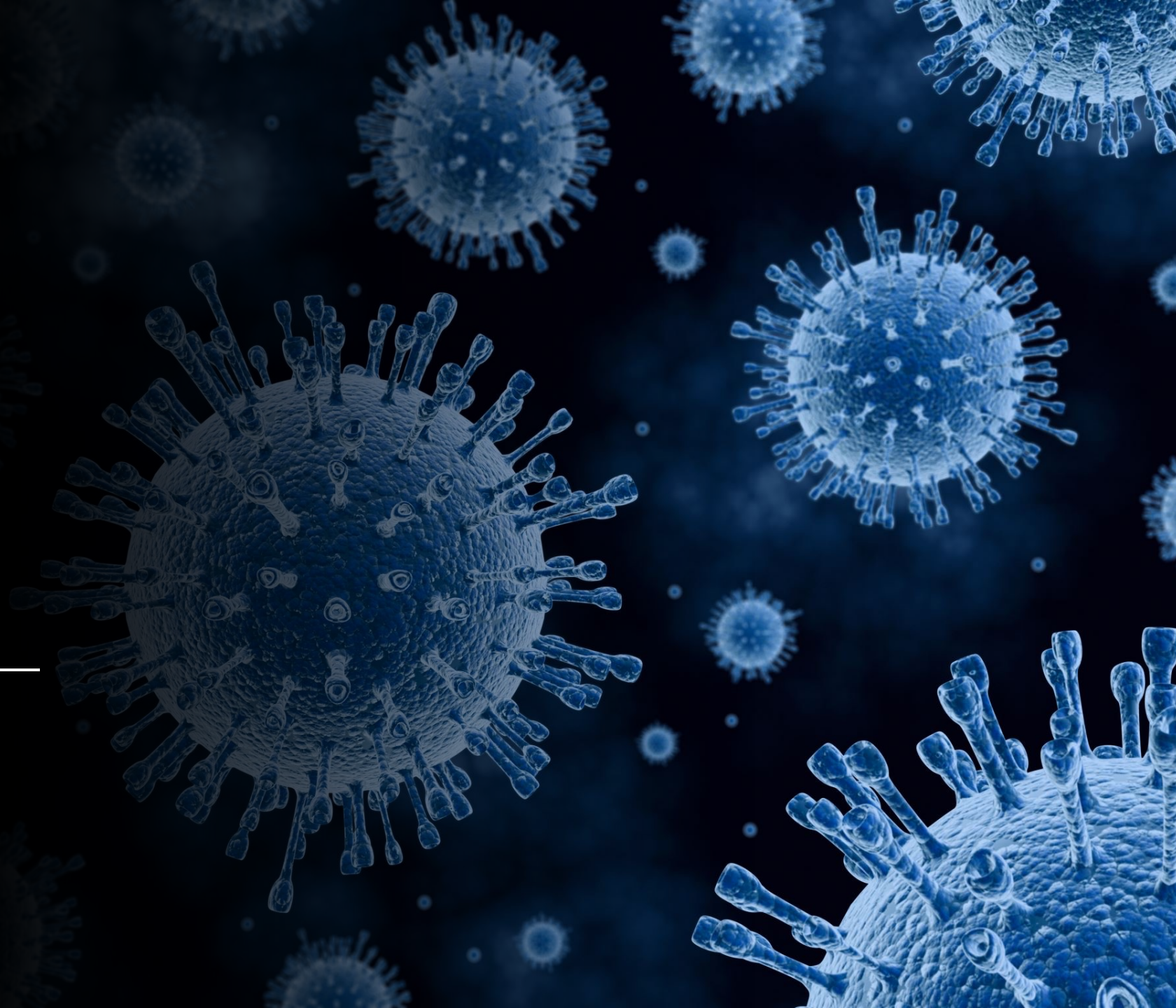
COVID-19 Update

Whitney Essex, APRN

Jorge Mera, MD



Outline

Previous Questions (Jorge Mera)

COVID-19 and pregnancy update (Whitney Essex)

Updates (Jorge Mera)

