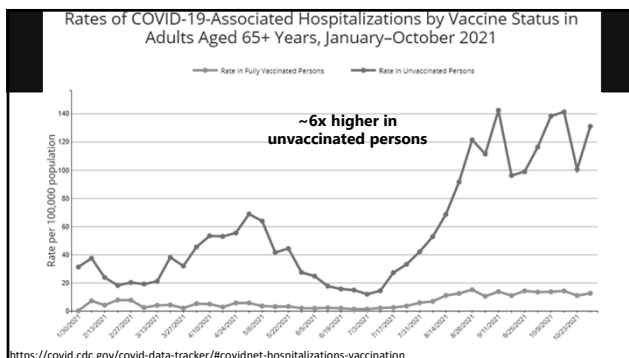
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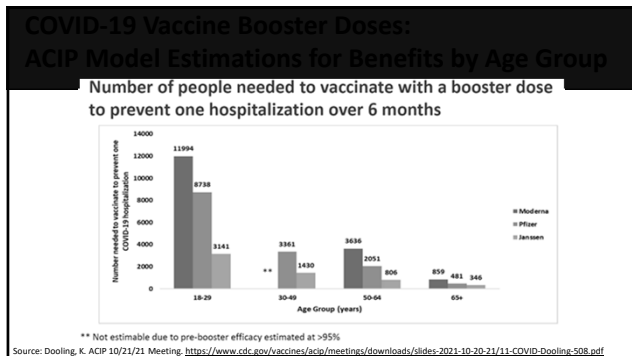
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COVID-19 Vaccine Booster Dose Recs: ACIP Working Group Questions to Address

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>

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Clinical Outcome Data from Ad26.COVS2-vaccinated people: Effects of Booster Dose

Country	Post-dose	Study Day	Symptomatic COVID-19 Ad26.COVS2.S vs Placebo	VE (95% CI)
United States	3001: Post-dose 1	Day > 28		70% (61, 77)
	3009: Post-booster	Day > 71		94% (59, 100)
Global* (All)	3001: Post-dose 1	Day > 28		53% (47, 58)
	3009: Post-booster	Day > 71		75% (55, 87)

VE% (95% CI)

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

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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 (≥ 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)

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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:**

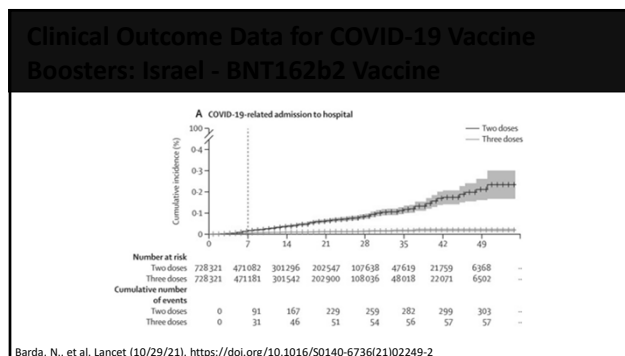
	Vaccinated with two doses	Vaccinated with three doses	1-risk ratio (95% CI)	Risk difference per 100,000 individuals (95% CI)
Admission to hospital	235	200.8	0.85 (0.80-0.91)	-206.4 (-245.5 - -167.3)
Severe disease	157	158.9	1.01 (0.95-1.07)	16.0 (-9.3 - 41.3)
Death	44	35.9	0.81 (0.69-0.95)	-24.8 (-31.0 - -18.5)

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

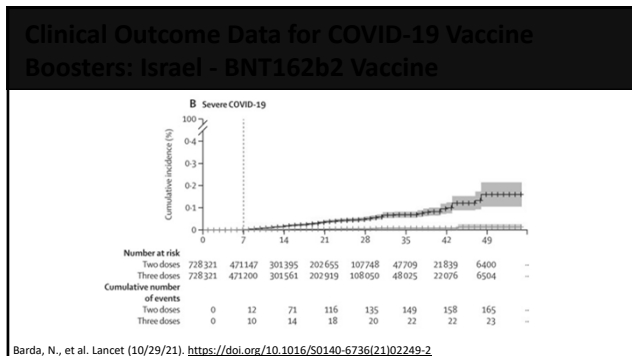
Estimates were obtained using the Kaplan-Meier estimator starting from day 7 after receipt of the third dose, in those who received it.

