

HOPE Conference, June 21, 2022

Advancing COVID-19 Treatment and Prevention: Lessons for Future Pandemics

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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, Efe Airewele, Courtney Tern

Part One: Advancing COVID-19 Treatment

Part Two: Advancing COVID-19 Vaccines

**Part Three: Lessons from COVID-19 and HIV for
Future Pandemics**

COVID-19 Management: March 2020



NEWS RELEASES

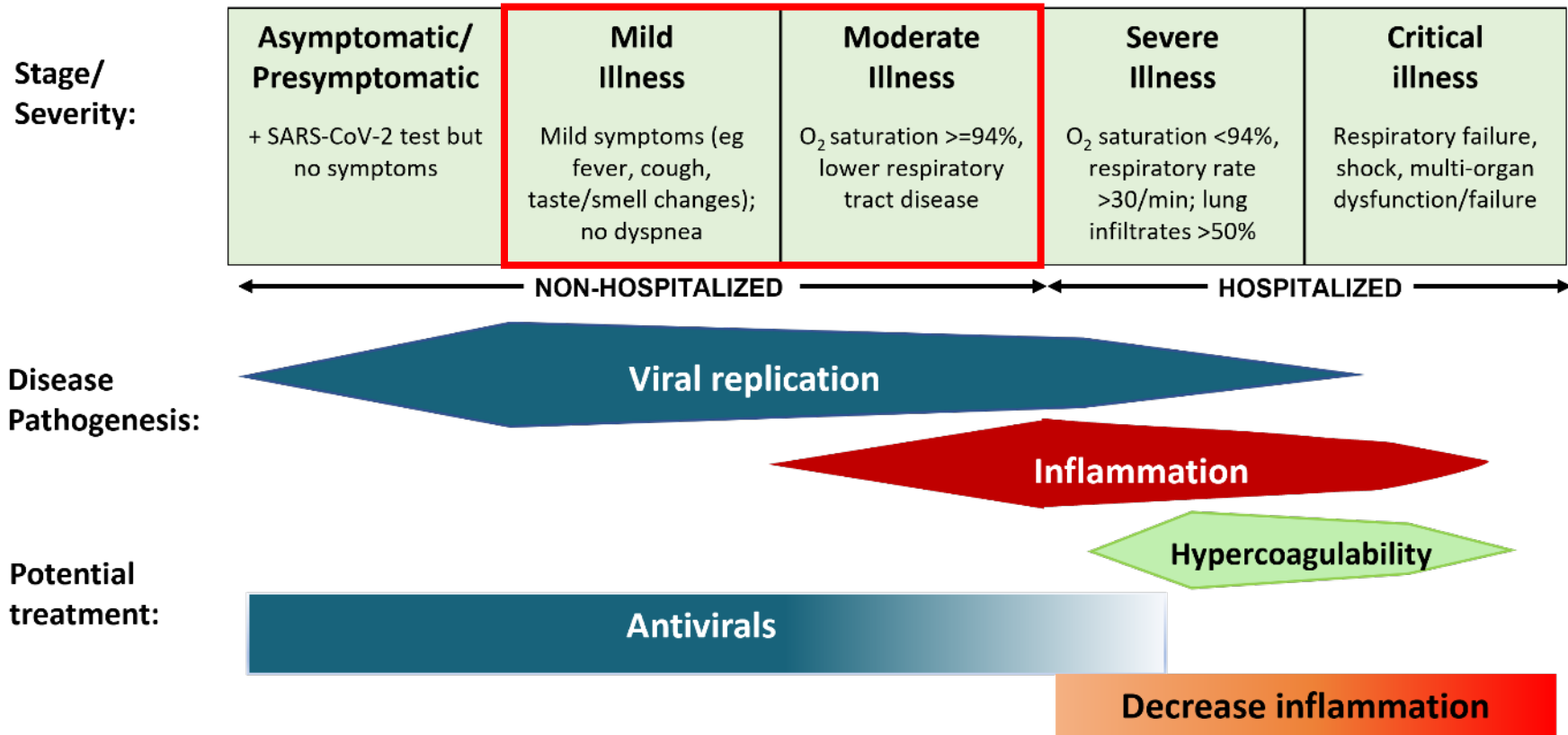
Tuesday, February 25, 2020

NIH clinical trial of remdesivir to treat COVID-19 begins

[News](#) > [Medscape Medical News](#)

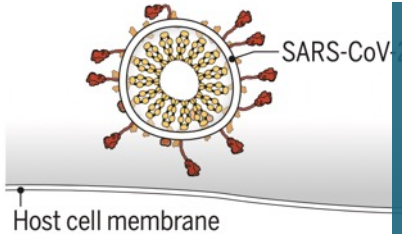
IDSA: No Recommendations for COVID-19 Treatment for Now, 'Knowledge Gaps' Cited

Treatment Across the COVID-19 Spectrum



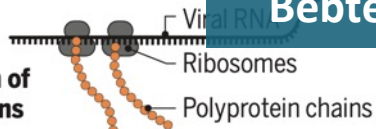
SARS CoV-2 Antivirals

1 Attachment and entry

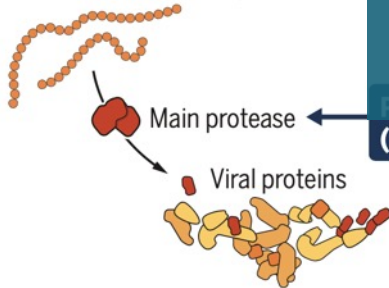


Anti-spike
antibodies, eg
sotrovimab
(Xevudy)
Bebtelovimab

2 Translation of viral proteins



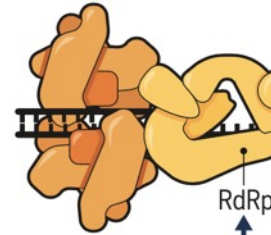
3 Proteolysis



Protease inhibitor:
Nirmatrelvir/ritonavir
(Pfizer)

4 RNA replication

Replication
transcription complex

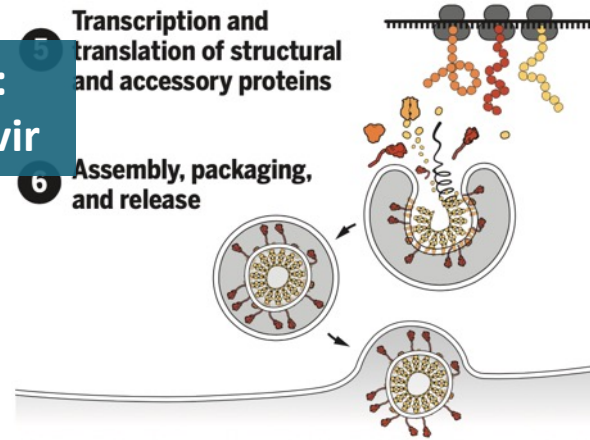


molnupiravir (Merck)

Molnupiravir
(Lagevrio)
Remdesivir
(Veklury)

5 Transcription and translation of structural and accessory proteins

6 Assembly, packaging, and release



Nirmatrelvir/ritonavir in High-Risk Patients with COVID-19

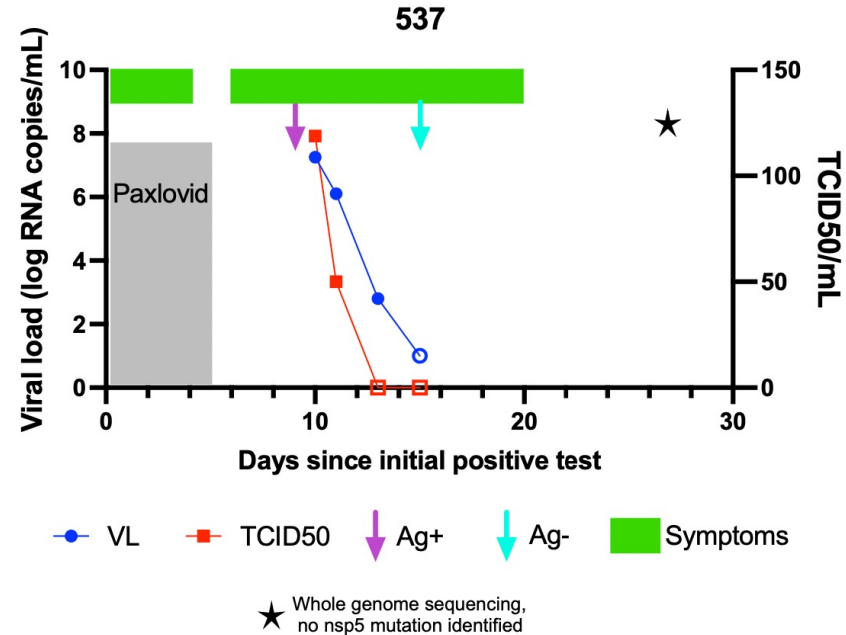
- Phase 2/3 EPIC HR: unvaccinated non-hospitalized patients at high risk for progression to severe COVID-19 and within 5 days of symptom onset
- Participants (n=2246) randomized to nirmatrelvir/ritonavir twice daily or placebo for 5 d
- About 10-fold reduction in viral load at day 5 relative to placebo

≤5 days of symptom onset	Hospitalization or death	% Reduction
NTV/rtv	8/1039 (0.8%) 0 deaths	88% P<0.0001
Placebo	66/1046 (6.3%) 12 deaths	

N/R authorized for treatment of mild-to-moderate COVID-19 in patients who are at high risk for progression and within 5 days of symptom onset

Nirmatrelvir/Ritonavir Rebound: MGH Case Series

- Seven individuals, ages 31 to 64 years; 3-5 vaccine doses
- 6 of 7 with symptomatic relapse, 4 to 7 days after end of N/R
- SARS CoV-2 level at relapse high: up to 10 million copies/mL
- 3 of 7 had positive viral cultures; days from diagnosis to negative viral culture, 14-19 days
- No viral resistance detected



Nirmatrelvir/Ritonavir Rebound

Rapid Relapse of Symptomatic Omicron SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir

Michael Charness (✉ michael.charness@va.gov)
VA Boston Healthcare System

- Case series of 10 non-immunosuppressed individuals with COVID
 - All fully vaccinated with at least one booster
- Improved after receiving N/R and had negative antigen or PCR tests
- Relapse of symptoms at days 9-12; usually cold symptoms
- Resolved without additional treatment
- Viral levels at relapse similar to that during initial infection
- Antigen tests became positive for at least 2-7 days (out to day 18)
- In 3 patients who had sequencing, no resistance detected
- Transmission thought to have occurred in 2 instances

Rebound after N/R: Questions and My Take

- What is incidence of symptomatic viral rebound after N/R? Is it higher than with no treatment or other therapies?
- What are risk factors for symptomatic rebound?
- Why is rebound occurring? Delayed antibody responses? Resistance? Other?
- How long are people contagious after rebound? For now, resetting isolation clock.
- What are the clinical implications of rebound?
- Should therapy duration be extended? Should second course of therapy be given? My take: In general, not extending therapy or retreating.