- COVID-19 Bivalent vaccine
- SARS-COV2 serology, clinical applications

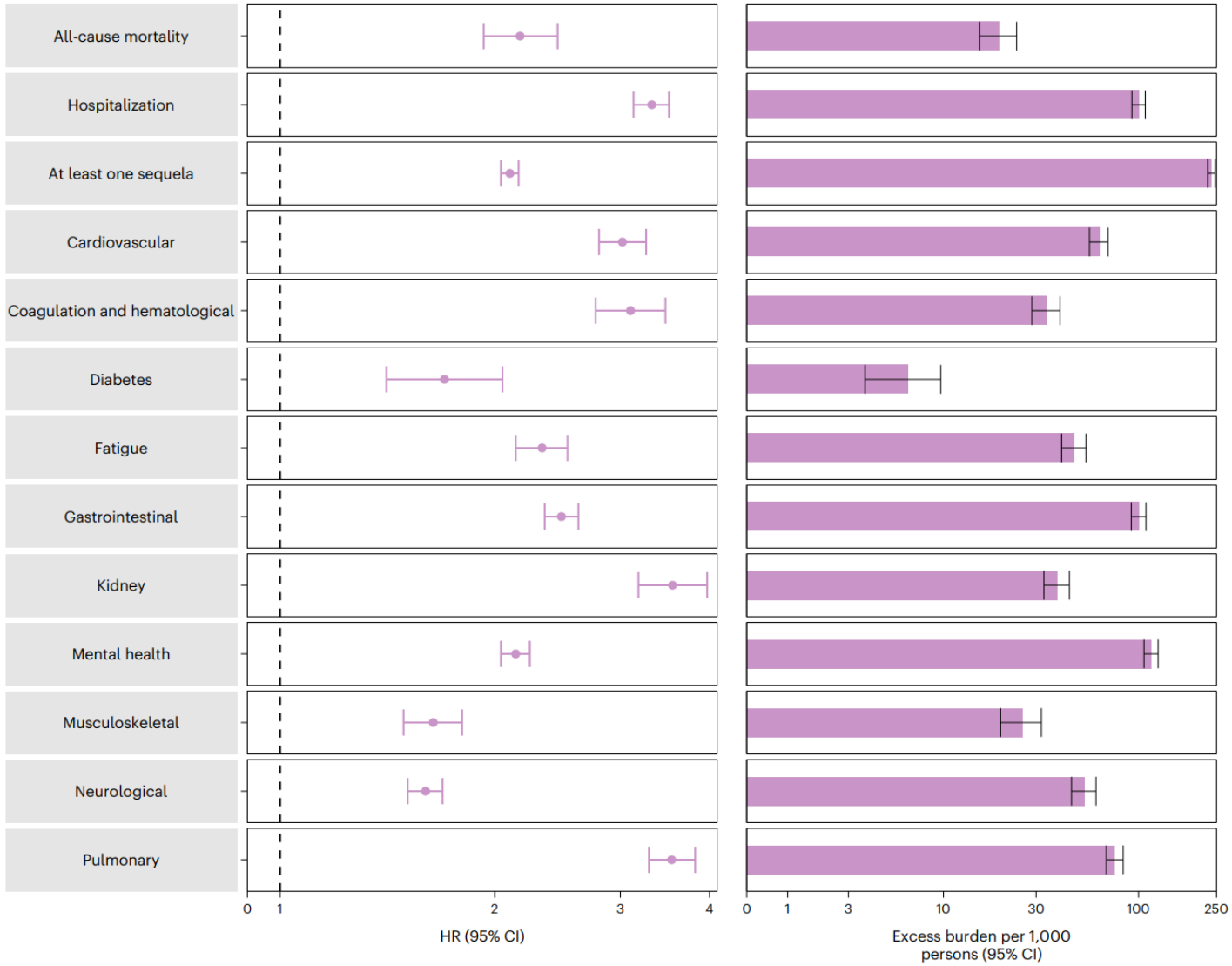
Horberg MA, Watson E, Bhatia M, et al. Nature Communications | (2022) 13:5822

Audience Questions

- **Is there a higher risk of Long COVID with cumulative infections? Is this correct? Is there data that support this?**
- Do we know if the risks of vaccination (myocarditis, etc) exponentially increase with the more shots that you get?
- Do Boosters increase the incidence of COVID-19 infections?