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)

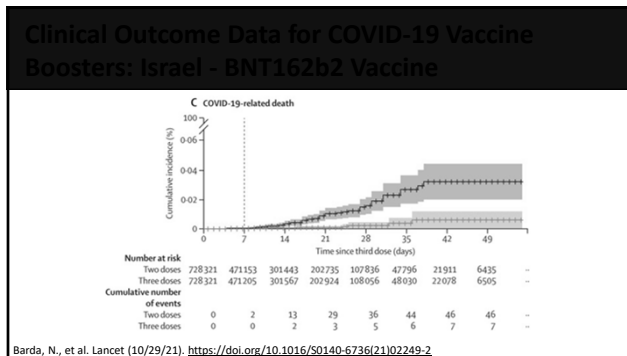
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Effects of COVID-19 Vaccine Boosters on Mortality: Israel - BNT162b2 Vaccine

- 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>

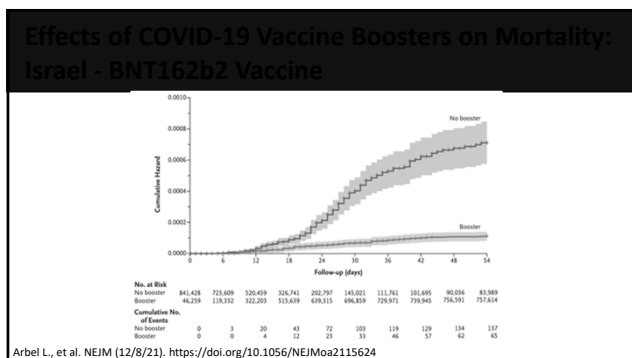
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Effects of COVID-19 Vaccine Boosters on Mortality: Israel - BNT162b2 Vaccine

- **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>

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But What About OMICRON

????????????

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12/10/21

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

By SARAH MILLER
Source: 12/10/21 07:07



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

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

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

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

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

<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biotech-provide-update-omicron-variant> (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-biotech-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/2021/12/10/...

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

BK Titiraji #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)

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

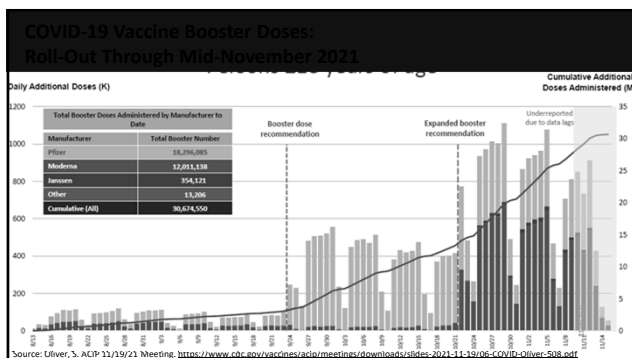
- **Top priority** should be **continued vaccination of unvaccinated individuals**
- Balance of benefits and risks **varies by age**
 - Older adults have the clearest benefit/risk balance
 - Myocarditis data after booster doses reassuring to date, continue to closely monitor
 - Increases in COVID-19 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>

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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>

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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	IF YOU RECEIVED Johnson & Johnson's Janssen
Who should get a booster: Everyone 18 years or older	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.	When to get a booster: At least 2 months after completing your primary COVID-19 vaccination.
Which booster should you get? <u>Any of the COVID-19 vaccines</u> authorized in the United States.	Which booster should you get? <u>Any of the COVID-19 vaccines</u> authorized in the United States.

