COVID-19: Update on Vaccines, Variants and Boosters

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Disclosures (past 2 years):
Member, NIH & Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels; Recommendations in this talk are my own and not necessarily those of the Panels

Acknowledgments: Arthur Kim, Jon Li, Annie Luetkemeyer, Jodian Pinkney, Renslow Sherer, Trip Gulick, Efe Airewele

Part One: Current COVID-19 Vaccines and Impact of Variants

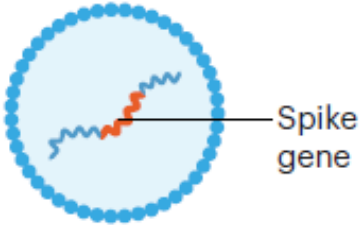
Part Two: COVID-19 Vaccines FAQs

Part Three: Future of COVID-19 Vaccines

COVID-19 Vaccines: Selected Platforms

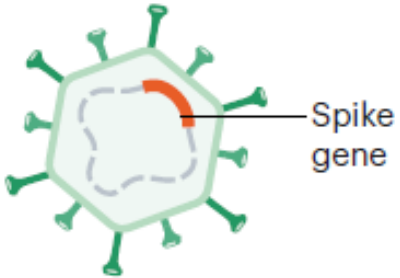
mRNA Vaccines

RNA vaccines consist of RNA encoding the spike protein and are typically packaged in LNPs



Viral Vector Vaccines

Replication-incompetent vector vaccines cannot propagate in the cells of the vaccinated individual but express the spike protein within them



Protein Subunit Vaccines

Recombinant spike-protein-based vaccines

Krammer Nature 2020;586:516-527.

Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3	
Nucleic acid (mRNA)	Moderna	Enrolled	Enrolled	FDA APPROVED
	Pfizer BioNTech	Enrolled	Enrolled	FDA APPROVED
Viral vector	AstraZeneca	Enrolled	Enrolled	
	Janssen; J&J	Enrolled	Enrolled	FDA EMERGENCY USE AUTHORIZATION (EUA GRANTED BY THE FDA)
	🇷🇺 Sputnik			
Protein subunit	Novavax	Enrolled	Enrolled	FDA EMERGENCY USE AUTHORIZATION Pending
	GSK, Sanofi	Enrolled	Enrolled	
Whole inactivated	🇨🇳 Coronavac	Enrolled	Enrolled	
	🇮🇳 Covaxin	Enrolled	Enrolled	

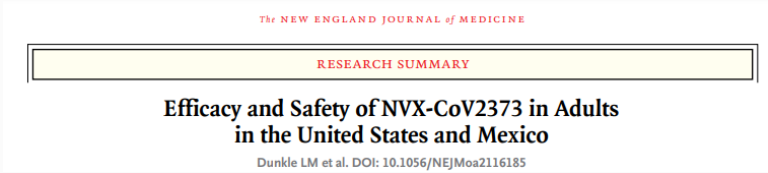
Phase 3 Trials: Efficacy Against Ancestral SARS CoV-2

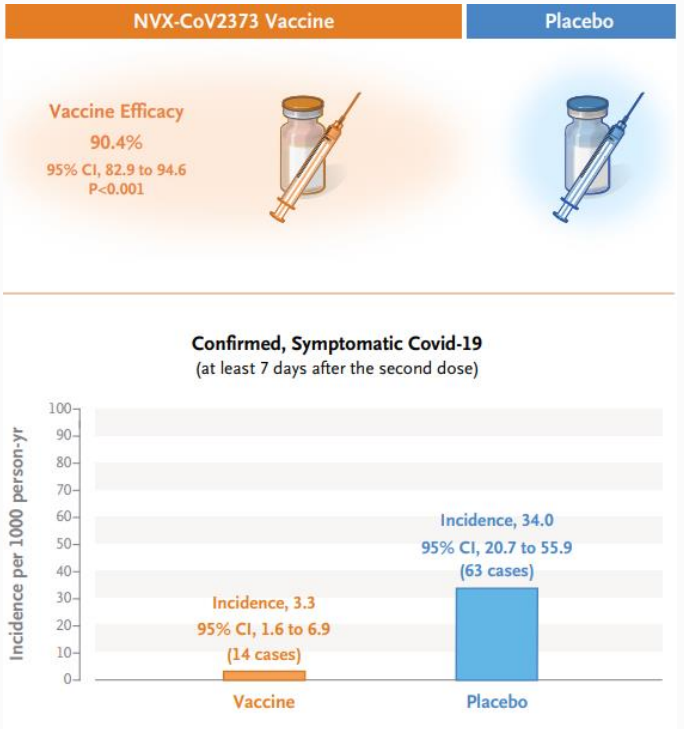
Vaccine	Type/ dose	Vaccine Efficacy (VE)	VE Against Severe Disease
BNT162b2 (*Pfizer-BioNTech*)	mRNA: spike protein/ 2 doses	95%	100%
mRNA-1273 (*Moderna*)	mRNA: spike protein/ 2 doses	95%	100%
Ad26.COV2.S *(Janssen)*	human adenovirus type 26/spike protein DNA 1 dose	66%	85% against severe/critical; 100% against hospitalization, death

Polack. NEJM. 2020;383:2603; Baden L et al NEJM, 2021; Doria-Rose N et al, NEJM, 2021; Sadoff J et al, NEJM, 2021

NVX-CoV2373

- Recombinant spike protein trimers assembled into nanoparticles with saponin-based adjuvant
- About 30,000 adults randomized 2:1 to receive 2 doses of vaccine or placebo, 21 days apart
- Vaccine efficacy, symptomatic COVID: 90%
- Vaccine efficacy, mod. to severe disease: 100%
- Predominant variant: alpha
- Cases of myocarditis/pericarditis reported
- Study in adolescents (12-17 years): 82% VE against delta
- June 7, 2022: FDA advisory panel recommended authorization





Dunkle LM, NEJM, 2022;
https://ir.novavax.com/2022-02-10-Novavax-Announces-Positive-Results-of-COVID-19-Vaccine-in-Pediatric-Population-of-PREVENT-19-Phase-3-Clinical-Trial

Relative immunogenicity

Immune responses over 6 mos. with Moderna, Pfizer, Janssen, Novavax vaccines

Neutralizing antibodies		Moderna ≈ Pfizer ≈ NVX > Janssen
CD4+ cell responses		100% of recipients of all 4 vaccines
Memory CD4+ cells		Moderna > Pfizer ≈ NVX > Janssen

mRNA vaccines: substantial declines in neutralizing Ab over 6 months; T cells smaller reductions; memory B cells increased

Zhang/Crotty, Cell, 2022

COVID-19 Vaccine Adverse Events

- **Most common:** pain at injection site, fatigue, myalgias
- **Axillary / cervical lymphadenopathy**
- **Myocarditis/pericarditis:** uncommon (~5-10/100,000)
  - Young males. Mild; most recover fully
- **Thrombosis with thrombocytopenia:** rare (~1/250,000), with Janssen
  - more common in women 30-49 years
  - cerebral venous sinus and splanchnic
- **Guillain-Barre syndrome:** rare (~1/125,000)
  - only with Janssen, not mRNA vaccines
- **Anaphylaxis:** very rare (~1/200,000)

Odds of being struck by lightning in a year: 1/500,000

A 72 year-old who signed up to test Moderna's Covid vaccine was struck by lightning 28 days after getting a dose of the real vaccine (Pictures: Getty/AP)

A volunteer who signed up for Moderna's coronavirus vaccine trial was struck by lightning 28 days after receiving the injection.