Acute and postacute sequelae associated with SARS-CoV-2 reinfection

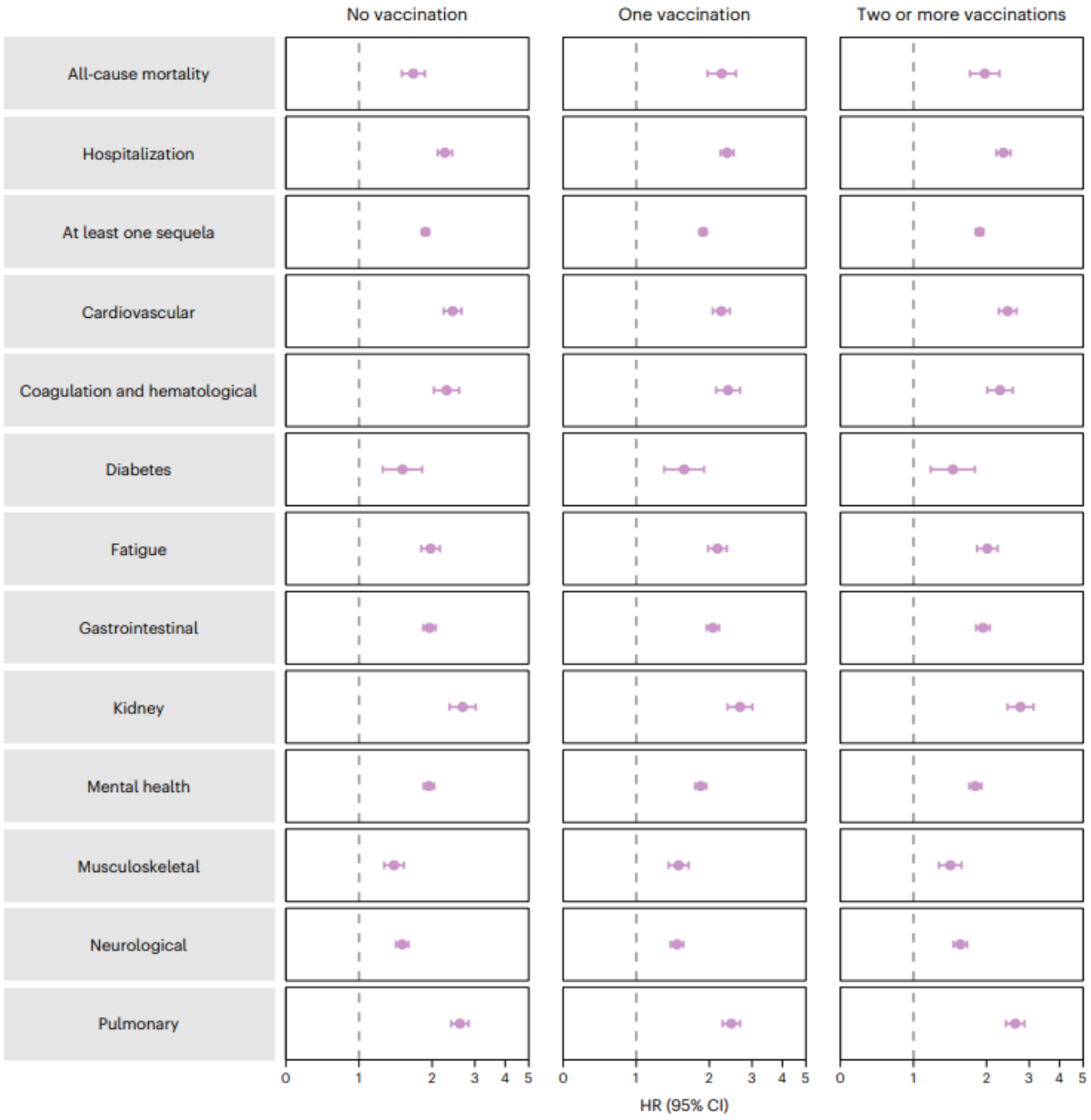
Risk and burden of sequelae in people with SARS-CoV-2 reinfection versus no reinfection. Risk and 6-month excess burden of all-cause mortality, hospitalization, at least one sequela and sequelae by organ system are plotted. Incident outcomes were assessed from reinfection to the end of the follow-up. Results from SARS-CoV-2 reinfection (n = 40,947) and no SARS-CoV-2 reinfection (n = 443,588) are compared. Adjusted HRs (dots) and 95% CIs (error bars) are presented, as are the estimated excess burden (bars) and 95% CIs (error bars). Burdens are presented per 1,000 persons at 6 months of follow-up from the time of reinfection.