EPIC SR: Nirmatrelvir/Ritonavir in Patients Not at High Risk

- 1,153 standard-risk (SR) individuals within 5 days of symptom onset randomized to receive N/R or placebo
- Standard risk: vaccinated with ≥ 1 risk factor for severe disease or no risk factor but unvaccinated
- Primary endpoint of self reported sustained alleviation of all symptoms not met
- COVID related medical visits (ED, urgent care, hospitalization, telehealth): nominally significant 62% decrease
- Hospitalizations/death: non-significant 51% reduction (Rx: 5/576; placebo: 10/569).
- In 721 vaccinated adults with ≥ 1 risk factor for severe COVID-19, non-significant 57% reduction in hospitalization/deaths (treatment: 3/361; placebo: 7/360).

Who Should Receive Nirmatrelvir/Ritonavir? My Take

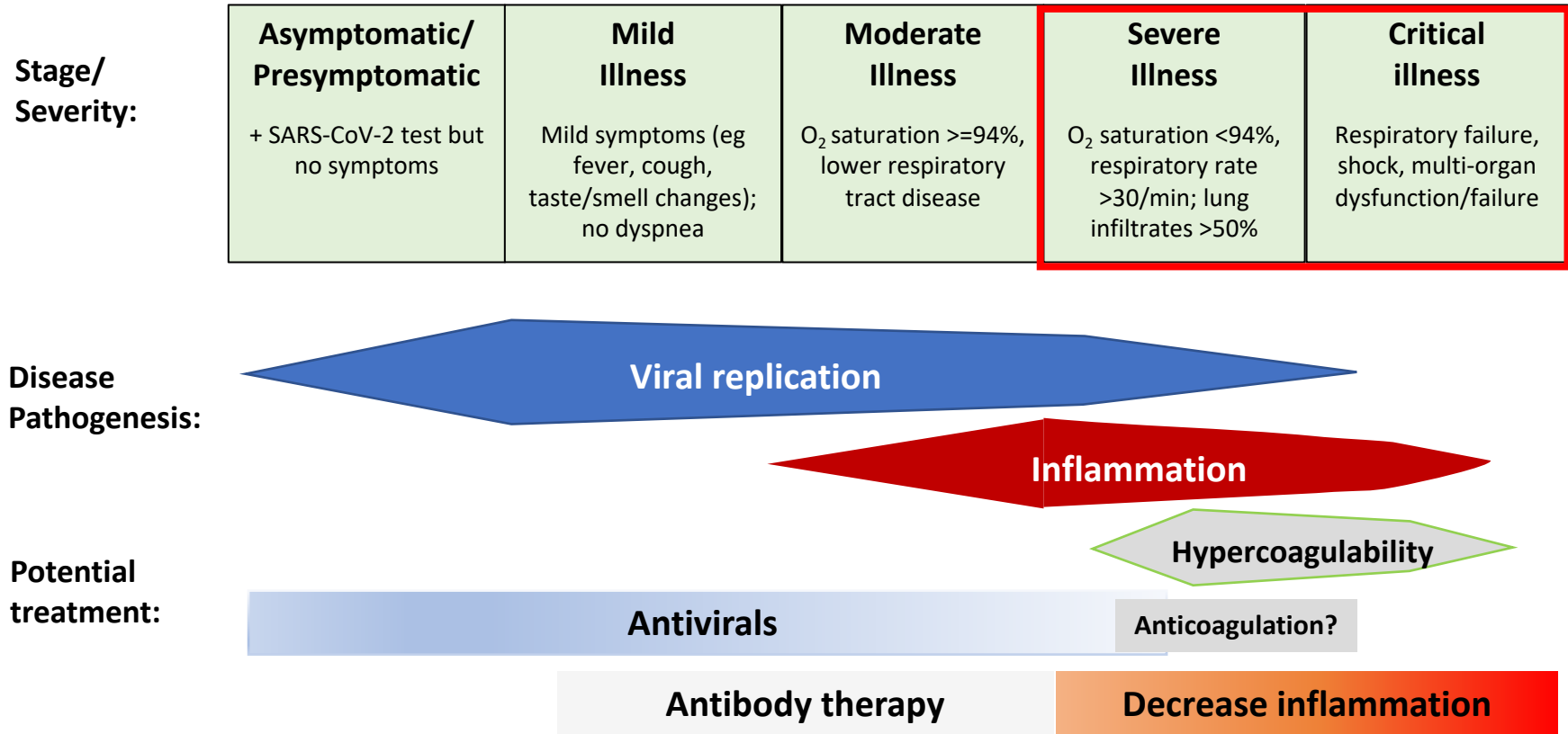
- Nirmatrelvir/ritonavir likely to be of greatest benefit among those who are at highest risk for severe COVID-19, which includes people who have been vaccinated if they have substantial risk factors for progression, such as older age, comorbidities, or immunocompromising conditions/medications
- In individuals who have been recently vaccinated and boosted and who do not have risk factors for progression, close monitoring without nirmatrelvir/ritonavir is reasonable

How do the therapies stack up?

	1) Nirmatrelvir/r	2) Remdesivir	3) Bebtelovimab	4) Molnupiravir
Efficacy (prevention hospitalization or death)	<ul style="list-style-type: none"> • Relative risk reduction: 88% • Absolute risk: 6.3%→0.8% • NNT: 18 	<ul style="list-style-type: none"> • Relative risk reduction: 87% • Absolute risk: 5.3%→0.7% • NNT: 22 	<ul style="list-style-type: none"> • Only phase 2 data • Efficacy in high-risk patients unknown 	<ul style="list-style-type: none"> • Relative risk reduction: 30% • Absolute risk: 9.7%→6.8% • NNT: 35
Pros	<ul style="list-style-type: none"> • Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy 	<ul style="list-style-type: none"> • Highly efficacious • Studied in pregnancy • Few/no drug interactions 	<ul style="list-style-type: none"> • Monoclonals typically safe in pregnancy • Few/no drug interactions 	<ul style="list-style-type: none"> • Oral regimen • Not anticipated to have drug interactions
Cons	<ul style="list-style-type: none"> • Drug drug interactions 	<ul style="list-style-type: none"> • Requires IV infusion on 3 consecutive days 	<ul style="list-style-type: none"> • Requires IV infusion followed by 1 hour observation 	<ul style="list-style-type: none"> • Low efficacy • Concern: mutagenicity • Not recommended in pregnancy/children

Hospitalized Patients with Severe or Critical COVID-19

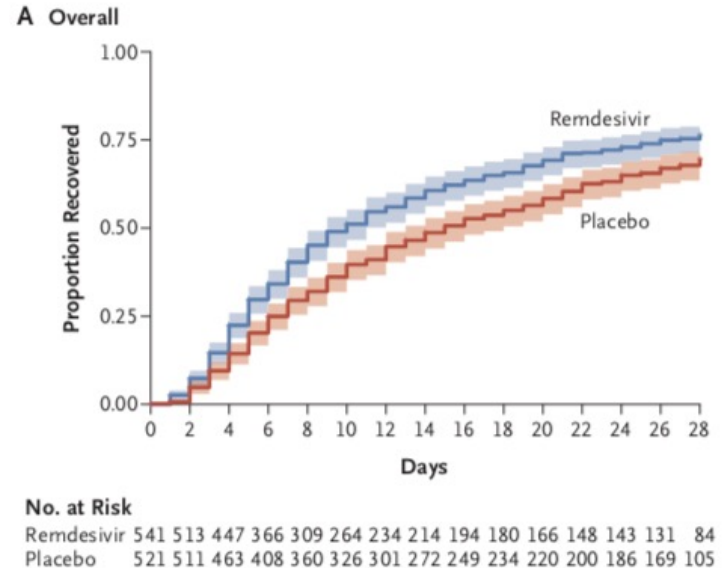
Treatment Across the COVID-19 Spectrum



Remdesivir (RDV)

- ACTT-1: hospitalized pts, lower respiratory tract infection randomized to RDV or placebo
 - Clinical recovery more rapid with RDV than placebo (10 vs 15 d)
 - Mortality at 29 days: 11.4% RDV, 15.2% placebo (hazard ratio 0.73, 95% CI, 0.52-1.03).
 - Benefit of RDV clearest in those on supplemental oxygen but not intubated

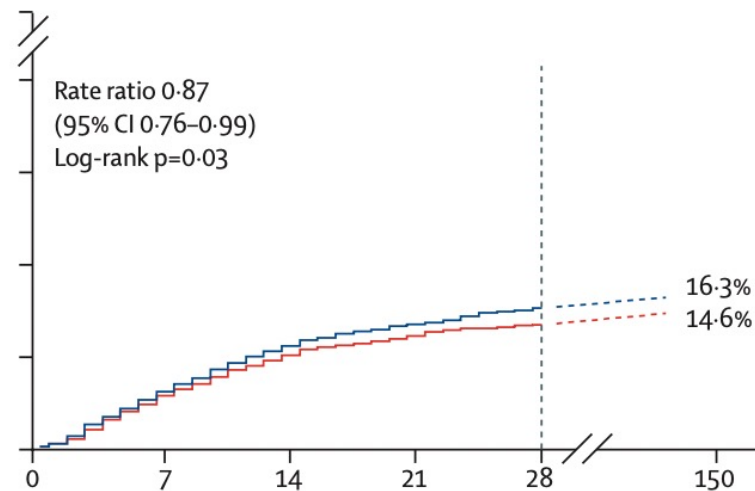
ACTT-1: Time to Recovery



What about WHO SOLIDARITY Trial?