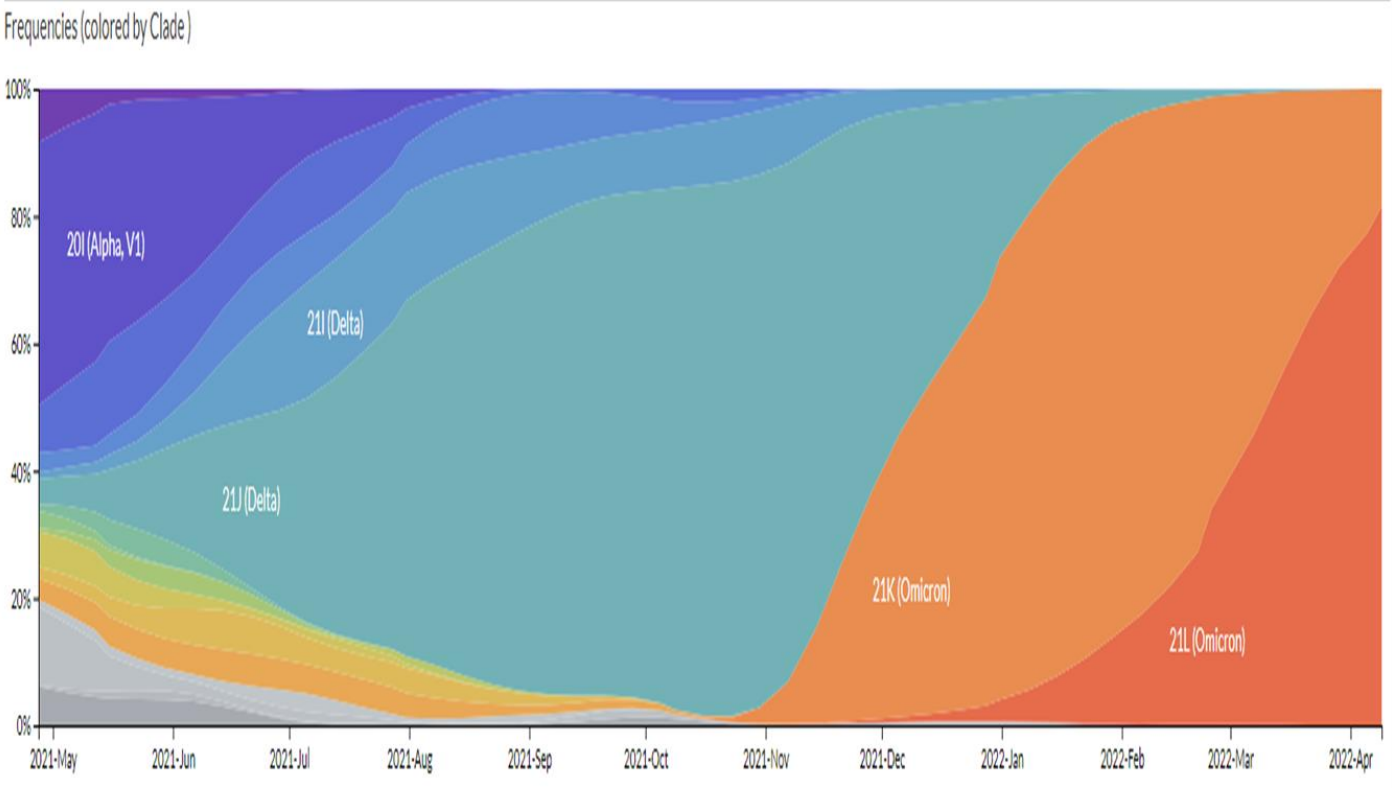
https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html

How have SARS CoV-2 Variants Affected Vaccine Efficacy?

How are SARS CoV-2 variants classified?

- US government SARS-CoV-2 Interagency Group defines several classes, including:
  - **Variants being monitored (VBM):** impact on medical countermeasures, severity, transmission but no longer detected or very low levels in the U.S.
    - **e.g. alpha, beta, gamma, delta…**
  - **Variant of concern (VOC):** evidence of ↑ transmissibility, ↑ severe disease, significant ↓ in neutralization by antibodies, ↓ effectiveness of treatments or vaccines, or diagnostic detection failures. e.g. **omicron**

Spread of variants: Alpha → Delta → Omicron



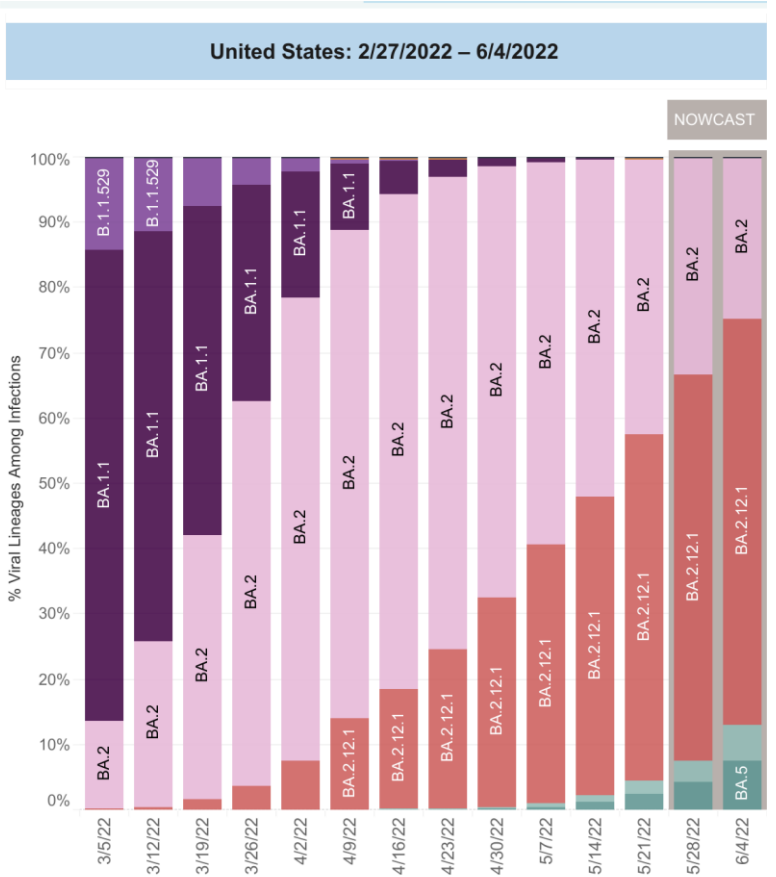
omicron 100%

BA-1 18%

BA-2 82%

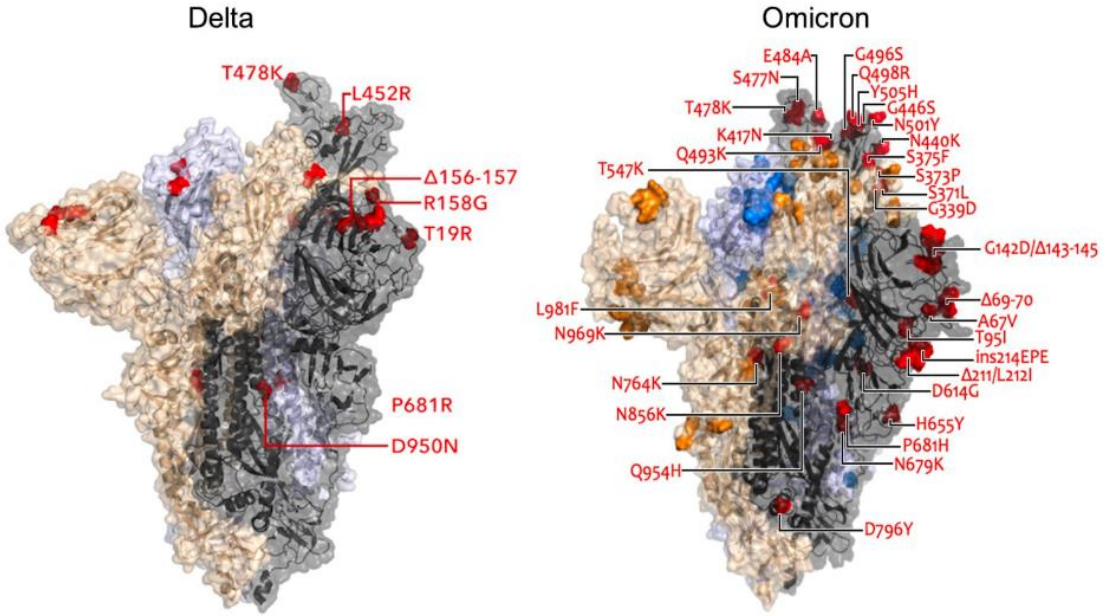
Spread of Omicron and its lineages

- Omicron subvariant BA.2 has replaced BA.1 throughout US
- Omicron sub-lineage BA.2.12.1 increasing in frequency throughout the US
- BA.4 and BA.5: now represent about 1 in 8 infections