Bowe, B., Xie, Y. & Al-Aly, Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med* (2022)

Acute and postacute sequelae associated with SARS-CoV-2 reinfection

Risk and burden of sequelae in people with SARS-CoV-2 reinfection versus no reinfection by vaccination status before reinfection. Risk of all-cause mortality, hospitalization, at least one sequela and sequelae by organ system are plotted. Incident outcomes were assessed from reinfection to the end of the follow-up. Results from SARS-CoV-2 reinfection (n = 40,947) versus no SARS-CoV-2 reinfection (n = 443,588) are compared. At the time of comparison, there were 51.3%, 12.6% and 36.2% with no, one and two or more vaccinations, respectively, among those who had reinfection. At the time of comparison, there were 41.1%, 11.7% and 47.2% with no, one and two or more vaccinations, respectively, among the no reinfection group. Adjusted HRs (dots) and 95% CIs (error bars) are presented.



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Booster dose of COVID-19 mRNA vaccine does not increase risks of myocarditis and pericarditis compared with primary vaccination: New insights from the vaccine adverse event reporting system

Methods:

- The CDC COVID Data Tracker and the VAERS were queried between December 11, 2020 and March 15, 2022.

- Incidence rates were calculated by cases of myocarditis/pericarditis divided by the number of vaccinated people or the total doses of COVID-19 mRNA vaccines.

Chen C, Fu F, Ding L, et al. Front Immunol. 2022 Sep 12;13:938322

Booster dose of COVID-19 mRNA vaccine does not increase risks of myocarditis and pericarditis compared with primary vaccination: New insights from the vaccine adverse event reporting system

Results:

- A total of 2,588 reports of myocarditis/pericarditis were identified after administration of primary-series COVID-19 mRNA vaccination
- A total of 269 cases were identified after the booster dose program during the study period.
- The incidence of myocarditis/pericarditis following booster COVID-19 mRNA vaccination was lower than that of primary series.

Conclusion:

- This study found that the booster dose of COVID-19 mRNA vaccination when compared with primary series course did not lead to an increase in the risks of myocarditis/pericarditis

Chen C, Fu F, Ding L, et al. Front Immunol. 2022 Sep 12;13:938322

Myocarditis/pericarditis Incidence Rates after Pfizer and Moderna COVID-19 Vaccine Administration

December 11, 2020 and March 15, 2022

	Total doses administered	Cases	Incidence rate*
Dose 1	243,897,183	738	3.03 (2.81-3.25)
Dose 2	199,808,526	1,850	9.26 (8.84-9.69)
In total	**443,705,709**	**2,588**	**5.83 (5.61-6.06)**
Booster dose			
Dose 3	94,662,809	269	**2.84** (2.51-3.20)

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- **Do we know if the risks of vaccination (myocarditis, etc) exponentially increase with the more shots that you get?**

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Do Boosters increase the incidence of COVID-19 infections?

Comparing incidence of COVID-19 infections in people who got the bivalent booster vs those who did not

- Can be very tricky
- There are no randomized studies

People who got boosted are probably more likely to

- Get tested if they get symptomatic than those who did not get a booster
- Get a PCR test compared to a home test if they get symptomatic than those who did not get a booster

Do Boosters increase the incidence of COVID-19 infections?