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

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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 #1:** Is he currently eligible to receive a booster dose?
 - Yes
 - 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?
 - Janssen/J&J
 - Moderna
 - Pfizer
 - Any of the above...whichever one he prefers

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Summary

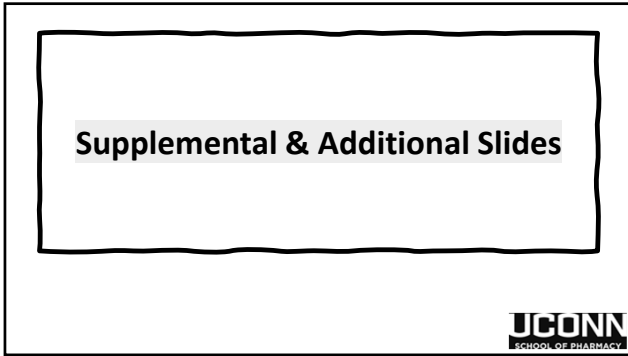
- Vaccine Boosters are **NOT** a new concept!!!
- The need for vaccine boosters does not mean "***tHe VaCciNeS dOn'T wOrk***"
- Vaccine efficacy vs. COVID-19 and the "optimal" administration series is a **continually-evolving** research area
 - Apparent now that the mRNA vaccines are best described as "**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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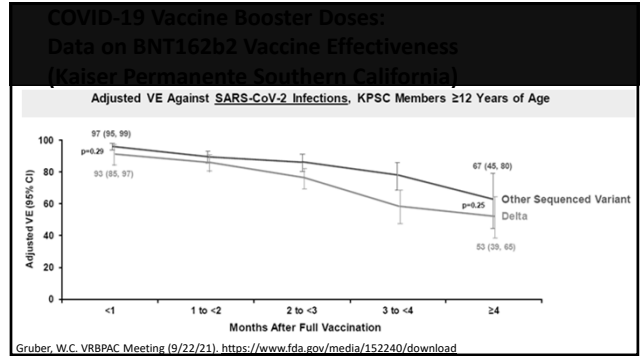
Thank you!!!

- Questions?

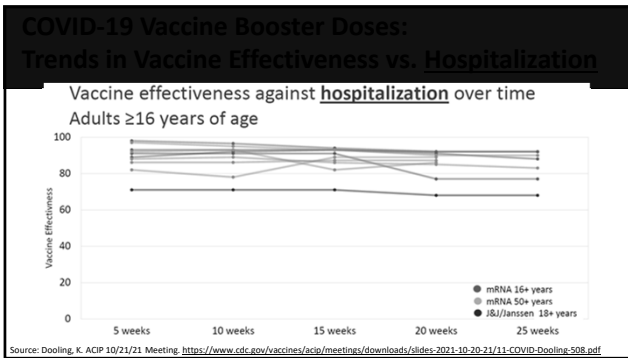
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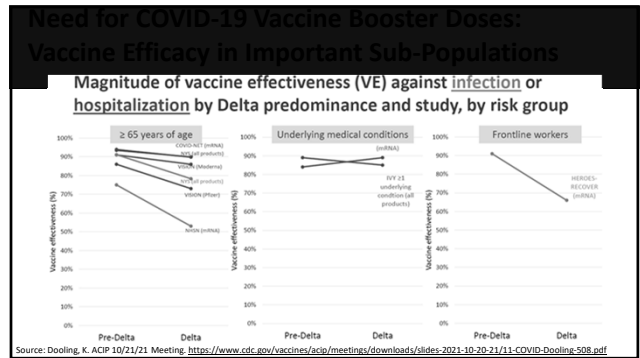
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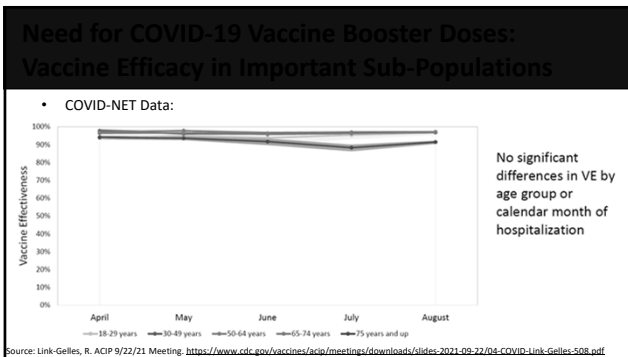
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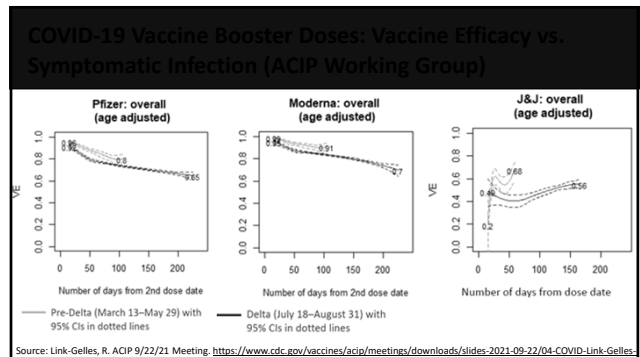
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Subgroup Analyses (Hospitalization) for COVID-19 Vaccine Boosters: Israel - Pfizer BNT162b2 Vaccine