https://covid.cdc.gov/covid-data-tracker/#variant-proportions

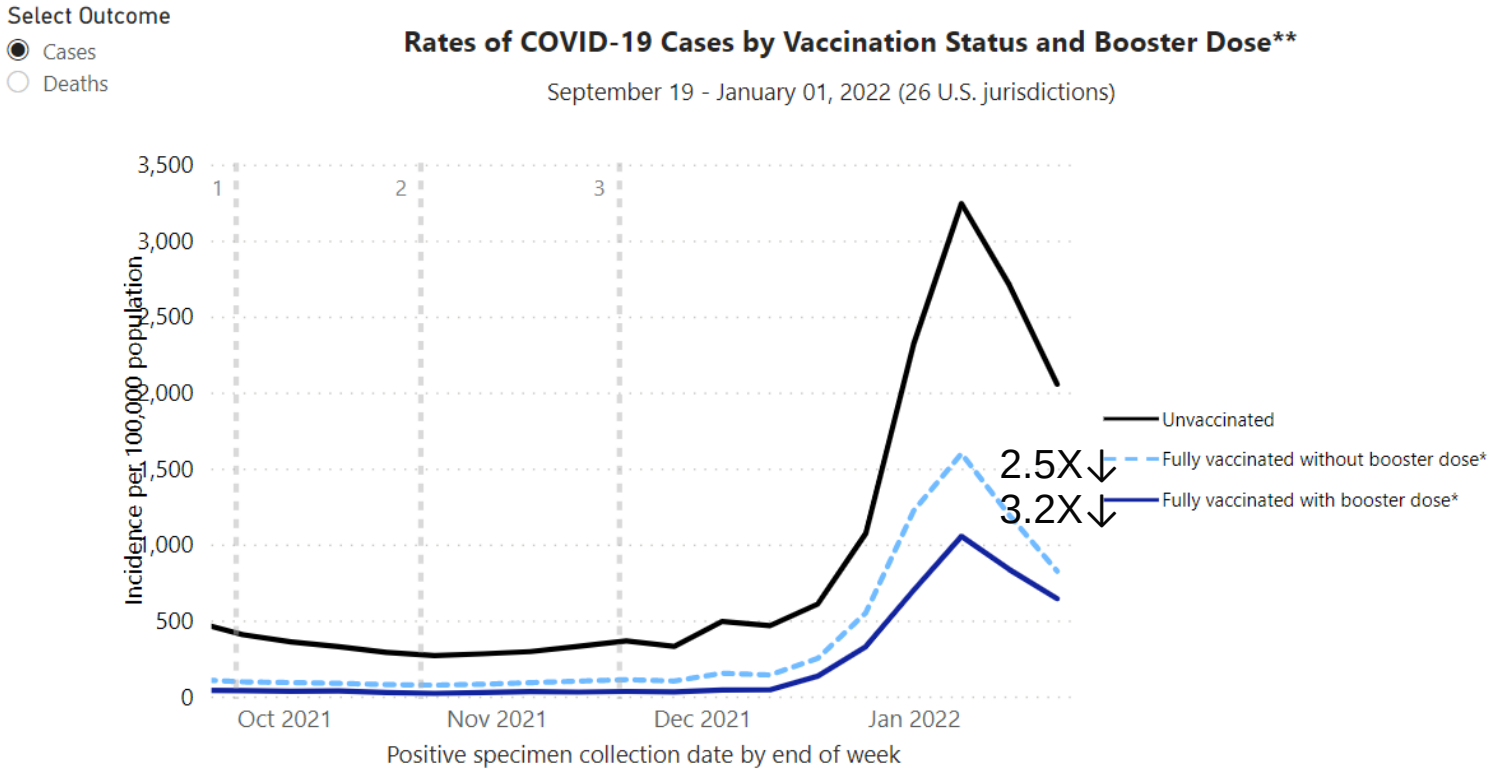
Omicron and Vaccine Efficacy



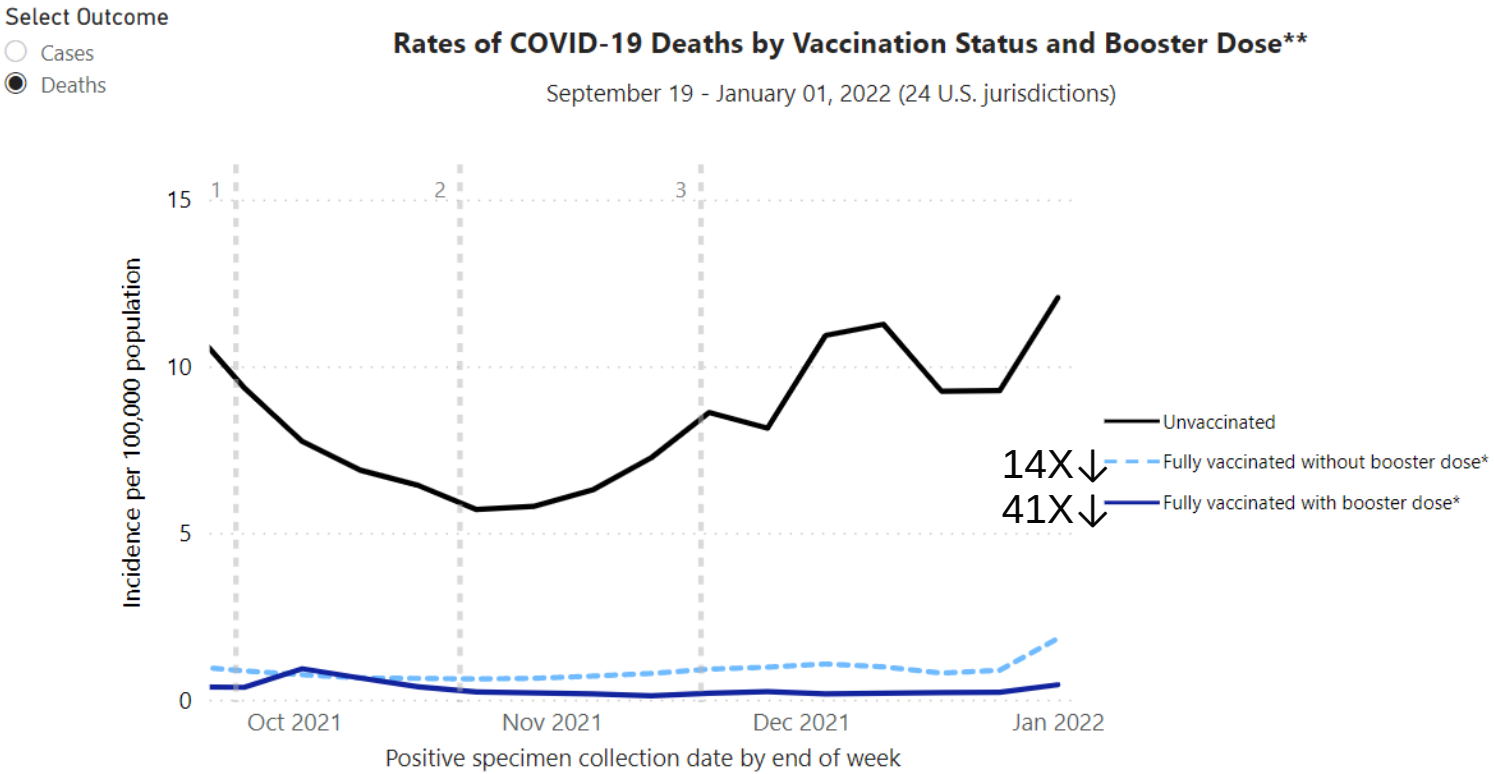
- >50 amino acid changes; ~30 in spike
- Decreased neutralization by vaccine-induced antibodies
- Decrease in vaccine efficacy against symptomatic COVID-19

Modified from slide from Dr. Arthur Kim

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



https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status



https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status

COVID-19 mRNA vaccines help protect against the most serious COVID-19 outcomes, even during Omicron*