- Open label randomized trial among COVID inpatients in >30 countries
- Prelim analysis: no RDV effect on mortality
- Final analysis (n=8275)
 - Overall mortality: 14.5% (RDV) vs. 15.6% (control). RR: 0.91, p=0.12
 - Pts not yet ventilated: mortality lower with RDV (11.9% vs. 13.5%, RR 0.86, p=0.02)
 - Progression to death or ventilation lower in RDV group (19.6% vs. 22.5%, RR 0.84)

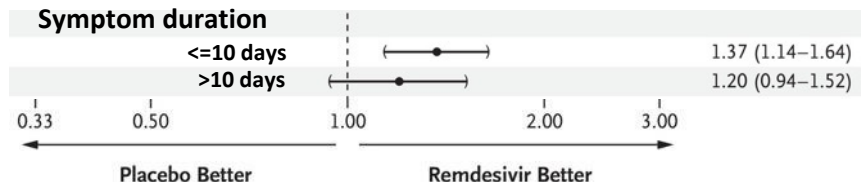
B Oxygen (low or high flow), but not ventilated



Where Does that Leave Remdesivir? My Take

- Early therapy more likely to confer benefit than later initiation

➤ ACTT-1 Time to Recovery

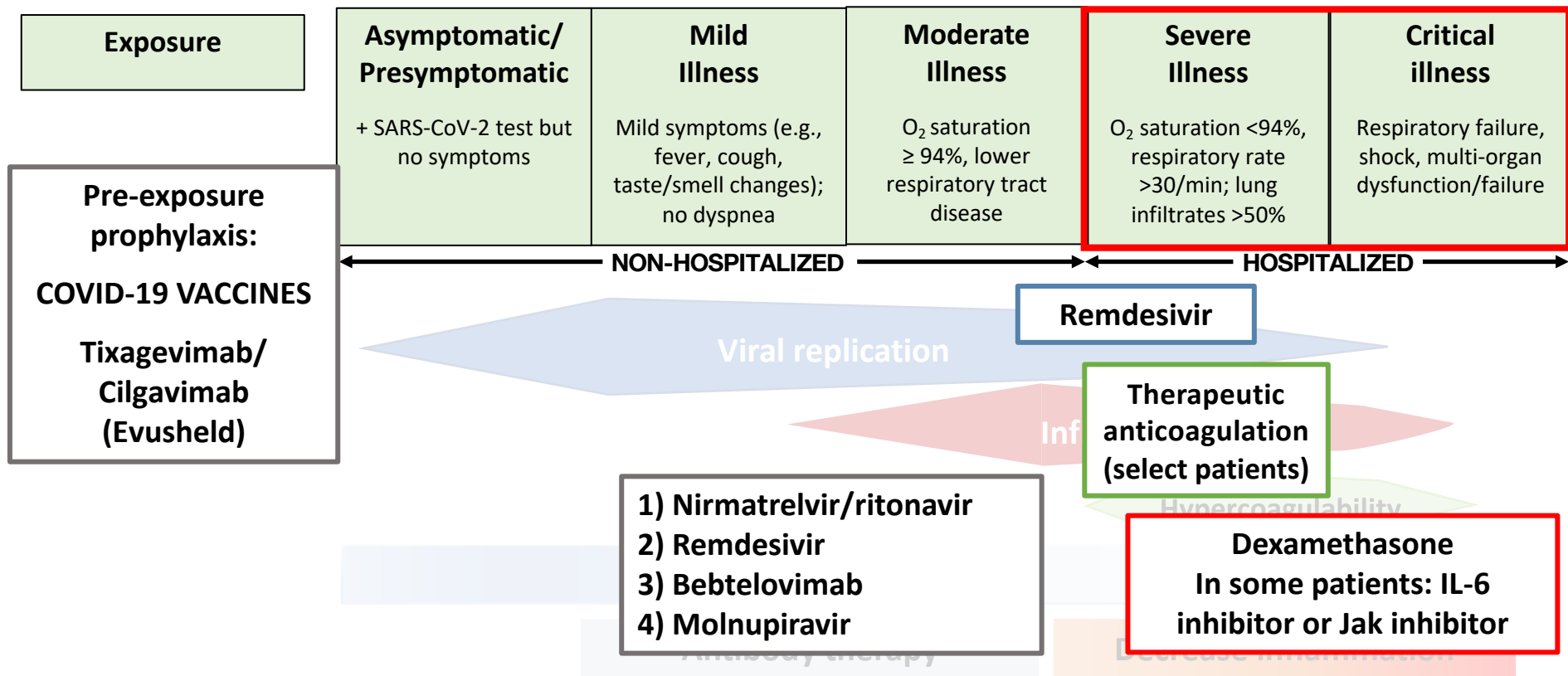


- PINETREE: RDV reduced hospitalization/death by 87% in high-risk non-hospitalized patients with symptoms ≤ 7 days
- RDV has a role in treating COVID-19 but benefit greatest if started early; if started when patient requiring increasing amounts of oxygen, combine with immunomodulation

Immunomodulation

- Dexamethasone 6 mg/day: reduces mortality in hospitalized patients with COVID-19 who require oxygen
- Outcomes with 12 mg dexamethasone numerically better than with 6 mg but differences not statistically significant
- In hospitalized patients who do not require oxygen, dexamethasone may be harmful
- In patients with rapidly progressive COVID-19 and hypoxemia, adding tocilizumab (IL-6 blocker) or baricitinib (Jak inhibitor) to dexamethasone is beneficial

Treatment Across the COVID-19 Spectrum



Future Directions in COVID-19 Therapy

- What is the benefit of therapies in lower risk patients (vaccinated, infected with Omicron)?
- What are optimal therapies for children with COVID-19?
- Will monotherapy select for viral resistance? Role of combination Rx?
 - Concern greatest for severely immunocompromised.
- How do we develop targeted therapies based on patients' levels of virus, inflammation, immune response?
- Does treatment prevent Long COVID (PASC)?

Part Two: Advancing COVID-19 Vaccines

Phase 3 Trials: Efficacy Against Ancestral SARS CoV-2

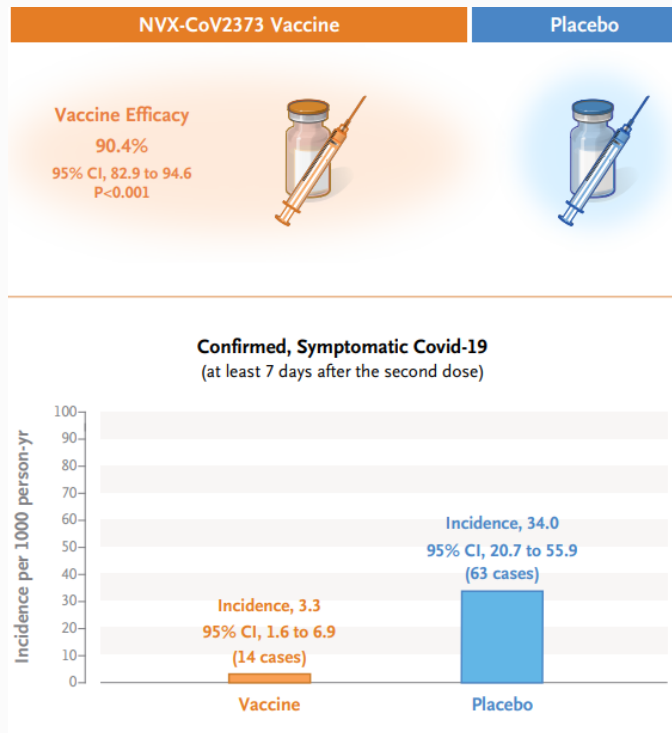
Vaccine	Type/ dose	Vaccine Efficacy (VE)	VE Against Severe Disease
BNT162b2 (<i>Pfizer-BioNTech</i>)	mRNA: spike protein/ 2 doses	95%	100%
mRNA-1273 (<i>Moderna</i>)	mRNA: spike protein/ 2 doses	95%	100%
Ad26.COV2.S (<i>Janssen</i>)	human adenovirus type 26/spike protein DNA 1 dose	66%	85% against severe/critical;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

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 against symptomatic COVID: 90%; against 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




Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico

Dunkle LM et al. DOI: 10.1056/NEJMoa2116185



Relative immunogenicity

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

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

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

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)