Limitations on incidence measurements of COVID-19 Infections

- Higher prevalence of previous infection among the unvaccinated and un-boosted groups
- Difficulty in accounting for time since vaccination and waning protection
- Possible differences in testing practices (such as at-home tests) and prevention behaviors by age and vaccination status.

These limitations appear to have less impact on the death rates

- CDC is assessing whether to continue using these case rate data to provide preliminary information on vaccine impact.

People who were unvaccinated

- Had a greater risk of testing positive for COVID-19 and a greater risk of dying from COVID-19 than people who were vaccinated

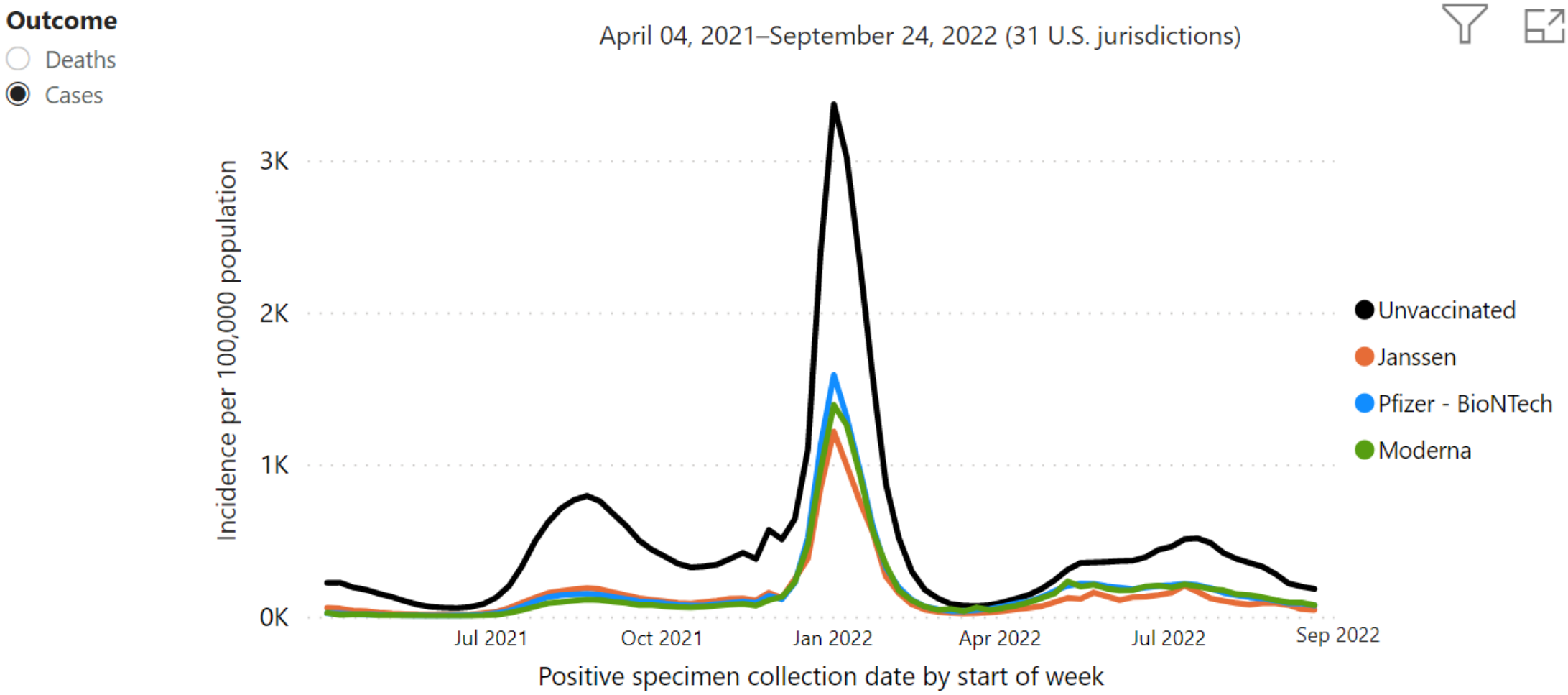
People who were vaccinated with a primary series *and* two additional or booster doses

- Had lower death rates
- Followed by people who received one additional or booster dose, compared with those *without* an additional or booster dose.