Adults who received 3 doses of a COVID-19 vaccine were **94% less likely** **to be put on a ventilator or die** from COVID-19 compared with adults who were not vaccinated

Stay up to date with COVID-19 vaccines

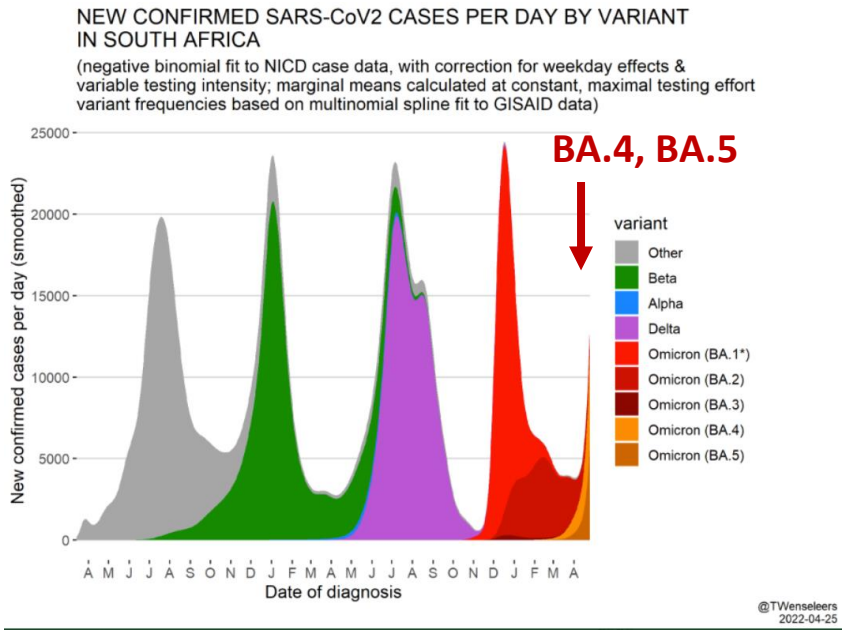
* Among adults aged 18 years and older hospitalized at 21 U.S. medical centers during March 11, 2021–January 24, 2022

bit.ly/MMWR7112e1

MMWR

What about Omicron Sublineages BA.4, BA.5?

- Emerging in South Africa; 1 in 8 infections in US
- Spike mutations (L452R, F486V, R493Q)
- Appear to be more transmissible than BA.2
- BA.4 and BA.5 may partially evade antibodies elicited by BA.1 infection but may still be neutralized by antibodies elicited by vaccine + BA.1 infection (hybrid immunity)



Khan K. https://www.medrxiv.org/content/10.1101/2022.04.29.22274477v1.full.pdf
Cao, Y, https://www.biorxiv.org/content/10.1101/2022.04.30.489997v1.full.pdf
https://covid.cdc.gov/covid-data-tracker/#variant-proportions

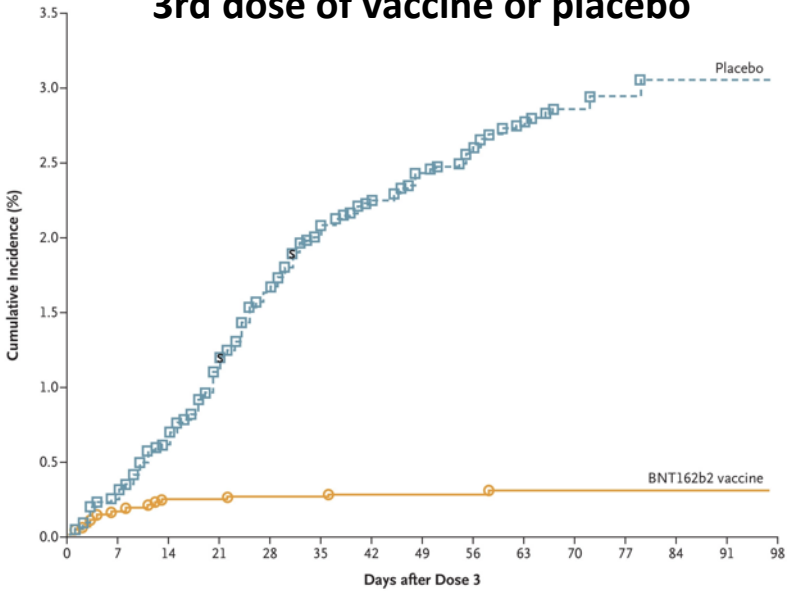
Part 2: COVID-19 Vaccines FAQ

- What are current recommendations for booster doses?
- How should we best protect immunocompromised people?
- What about tixagevimab/cilgavimab for pre-exposure prophylaxis?
- How soon after receiving anti-SARS CoV-2 monoclonal antibodies should a person receive a vaccine?
- What should be done for a person who received a COVID-19 vaccine authorized by WHO but not FDA

What is the Evidence that Vaccine Efficacy against Covid Wanes after Two Doses?

- Participants in original Pfizer vaccine trial ≥6 months after 2nd dose randomized to 3rd dose (n=5081) or placebo (n=5044)
- Delta was predominant variant
- Vaccine efficacy for booster: 95%
- Only 2 participants in placebo group and 0 in 3rd dose group developed severe Covid

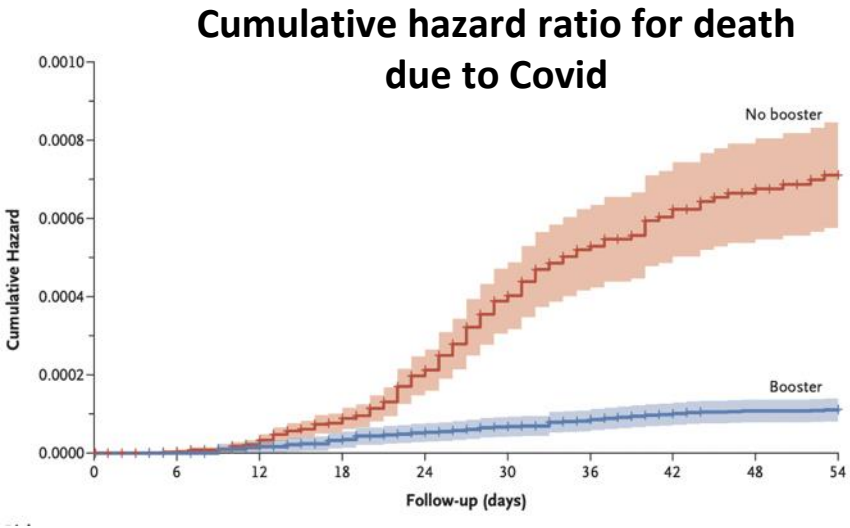
Cumulative incidence of Covid after 3rd dose of vaccine or placebo



Moreira ED, NEJM, 2022

What is Evidence that 3rd dose Protects Against Severe Covid or Death?

- Observational studies during Delta surge
- Israeli Ministry of Health:
  - >= age 60, > 5 mo. from 2nd dose
  - Severe Covid about 20-fold lower in those who received 3rd vaccine dose
- Clalit Health Services study:
  - > age 50, > 5 mo. from 2nd dose
  - 90% lower mortality with 3rd dose

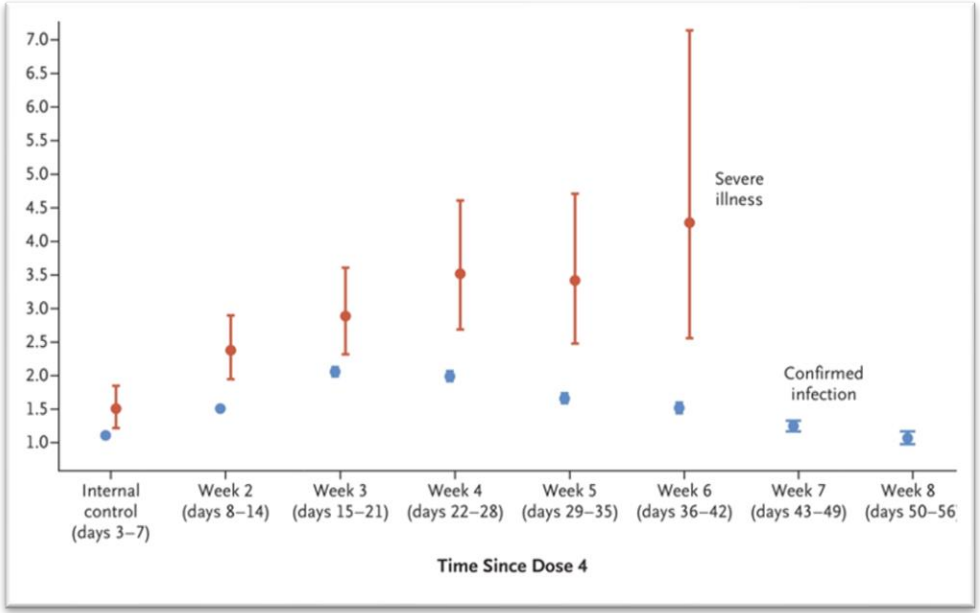


Bar-On YM et al, NEJM, 2021; Arbel, NEJM, 2021

What about 4th vaccine dose?