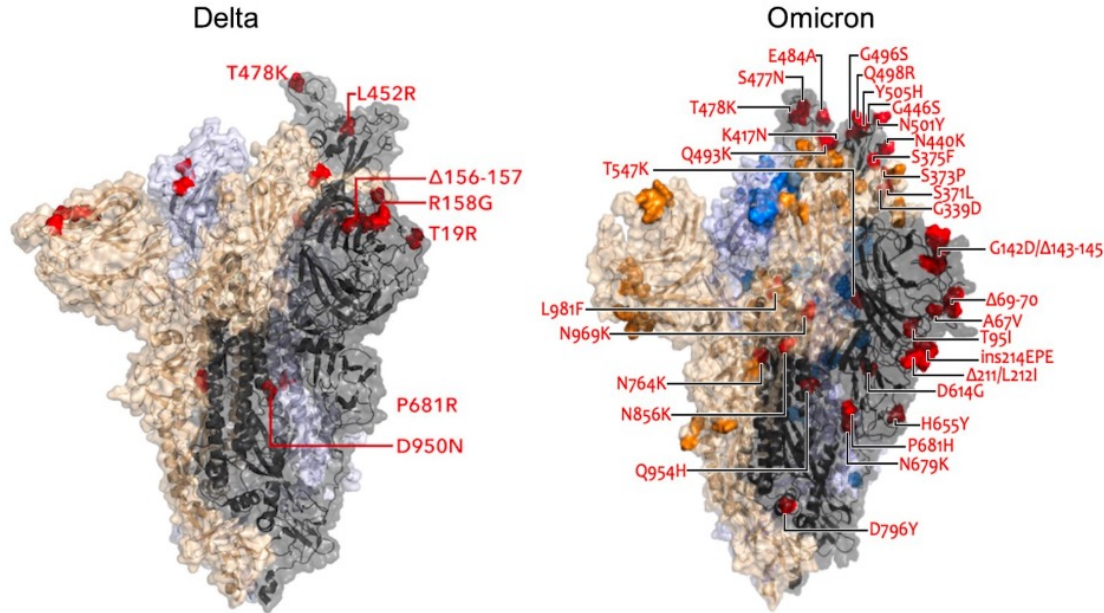
**Odds of being struck by lightning
in a year: 1/500,000**



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.

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>

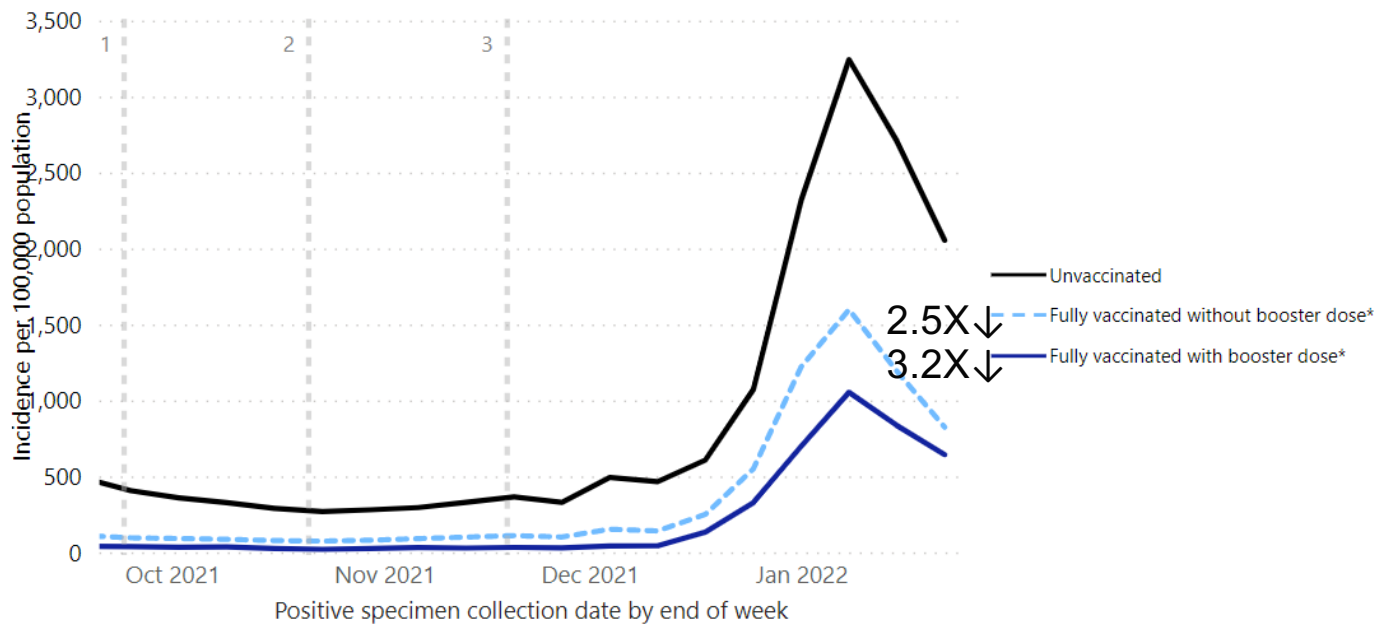
Select Outcome

● Cases

○ Deaths

Rates of COVID-19 Cases by Vaccination Status and Booster Dose**

September 19 - January 01, 2022 (26 U.S. jurisdictions)



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

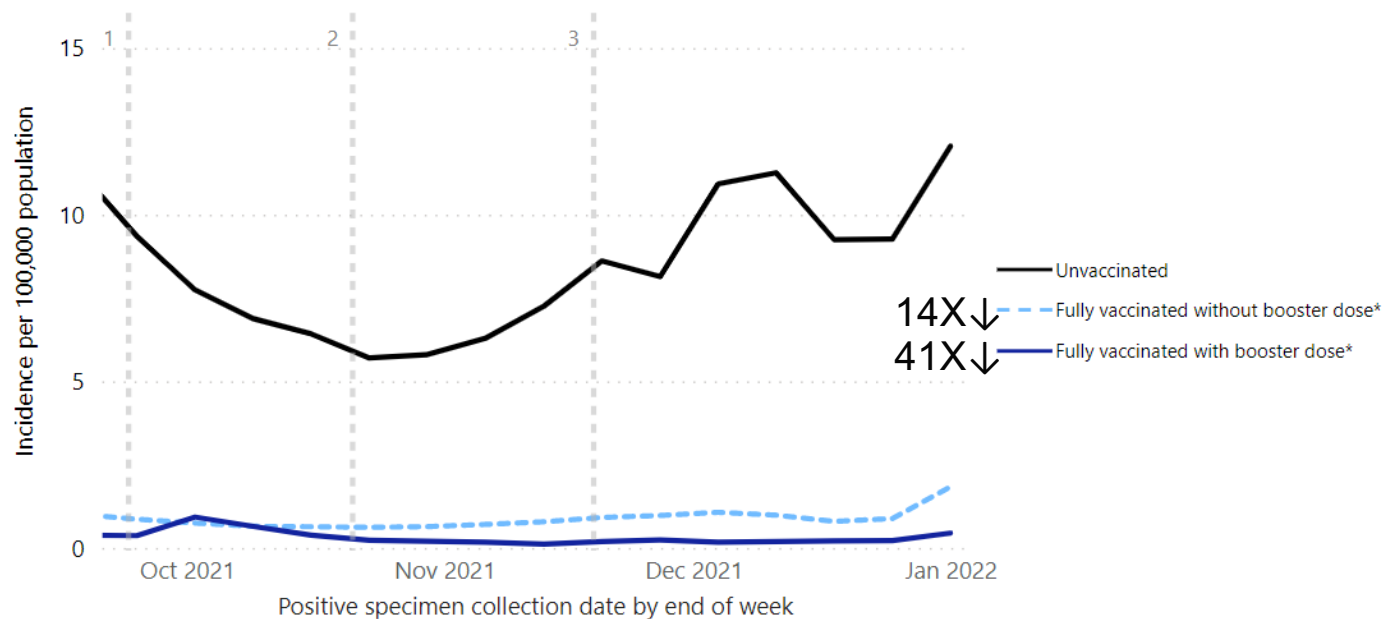
Select Outcome

○ Cases

● Deaths

Rates of COVID-19 Deaths by Vaccination Status and Booster Dose**

September 19 - January 01, 2022 (24 U.S. jurisdictions)



<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

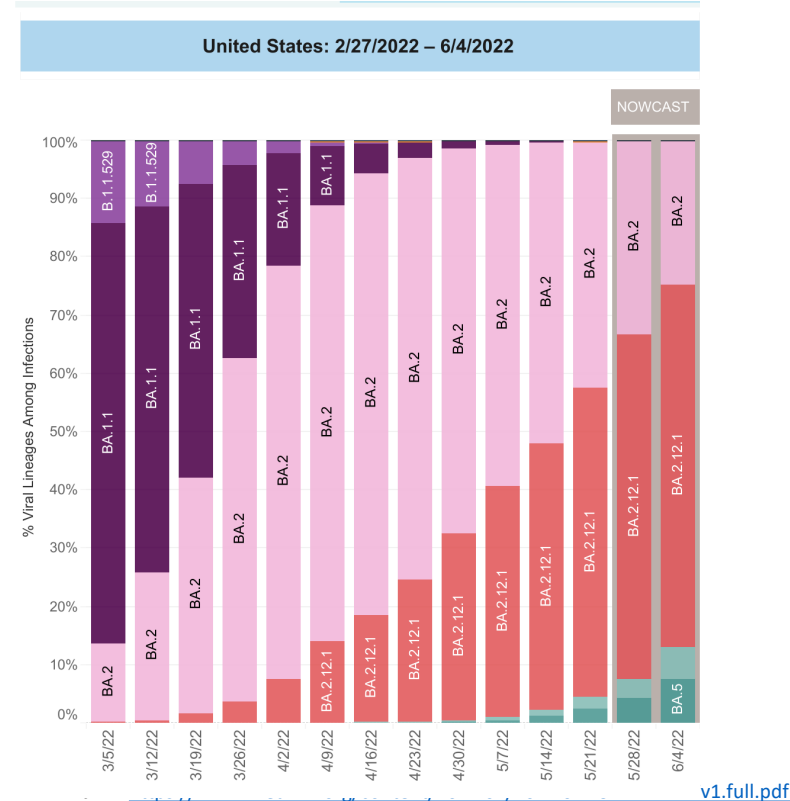
bit.ly/MMWR7112e1

MMWR



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

- Led to recent surge in South Africa
- 1 in 8 infections in US; about 1 in 5 infections in Texas
- 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)