	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	Events	Risk per 100 000 individuals		
Admissions to hospital								
Sex								
Male	458 553	140	321.6	21	25.2	92% (85 to 97)	296.4 (177.2 to 443.7)	
Female	483 548	91	132.1	8	5.0	96% (93 to 99)	127.1 (82.2 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	463 660	14	13.4	2	1.5	89% (60 to 100)	11.9 (4.3 to 22.3)	
1-2	336 850	61	113.5	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)

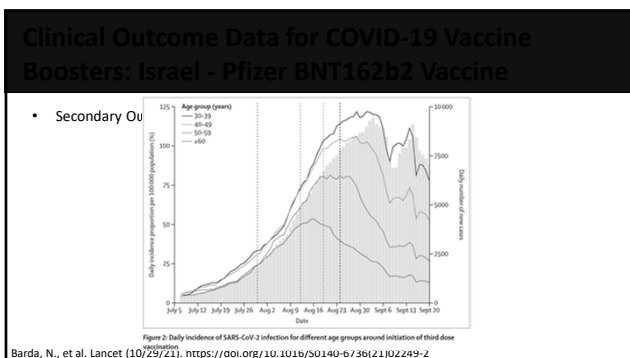
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Subgroup Analyses (Severe Disease) for COVID-19 Vaccine Boosters: Israel - Pfizer BNT162b2 Vaccine

	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 individuals	Events	Risk per 100 000 individuals	Events	Risk per 100 000 individuals		
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 6.4)	
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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COVID-19 Vaccine Booster Doses: Aug. 2021 ACIP Working Group/CDC Recommendations

Public Health Problem

- 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

Benefits and Harms

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

Source: 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

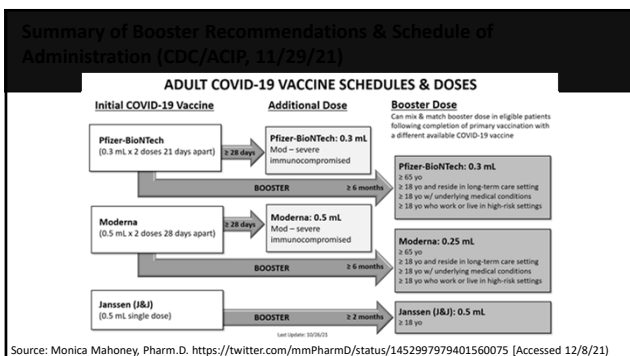
- Underlying medical conditions, particularly if not well controlled

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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