- Observational study during Omicron surge: comparing 4th dose to 3rd dose
- Israeli Ministry of Health (age >=60):
  - Severe Covid: 2.3 to 3.5-fold lower in those who had 4th dose (out to at least 6 weeks)
  - Infection about 2-fold lower in those who received 4th dose, but protection wanes

Adjusted rate ratio (3-dose:4-dose)

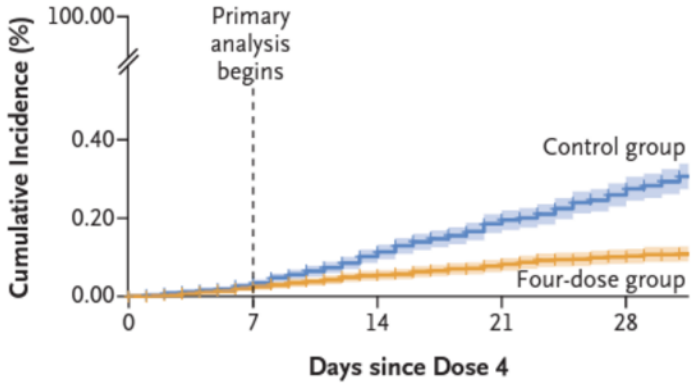


Bar-On YM et al, NEJM, 2022; Arbel, NEJM, 2022

What about 4th vaccine dose?

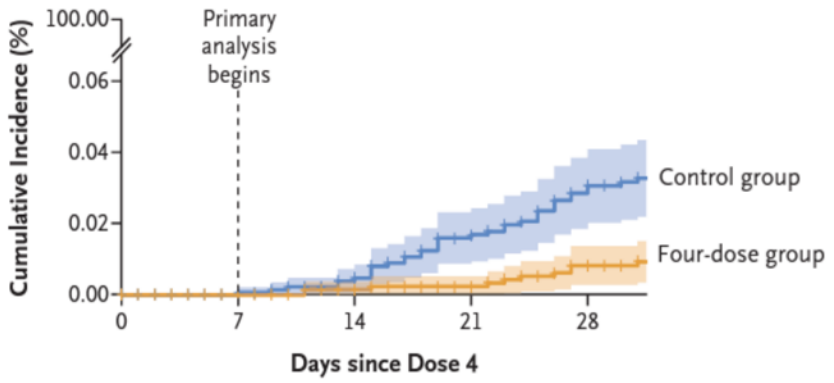
- Clalit Health Services study: Compared outcomes among those age >= 60 years who had received 4th dose vs those who had received 3rd dose at least 4 months earlier

COVID-19-Related Hospitalization



Day 14 to 30 Relative VE: 72% (95% CI: 63% – 79%)

Death from COVID-19



Day 14 to 30 Relative VE: 76% (95% CI: 48% – 91%)

Magen O, NEJM, 2022

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

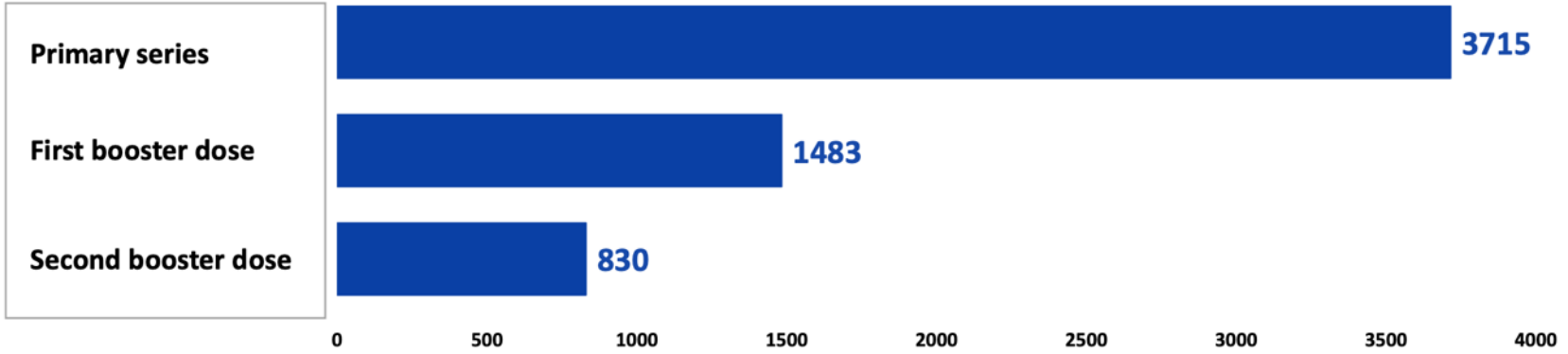
Scenario:

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

For every million series completed

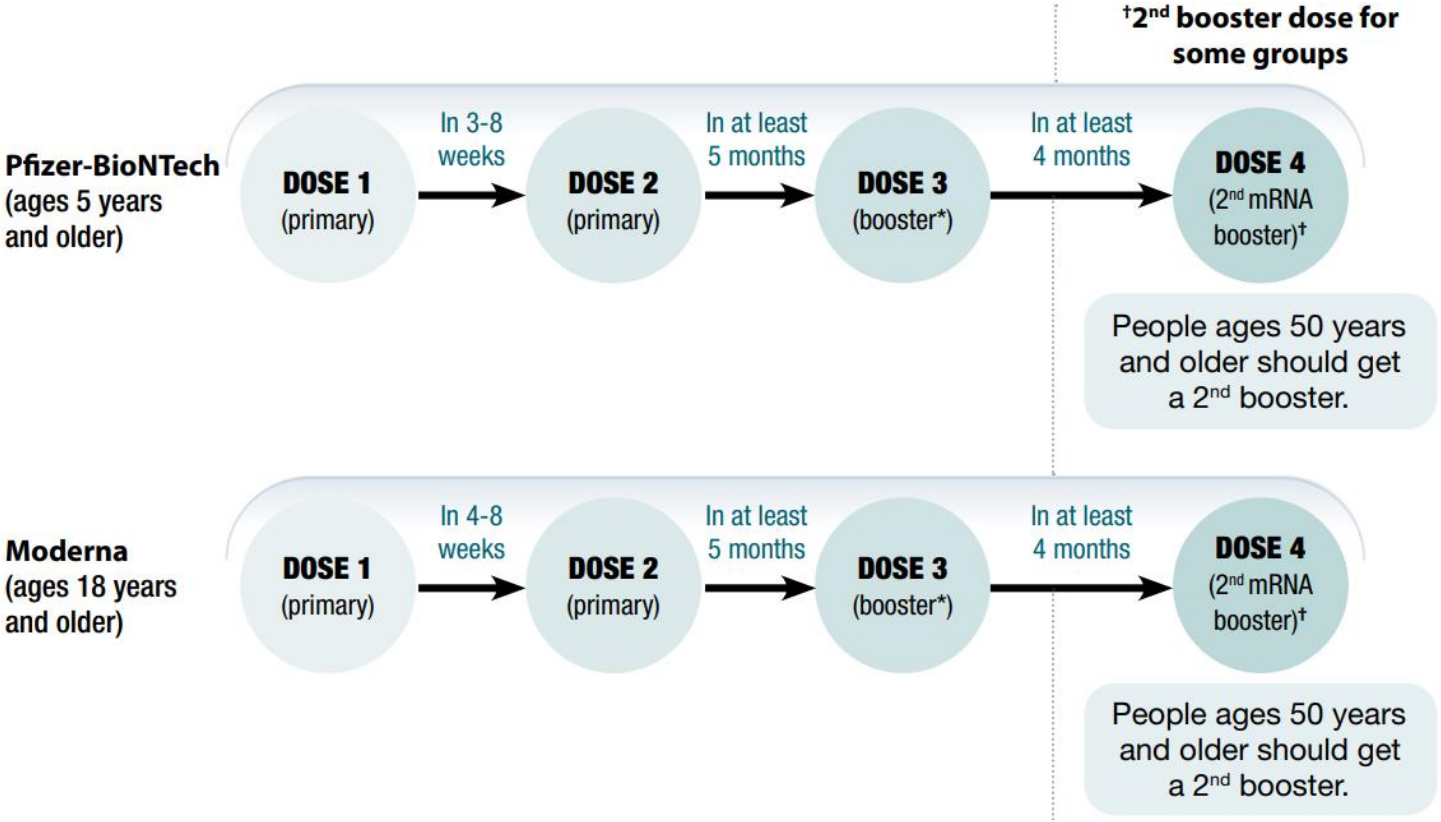
Vaccine series	VE for hospitalization
Primary series	55%
Primary series + one booster dose	88%
Primary series + two booster doses	95%