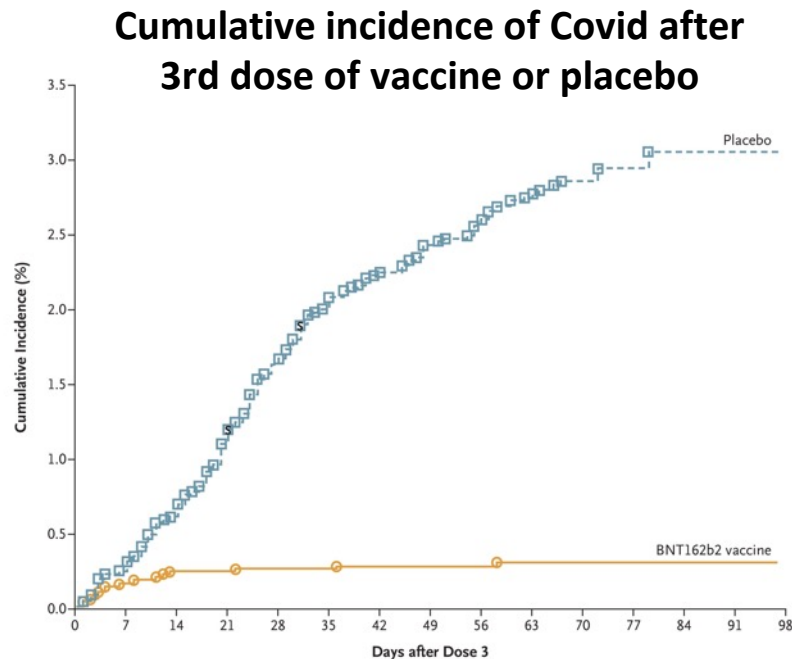


COVID-19 Vaccines: FAQ

- What are current recommendations for booster doses?
- How should we best protect immunocompromised people?
- What about tixagevimab/cilgavimab for pre-exposure prophylaxis?
- What about vaccines for children under the age of 5 years?

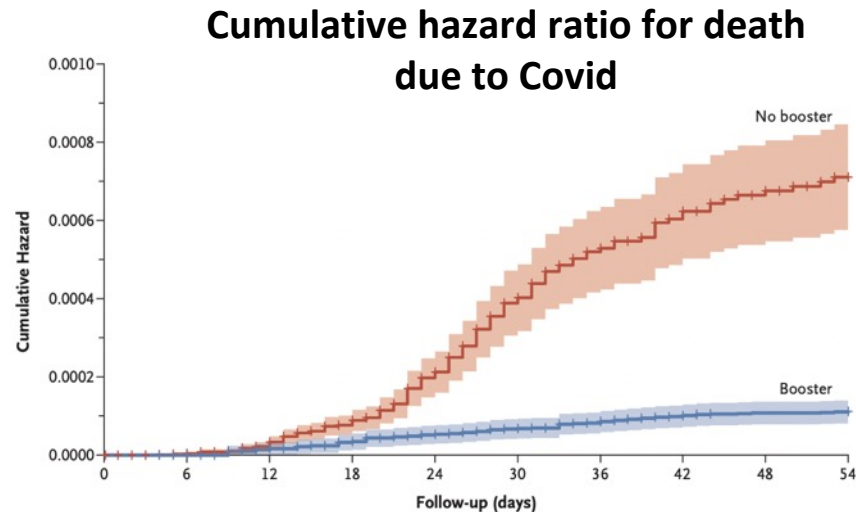
What is the Evidence that Vaccine Efficacy against Covid Wanes after Two Doses?

- 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



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

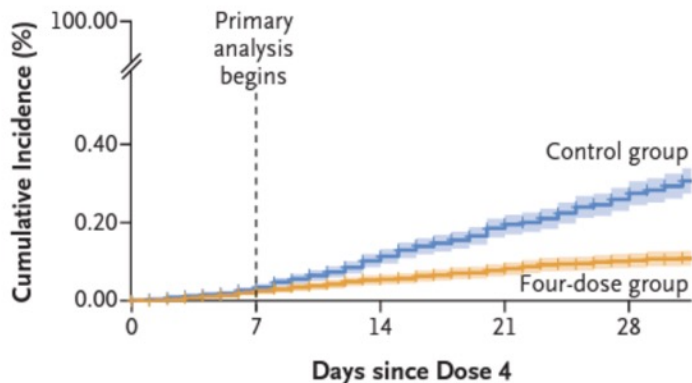
- Observational studies during Delta surge
- Israeli Ministry of Health:
 - \geq age 60, > 5 mo. from 2nd dose
 - Severe Covid about 20-fold lower in those who received 3rd vaccine dose
- Clalit Health Services study:
 - $>$ age 50, > 5 mo. from 2nd dose
 - 90% lower mortality with 3rd dose



What about 4th vaccine dose?

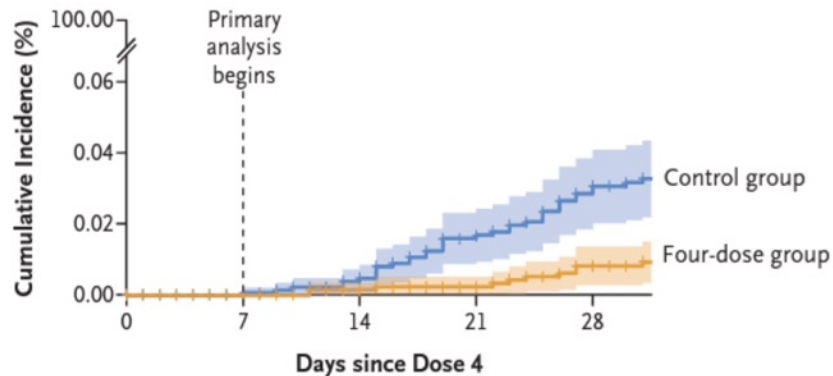
- Clalit Health Services study (Israel): Compared outcomes among those age ≥ 60 years who had received 4th dose vs those who had received 3rd dose at least 4 months earlier