All vaccinated groups had lower risk of dying from COVID-19 compared with people who were unvaccinated

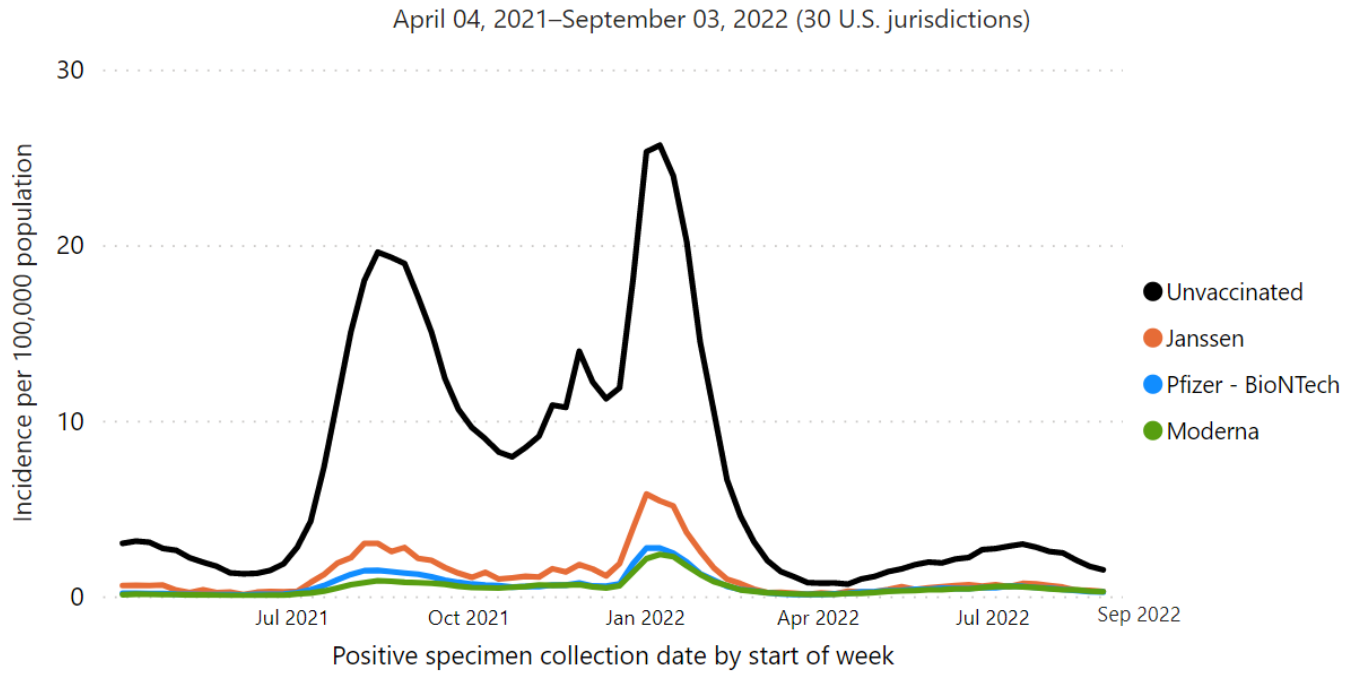
https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status; Accessed November 17,2022

Rates of COVID-19 Cases by Vaccination Status and Primary Series Vaccine Type in Ages 6 Months and Older



https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed November 17,2022

Rates of COVID-19 Death by Vaccination Status and Primary Series Vaccine Type in Ages 6 months and older



Unvaccinated people aged 6 months and older had:

2.7X
Risk of Testing Positive for COVID-19

AND

6X
Risk of Dying from COVID-19

in August 2022, and

2.5X
Risk of Testing Positive for COVID-19

in September 2022, compared to people vaccinated with at least a primary series.