COVID-19-Associated Hospitalizations Prevented per Million Series Completed



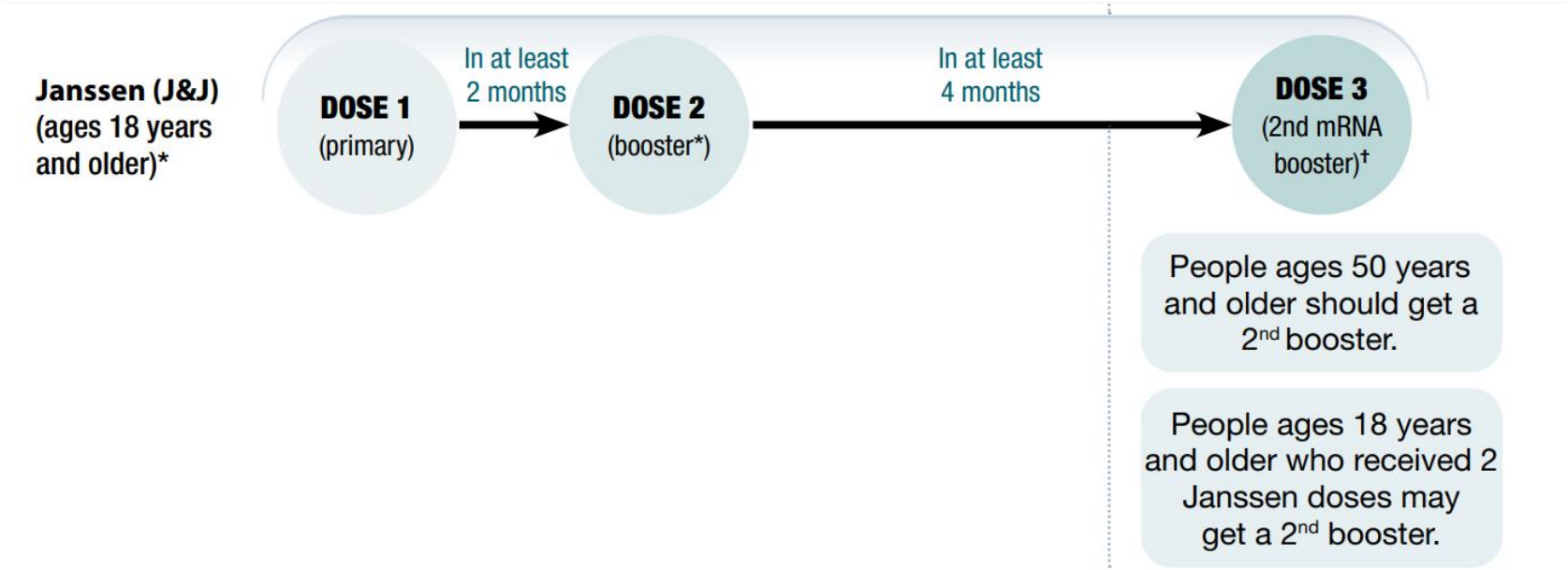
VE: Vaccine Effectiveness; [1] VE estimate from IVY and VISION: https://covid.cdc.gov/covid-data-tracker/#vaccine-effectiveness; [2] Relative VE estimate for 4th dos https://www.nejm.org/doi/pdf/10.1056/NEJMoa2201688?articleTools=true; COVID-NET hospitalization rates from the week of February 26, 2022

COVID-19 Vaccine Recommendations for Most People



https://www.cdc.gov/vaccines/covid-19/downloads/COVID-19-vacc-schedule-at-a-glance-508.pdf

COVID-19 Vaccine Recommendations for Most People: Janssen (J and J)



https://www.cdc.gov/vaccines/covid-19/downloads/COVID-19-vacc-schedule-at-a-glance-508.pdf

2nd Booster Dose Product

- 2nd booster dose should be an mRNA COVID-19 vaccine (i.e., Pfizer-BioNTech or Moderna).
- Janssen COVID-19 Vaccine is not authorized for use as a second booster.
- Booster doses may be heterologous.
  - Eligible people ages 12–17 years can only receive Pfizer-BioNTech COVID-19 Vaccine.
- The dosage is the same as the first booster dose
  - Pfizer-BioNTech (gray or purple cap): 0.3 mL (30 mcg)
  - Moderna (red cap): 0.25 mL (50 mcg)

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

ACIP, April 20, 2022

How Should We Best Protect Immunocompromised People?

- Patients who have immunocompromising conditions or are receiving immunosuppressive medications may not mount an adequate immune response to COVID-19 vaccination

- Who is considered immunocompromised?

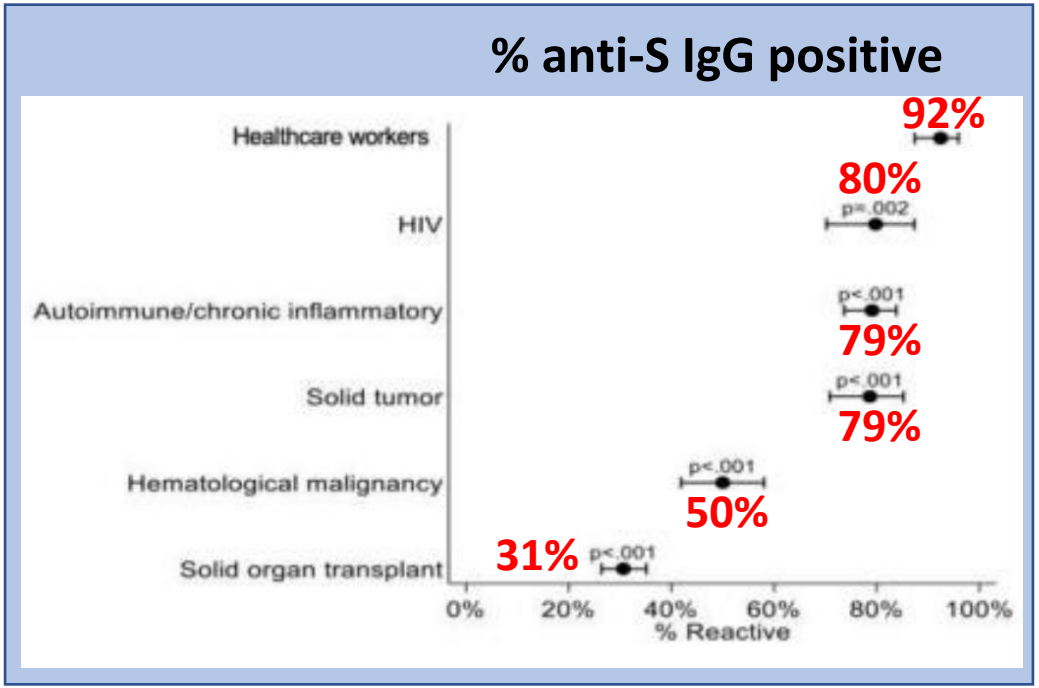
Moderate to Severe Immunocompromising Conditions and Treatments