COVID-19-Related Hospitalization



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

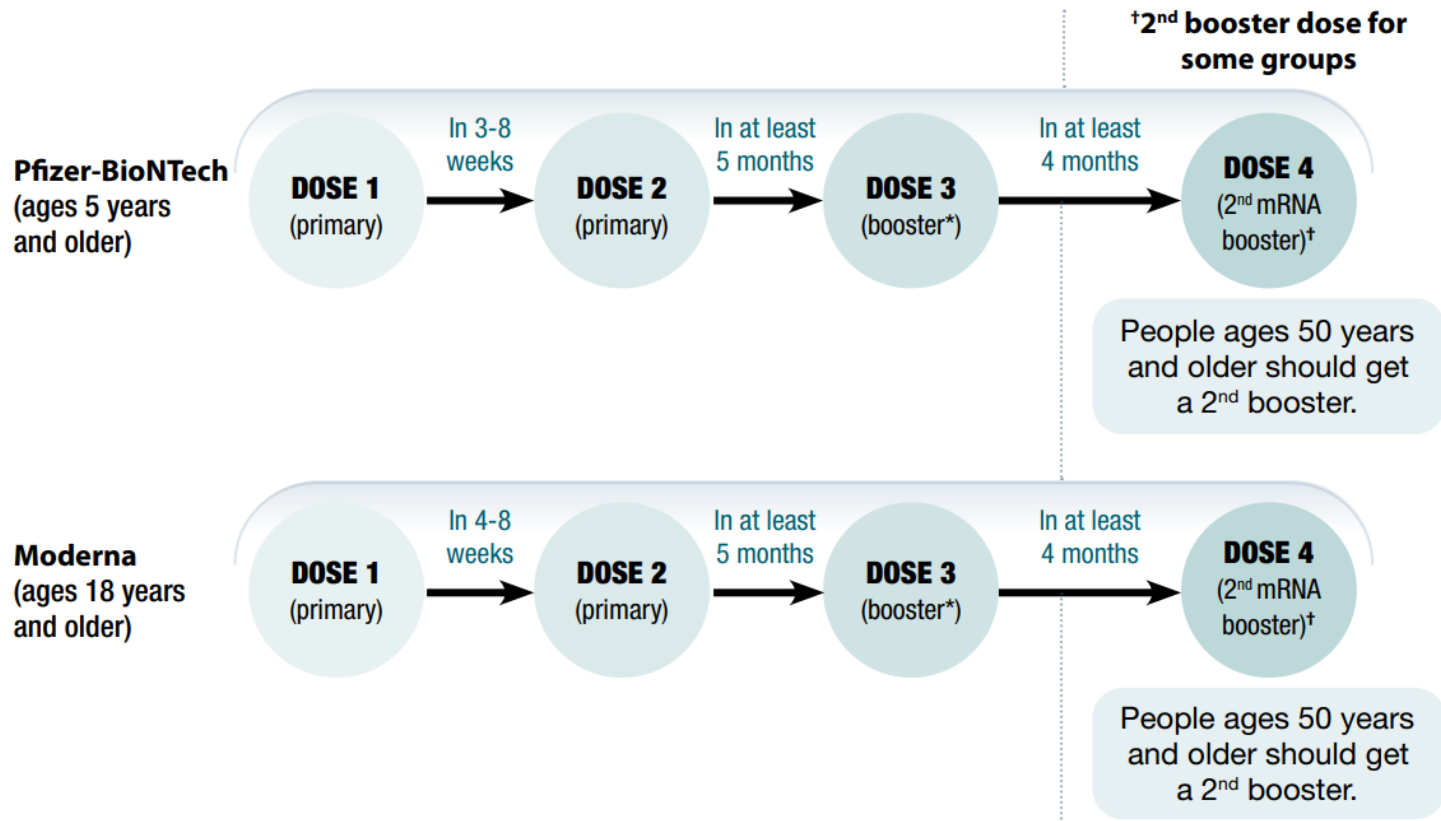
Death from COVID-19



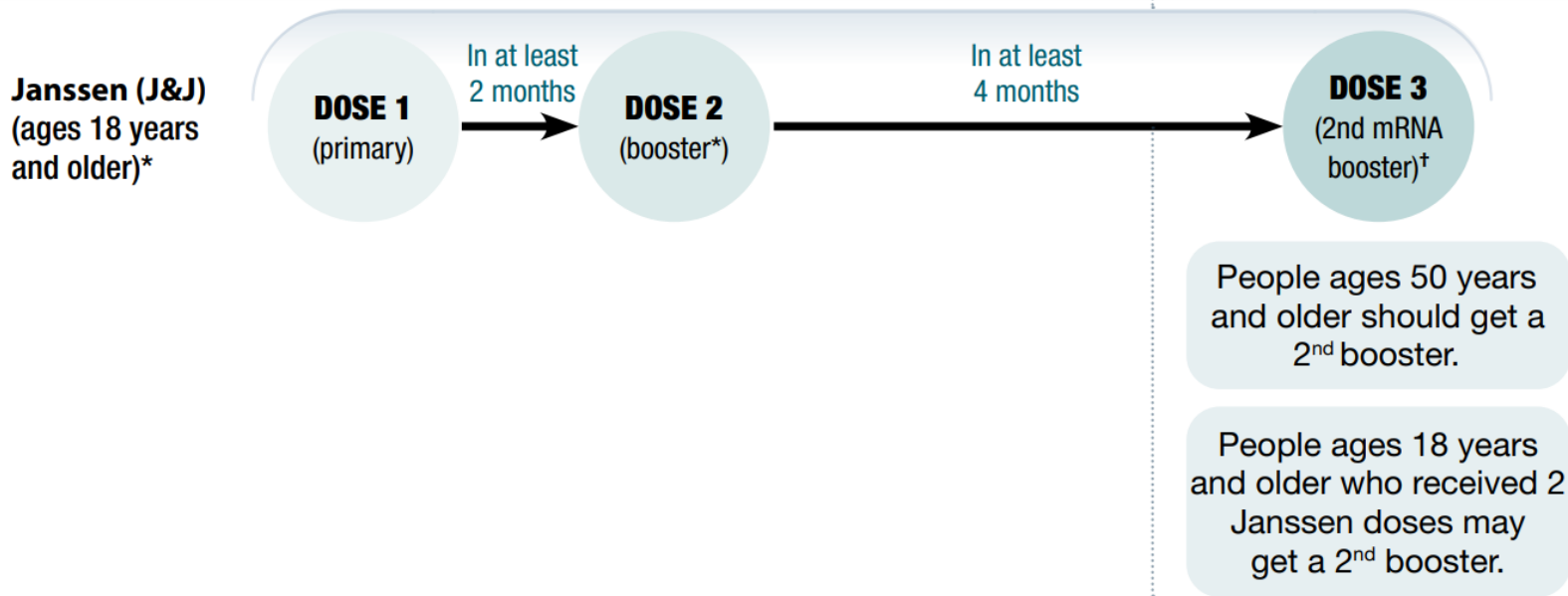
Day 14 to 30 Relative VE: 76% (95% CI: 48% – 91%)



COVID-19 Vaccine Recommendations for Most People



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



How Should We Best Protect Immunocompromised People?

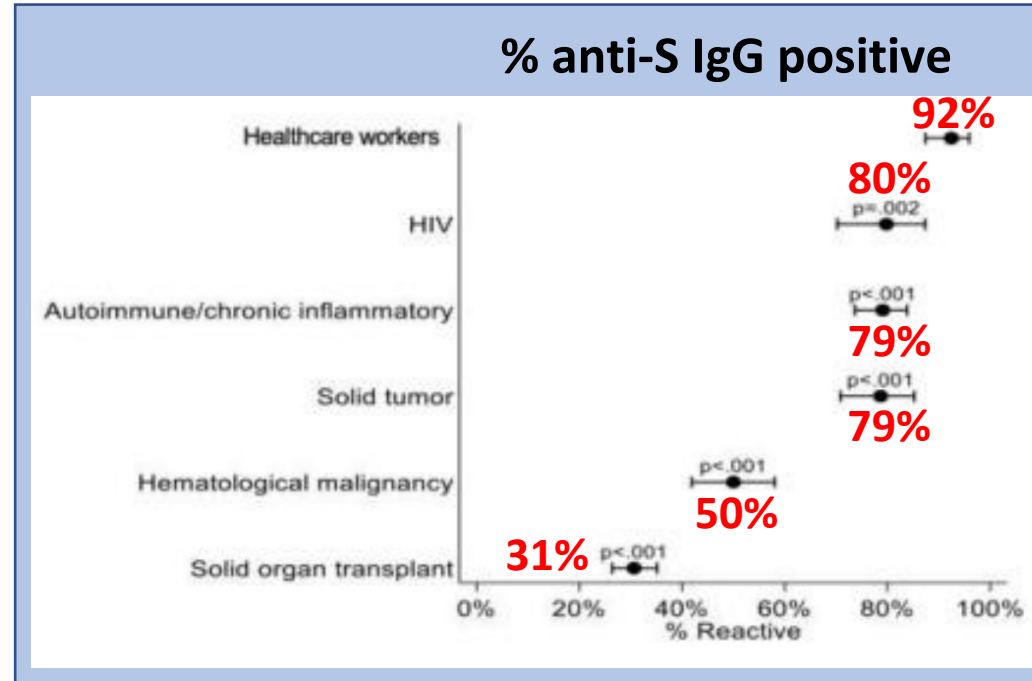
- Patients who have immunocompromising conditions or are receiving immunosuppressive medications may not mount an adequate immune response to COVID-19 vaccination
- Who is considered immunocompromised?

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)

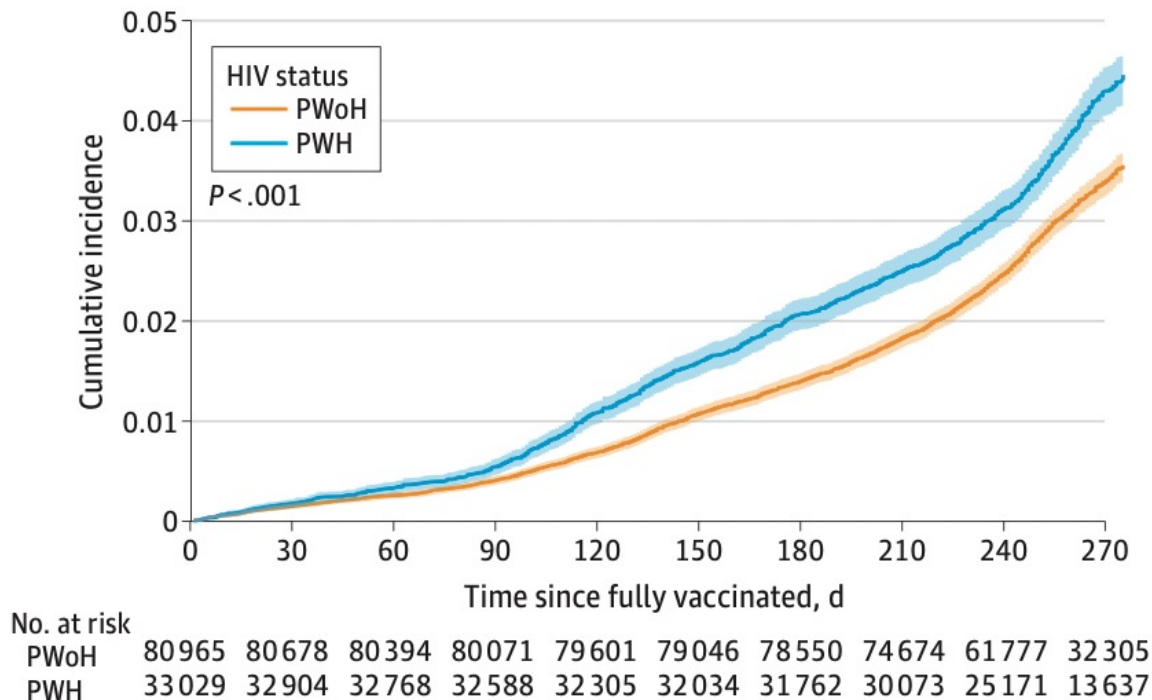
Are Some More Immunocompromised Than Others?