Source: CDC COVID-19 Response, Epidemiology Task Force, Surveillance & Analytics Team, Vaccine Breakthrough Unit

https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status
Accessed November 17,2022

COVID-19 and Pregnancy

Outline

- General Concepts
- Data
  - Definitions
- Vaccination
- Risk factors
- Outcomes
- Treatment

General Concepts

- Infection can be asymptomatic or symptomatic, just like general population
- If symptomatic, there is increased risk of severe disease and increased risk of pregnancy complications, such as preterm birth
- In utero transmission is rare
- There is no difference in rates of miscarriage
- Also no difference in rates of congenital anomalies
- Neonatal outcomes are good overall
- Vaccines are safe and reduce risk of disease and decrease severity of disease
- Treatments are available
- Definition: Severe outcomes of COVID-19 are defined as hospitalization, admission to the intensive care unit (ICU), intubation or mechanical ventilation, or death

COVID-19 in Pregnancy Data

- From Jan 22, 2020 to April 11, 2022:
  - 198,598 were pregnant and diagnosed with COVID-19 in the US
    - Hospitalization data available for 160,857
  - Of the 160,857, there were 31,959 hospitalized **19.9%**
    - 18,764 had ICU data available
  - 970 pregnant women (123 studies, 179,981 women) with confirmed COVID-19 died from any cause

(Allotey et al., 2022)

Statistics of Note

- Moderate, severe, or critical illness develops in almost 10% of pregnant patients
  - 90% recover without hospitalization
- 13% ICU admission in pregnant
  - vs. 6.9% in non-pregnant
- 62% higher chance of pre-eclampsia than pregnant without COVID-19
- 8.8% preterm delivery in pregnant with COVID-19
  - vs. 5.5% in pregnant without COVID-19

(Allotey et al., 2022)

Pregnancy Data: Delta vs. pre-Delta

- When comparing pregnant women aged 15-44 in the pre-Delta period (January 1, 2020 – June 26, 2021) with those in the Delta period (June 27, 2021 – December 25, 2021):
  - The risk of **admission to an ICU was 41% higher** in the Delta period.
  - The risk of **invasive ventilation or ECMO was 83% higher** in the Delta period.
  - The **risk of death in the Delta period was 3.3 times** the risk in the pre-Delta period.
- Pregnant vs. non-pregnant
  - 5 times the risk of admission to an ICU
  - 76% increased risk of invasive ventilation or ECMO
  - Six times more likely to die as compared to pregnant women without COVID

(CDC, 2022)

Preventing COVID-19 in Pregnancy

- Counsel about the increased risk for severe disease from SARS-CoV-2 infection and recommend ways to protect themselves and their families from infection (and document this education!)
- Typical prevention measures:
  - Vaccination
  - Handwashing, masking, social distancing
- Pre-Exposure Prophylaxis (PrEP) with anti-SARS-CoV-2 monoclonal antibodies (mAbs)
  - Should not be withheld due to pregnancy

COVID-19 Vaccination

- Safe and effective in pregnancy and when breastfeeding
- Recommended for all pregnant, pre-pregnant, or recently pregnant
- Includes primary series plus booster doses
  - A bivalent mRNA booster is preferred
- Non-vector-based vaccine is preferred (in no particular order)
  - Pfizer-BioNTech (mRNA vaccine)
  - Moderna (mRNA vaccine)
  - Novavax (protein subunit vaccine)
- Why are these preferred?
  - Rare cases of thrombosis following vaccination with vector-based vaccines, with females at higher risk than males (Johnson & Johnson-Janssen)

(ACOG, 2022)

COVID-19 Vaccination

- COVID infection in pregnant people who had full vaccination is not associated with increased risk of adverse outcomes
- No increase in stillbirths and no increase in preterm births for those fully vaccinated
- During the Omicron surge, infants under six months old with COVID had the second highest hospitalization rates
  - Maternal COVID primary series vaccination protected infants under six months old from severe disease and hospitalizations due to COVID

https://www.ama-assn.org/delivering-care/public-health/novavax-booster-covid-vaccines-pregnancy-and-boosters-kids-sandra