- Active treatment for cancer
- Solid-organ transplant recipient and taking immunosuppressive therapy
- Receipt of CAR-T-cell or hematopoietic stem cell transplant
- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection (CD4 <200; history of AIDS defining illness without immune reconstitution; clinical manifestations of symptomatic HIV)
- High-dose corticosteroids (>=20 mg prednisone/d for >=2 wk), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapy, TNF blockers, other immunosuppressive/immunomodulatory agents (e.g., B-cell depleting agents)

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

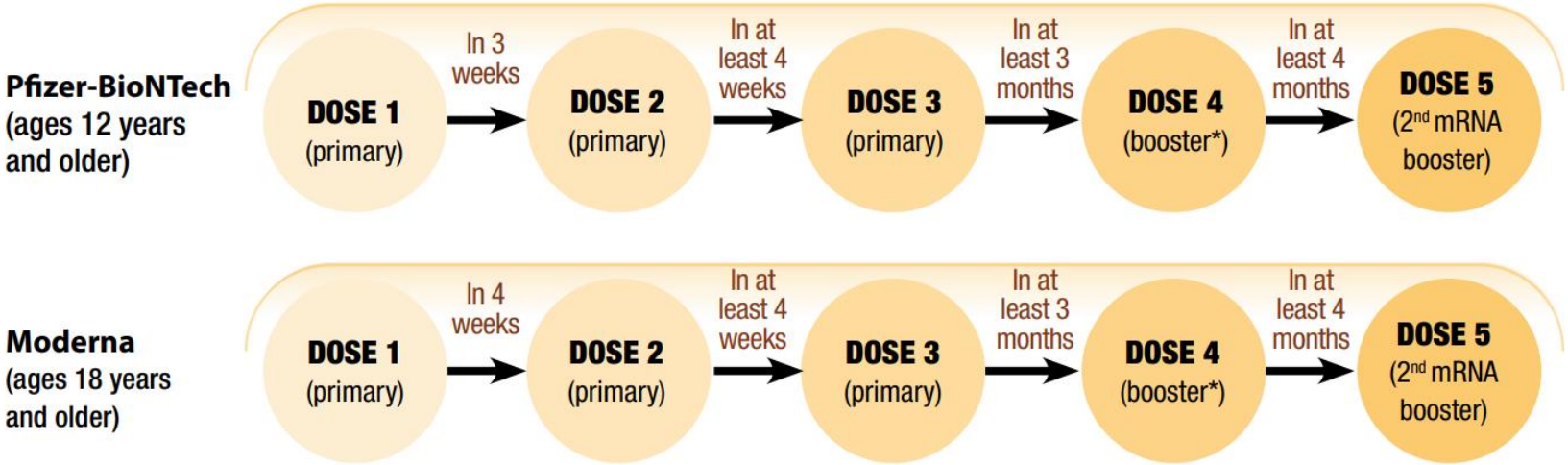
Are Some More Immunocompromised Than Others?

- Fully vaccinated individuals: 1099 immunocompromised, 172 health care workers (HCW)
- Seropositivity rates lowest in SOT recipients, those with hematologic malignancies as compared to people with HIV, solid tumors, autoimmune conditions, HCW
- Recipients of anti-CD20 antibodies had especially low rates of seropositivity



Haidar G et al, CID, 2022

COVID-19 mRNA Vaccine Schedule for People who are Moderately or Severely Immunocompromised



If possible, give vaccine >=2 wks before initiation or resumption of immunosuppressive therapies

https://www.cdc.gov/vaccines/covid-19/downloads/COVID-19-vacc-schedule-at-a-glance-508.pdf

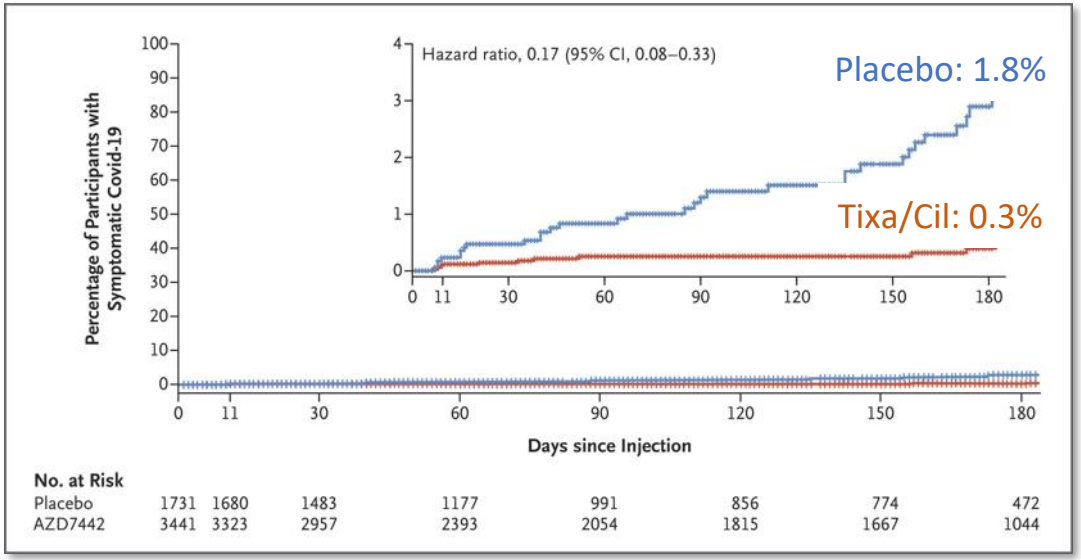
PROVENT: Tixagevimab/cilgavimab (AZD7442) for Pre-exposure prophylaxis

ORIGINAL ARTICLE

Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19

- Tixagevimab/cilgavimab: anti-SARS CoV-2 monoclonal antibodies (half life ≈90 days)
- 5197 participants randomized 2:1 to receive single IM dose of tixagevimab + cilgavimab (150/150 mg) or placebo
- Unvaccinated
- 3.8% immunocompromised

83% reduction in symptomatic Covid in tixagevimab/cilgavimab group



Levin M et al, NEJM, April 20, 2022

Tixagevimab/cilgavimab for COVID-19 Pre-Exposure Prophylaxis

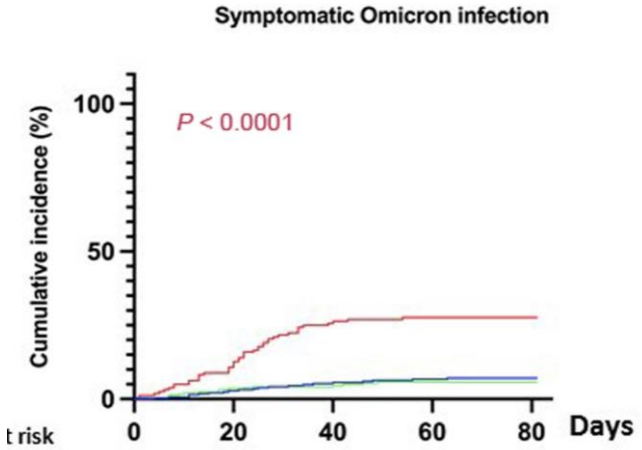
- **FDA EUA**:
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and**
  - May not mount an adequate immune response to COVID-19 vaccination ***or***
  - For whom vaccination is not recommended due severe adverse reaction
- Based on decreased activity against Omicron BA.1 sub-variant, FDA recommended increased dose of tixagivimab/cilgavimab (300/300 mg)
- Wait 2 weeks *after* vaccination to administer tixagevimab/cilgavimab

https://www.fda.gov/media/154701/download

Real World Data Showing Efficacy of Tixagevimab plus Cilgavimab during Omicron Surge

- **US VA study**
  - 1848 patients (mostly vaccinated) who received antibodies compared to propensity matched controls who did not
  - Lower incidence of COVID, hospitalization, all-cause mortality (HR 0.36)

- **Kidney transplant recipients in France**
  - Lower incidence of COVID, hospitalization and death with antibodies



Young-Xu, Y. et al. medRxiv 2022.05.28.22275716; doi: https://doi.org/10.1101/2022.05.28.22275716.
Bertrand, D. et al. Kidney International (2022).