- 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

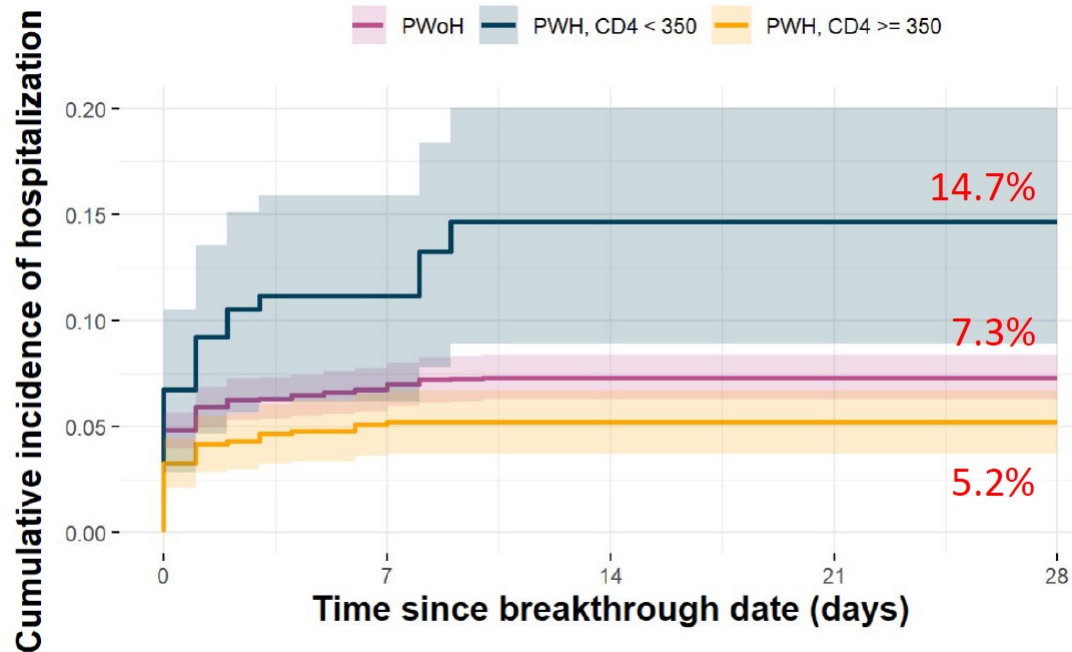


Breakthrough Infection Risk Higher in Vaccinated People with HIV than People without HIV

A Cumulative incidence of SARS-CoV-2 vaccine breakthrough by HIV status



Risk of Hospitalization after Breakthrough Infection Higher in PWH with CD4 Cell Count <350

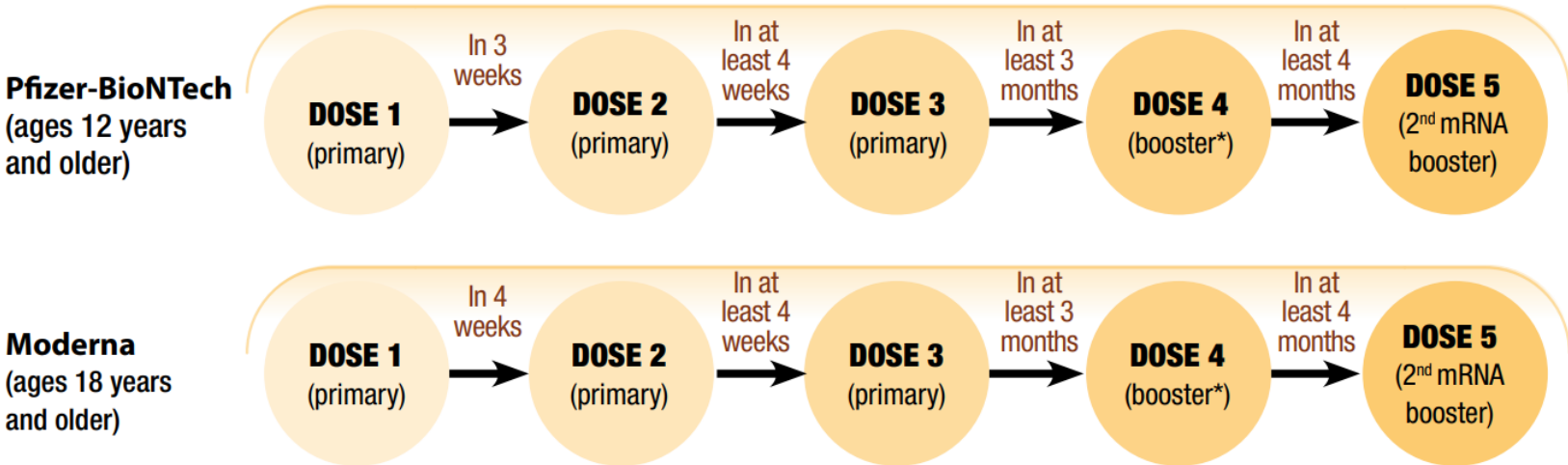


Everyone should get vaccinated and boosted.

Among those with a breakthrough infection, **people with HIV and a CD4 <350 cells/mm³** had a 59% increase in the risk of hospitalization relative to people without HIV and **may benefit from additional primary series or booster vaccine doses.**

(adjusted relative risk = 1.59 [0.99, 2.46], p=0.49)

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

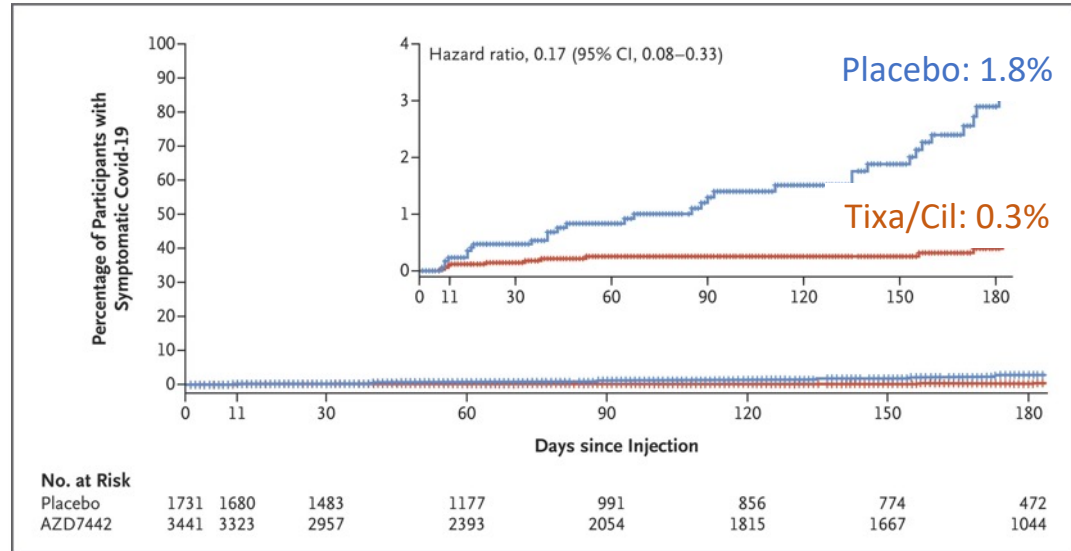
PROVENT: Tixagevimab/cilgavimab (AZD7442) for Pre-exposure prophylaxis

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

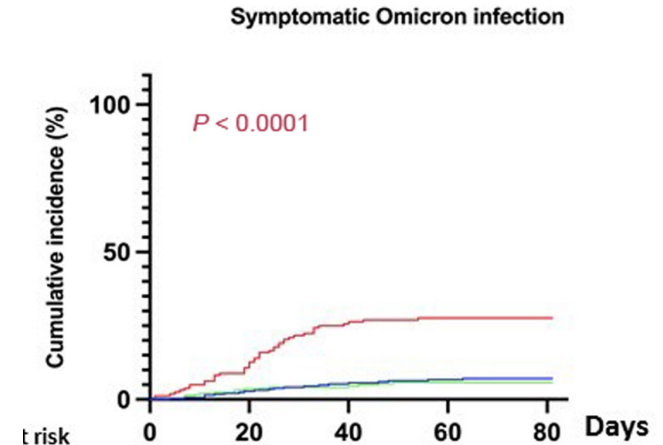
Real World Data Showing Efficacy of Tixagevimab plus Cilgavimab during Omicron Surge

- **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



What about vaccines for children under 5 years?

Moderna COVID-19 vaccine: Children ages 6 months—5 years

- 38% efficacy after two doses
- Antibody levels after 2 doses similar to antibody levels in individuals ages 18-25 years
- Reactogenicity consistent with other recommended vaccines in this age group

Pfizer BioNTech COVID-19 vaccine: Children ages 6 months-4 years

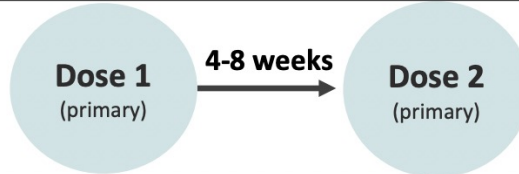
- Antibody levels after 3 doses similar to antibody levels after 2 doses in individuals ages 16-24 years
- 80% efficacy but small numbers: 3/992 vaccinees; 7/464 placebo

Children who are NOT moderately or severely immunocompromised

Pfizer-BioNTech
(6 months–4 years)

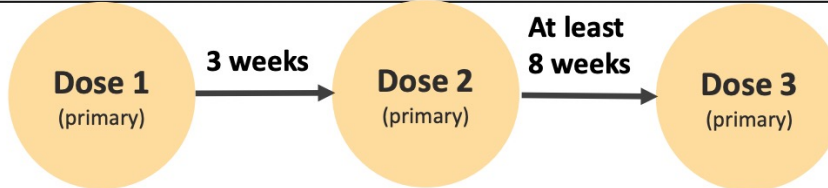


Moderna
(6 months–5 years)

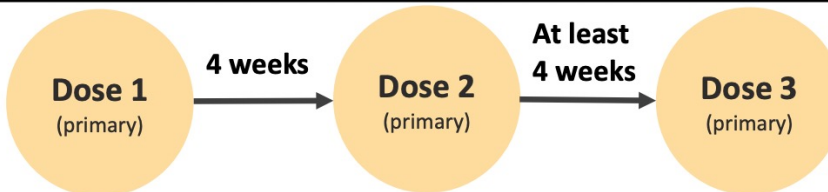


Children who ARE moderately or severely immunocompromised

Pfizer-BioNTech
(6 months–4 years)



Moderna
(6 months–5 years)



Part Three: Lessons from COVID-19 and HIV for Future Pandemics

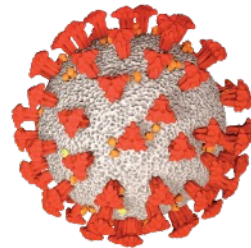
Lesson # 1:

Randomized Clinical Trials Critical to Identify What Does and Doesn't Work



Treatment with Indinavir, Zidovudine, and Lamivudine in Adults with Human Immunodeficiency Virus Infection and Prior Antiretroviral Therapy

Roy M. Gulick, M.D., M.P.H., John W. Mellors, M.D., Diane Havlir, M.D., Joseph J. Eron, M.D., Charles Gonzalez, M.D., Deborah McMahon, M.D., Douglas D. Richman, M.D., Fred T. Valentine, M.D., Leslie Jonas, B.S., Anne Meibohm, Ph.D., Emilio A. Emini, Ph.D., Jeffrey A. Chodakewitz, M.D., et al.