In someone who received anti-SARS CoV-2 monoclonal antibody, how long should you wait before giving a Covid vaccine?

- Previous theoretic concern that the anti-SARS CoV-2 antibody might affect vaccine-induced immune response

Timing of Covid vaccination after anti-SARS CoV-2 monoclonal antibodies

- CDC previously recommended deferring vaccination for 90 days after anti-SARS CoV-2 monoclonal Ab if used for treatment

- Revised guidance: **no recommended deferral period**
  - Based on study among nursing home residents and staff in which recipients of bamlanivimab mounted strong immune response to mRNA vaccines even when given before 90 days

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html
Benschop RJ et al. medRxiv 2021.12.15.21267605; doi:https://doi.org/10.1101/2021.12.15.21267605

Person who received COVID-19 Vaccine Authorized by WHO but not FDA

- Examples: protein subunit: Novavax; viral vector: CanSino, Astra Zeneca; inactivated: Covaxin, Covilo, CoronaVac

Vaccination History	Recommended Action
Received all recommended primary doses for that vaccine	• **Do not repeat primary series** • **Administer mRNA vaccine booster dose at least 5 months after last primary series dose** • **Administer second booster dose if eligible**

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#appendix-a

COVID-19 Vaccines: Other Recent Updates

- **mRNA vaccines preferred** for initial vaccine and boosters
- **Standard interval** (3 weeks for Pfizer; 4 weeks for Moderna) between 1st and 2nd doses remains the recommended interval for moderate-severe immunocompromised, ≥65 yo, others who need rapid protection
- For primary series: A longer **8-week interval** between 1st and 2nd doses may be optimal for some people ≥12 y.o., especially males 12-39 y.o.

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (last updated April 21, 2022)

Part Three: Future of COVID-19 Vaccines

What about vaccines for children under the age of 5 years?

2022 Meeting Materials, Vaccines and Related Biological Products Advisory Committee

June 14-15, 2022

The meeting presentations will be heard, viewed, captioned, and recorded through an online teleconferencing platform. The committee will meet in open session to discuss the following: On June 14, 2022, under Topic 1, the committee will meet in open session to discuss amending the EUA of the Moderna COVID-19 mRNA vaccine to include the administration of the primary series to children and adolescents 6 years through 17 years of age. On June 15, 2022, under Topic II, the committee will meet in open session to discuss amending the EUA of the Moderna COVID-19 mRNA vaccine to include the administration of the primary series to infants and children 6 months through 5 years of age, and also to discuss amending the EUA of the Pfizer-BioNTech COVID-19 mRNA vaccine to include the administration of the primary series to infants and children 6 months through 4 years of age.

Future of COVID-19 Vaccines

- Annual boosters matched to circulating variants (similar to influenza)
- Vaccines that elicit greater mucosal immunity (eg nasal delivery)
- Universal coronavirus vaccines

The NEW ENGLAND JOURNAL of MEDICINE

The Future of SARS-CoV-2 Vaccination — Lessons from Influenza

Arnold S. Monto, M.D.

Intranasal COVID-19 vaccines: From bench to bed

Aqu Alu,[1] Li Chen,[1] Hong Lei Yuquan Wei Xiaohe Tian, and Xiawei Wei **

Laboratory of Aging Research and Cancer Drug Target, State Key Laboratory of Biotherapy and Cancer Center, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu 610041, China

Universal Coronavirus Vaccines — An Urgent Need

David M. Morens, M.D., Jeffery K. Taubenberger, M.D., Ph.D., and Anthony S. Fauci, M.D.

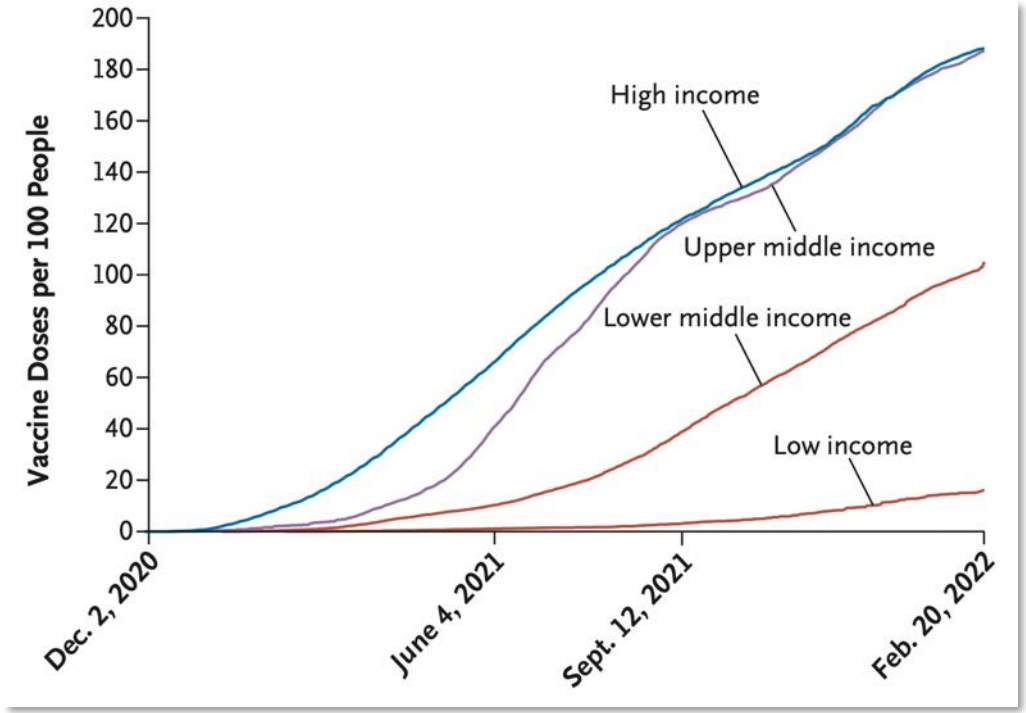
Monto AS. N Engl J Med. 2021; Alu A, EBioMedicine. 2022; Morens DM, N Engl J Med. 2022

Overcoming Vaccine Hesitancy

- **Confidence** in strength of evidence of vaccine efficacy and safety
  - 10 years of research & massive clinical experience
  - “Protection of self, family, community”
  - Even against new variants, vaccines prevent hospitalizations/death
  - Vaccines seem to reduce likelihood long Covid
- **Candor and patience**
  - Serious side effects are rare; COVID is higher risk than vaccine
  - Discuss what concerns are holding them back
  - Build on patients’ trust in you
    - Randomized trial published in Nature showed that communicating doctors’ views on vaccines increases COVID vaccination (Bartoš et al. 2022)

Modified from slide from Dr. Renslow Sherer with input from Dr. Jodian Pinkney

Equity



EDITORIALS

Addressing Vaccine Inequity — Covid-19 Vaccines as a Global Public Good

David J. Hunter, F.Med.Sci., Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Lindsey R. Baden, M.D., Jeremy J. Farrar, M.D., Ph.D., Mary Beth Hamel, M.D., M.P.H., Dan L. Longo, M.D., Stephen Morrissey, Ph.D., and Eric J. Rubin, M.D., Ph.D.

NEJM March 24, 2022

The New York Times

GLOBAL HEALTH

The Drive to Vaccinate the World Against Covid Is Losing Steam

Rates are stalling in most low-income countries well short of the W.H.O.'s goal to immunize 70 percent of people in every nation.

April 23, 2022

Lessons from HIV and COVID-19

- Pressure to deploy interventions must be tempered by importance of finding out if treatment or vaccine works
- Randomized trials can and must be done during pandemic
- Equity must be at the center of our response

Siedner M, Gandhi RT, Kim AY, JID, 2020