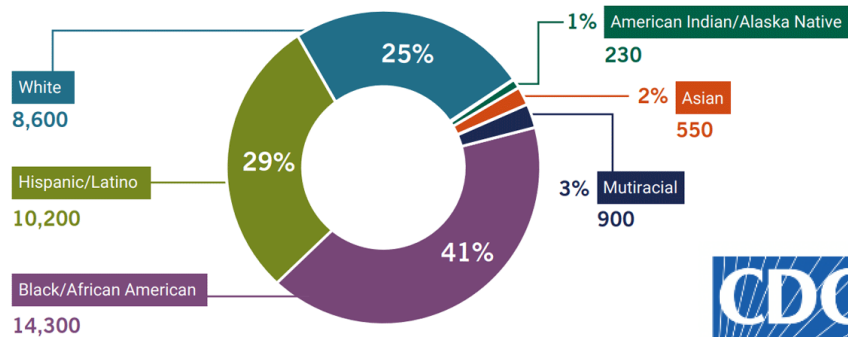


COVID-19
Prevention Network

Lesson # 2:

Disproportionate Impact of HIV and COVID-19 on Vulnerable Populations

HIV Incidence by Race, Ethnicity, 2019



<https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics>

<https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html>



Risk for COVID-19 Infection, Hospitalization, and Death by Race, Ethnicity

Rate ratios compared to White, Non-Hispanic persons	Black or African American persons	Hispanic or Latino persons
Cases	1.1x	1.5x
Hospitalization	2.4x	2.3x
Death	1.7x	1.8x

HIV and COVID-19: Mass General Hospital Series

- People with HIV with confirmed or probable COVID-19 in March/April 2020
- ~80% racial/ethnic minorities

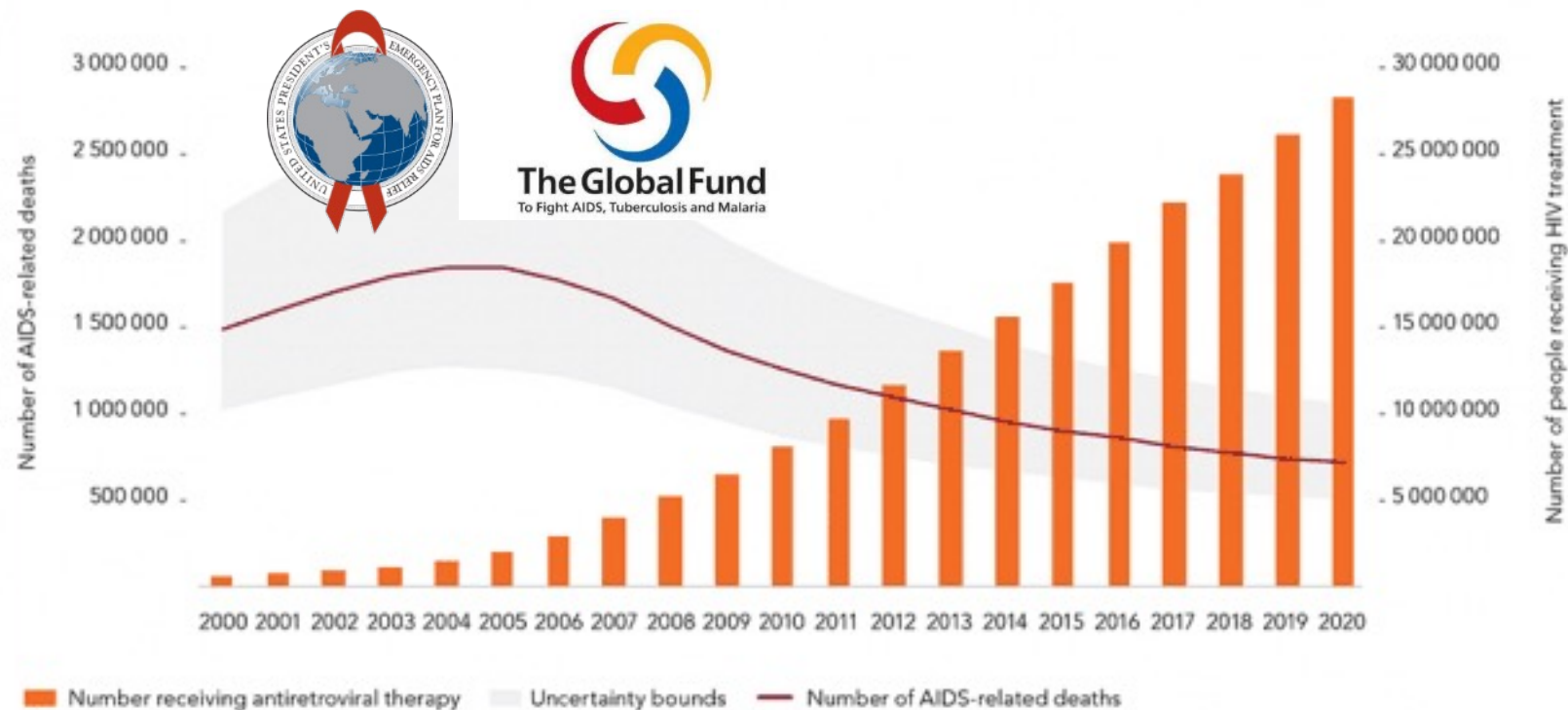
Disproportionate burden of coronavirus disease 2019 among racial minorities and those in congregate settings among a large cohort of people with HIV

Eric A. Meyerowitz^a, Arthur Y. Kim^{a,b}, Kevin L. Ard^{a,b}, Nesli Basgoz^{a,b},
Jacqueline T. Chu^{a,b,c}, Rocio M. Hurtado^{a,b,d}, Catherine K. Lee^a,
Wei He^c, Theresa Minukas^a, Sandra Nelson^{a,b}, Bisola O. Ojikutu^{a,b},
Greg Robbins^{a,b}, Sarimer Sanchez^a, Virginia A. Triant^{a,b,c,e},
Kimon Zachary^{a,b} and Rajesh T. Gandhi^{a,b}

Lesson # 3:

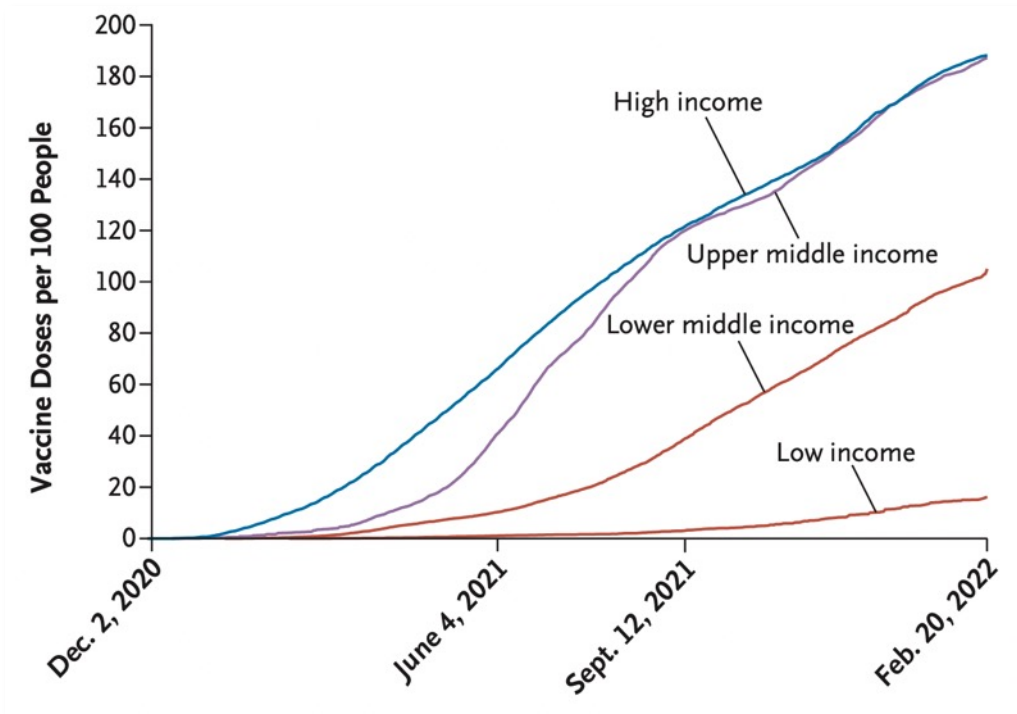
**Inequitable Access to Treatments, Vaccines and
Diagnostics Needs to Be Addressed by Advocacy**

Numbers of AIDS-related deaths and people receiving HIV treatment, global, 2000–2020



Source: UNAIDS epidemiological estimates, 2021.

COVID-19 Vaccine Inequity



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

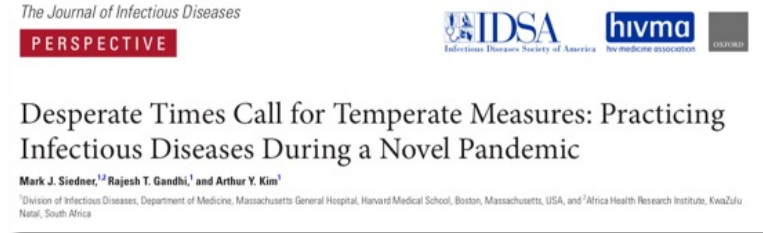
The Drive to Vaccinate the World Against Covid Is Losing Steam

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 for Future Pandemics

- 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