Pre-Exposure Prophylaxis for COVID-19

- Pregnant patients qualify for PrEP with anti-SARS-CoV-2 mAbs
  - if they are unable to mount an adequate immune response to vaccination, or
  - They cannot receive a COVID-19 vaccine due to the potential for a severe reaction to the vaccine or its components
- IgG mAbs would be expected to cross the placenta
- No data on the use of these mAbs in pregnant patients; however, other IgG products have been safely used in pregnancy when indicated
- Tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld)

Tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld)

- For adults and adolescents (aged ≥12 years and weighing ≥40 kg), including pregnant women, who are:
  - Vaccinated, but also moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination
  - Not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components
- It is not used for treatment or post-exposure prophylaxis (PEP)

Tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld)

Authorization:

- Emergency use only, not FDA approved
- Pre-Exposure Prophylaxis only – not for treatment – not for post-exposure prophylaxis

Dosing:

- Tixagevimab 300 mg plus cilgavimab 300 mg administered as 2 consecutive 3-mL intramuscular injections
  - **Renal dosing:** No dosage adjustment necessary – can be given to dialysis patients as well
- Approved for those aged ≥12 years and weighing ≥40 kg

Timing:

- Given every 6 months
- If a person has received a COVID-19 vaccine, tixagevimab plus cilgavimab should be administered at least 2 weeks after vaccination

Highest Risk for Severe COVID-19

- Age
  - Strongest risk factor for severe COVID-19 outcomes
- Underlying conditions
  - The more comorbidities, the greater the risk level
- Race and Ethnicity
  - People from racial and ethnic minority groups are dying from COVID-19 disproportionately
  - When compared to non-Hispanic whites, more likely to be hospitalized, be admitted to the ICU, and die from COVID-19 at younger ages

(CDC, 2022)

Risk levels for severe COVID-19 outcomes: Underlying conditions

(CDC, 2022)

Risk Levels by Underlying Condition

Higher Risk for severe COVID-19 outcomes

Asthma and Chronic Lung Diseases; Cancer; Cerebrovascular disease

Chronic kidney or liver disease; Diabetes mellitus, type 1 and type 2; Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)

HIV (human immunodeficiency virus)

Some mental health disorders; Disabilities; Dementia

Obesity (BMI ≥30 or ≥95th percentile in children)

Primary Immunodeficiencies; Use of corticosteroids or other immunosuppressive medications

Pregnancy and recent pregnancy

Physical inactivity; Smoking, current and former

Solid organ or hematopoietic cell transplantation; Tuberculosis

(CDC, 2022)

Risk Levels by Underlying Condition

Suggestive higher risk for severe COVID-19

- Overweight (BMI ≥25, but <30)
- Sickle cell disease
- Substance use disorders
- Thalassemia

Mixed evidence for severe COVID-19

- Alpha 1 antitrypsin deficiency
- Bronchopulmonary dysplasia
- Hepatitis B
- Hepatitis C
- Hypertension

(CDC, 2022)

Severe COVID-19 Disease In Pregnancy

- Associations
  - Increased maternal age
  - High body mass index
  - Any pre-existing maternal comorbidity
  - Chronic hypertension
  - Pre-existing diabetes
  - Pre-eclampsia

(Allotey et al., 2022)

Managing COVID-19 in Pregnancy

- Therapeutic management of pregnant patients with COVID-19 should be the same as for non-pregnant patients, with a few exceptions (discussed later)
- The COVID-19 Treatment Guidelines Panel **recommends against** withholding COVID-19 treatments or vaccination from pregnant or lactating individuals specifically because of pregnancy or lactation
- If hospitalization is indicated, it should be in a facility that can conduct maternal and fetal monitoring
  - Consult with obstetric, maternal-fetal medicine, infectious disease, pulmonary-critical care, and pediatric specialists, as appropriate

NIH COVID-19 Treatment Guidelines

For outpatients not requiring supplemental oxygen

For All Patients:

- All patients should be offered symptom management (AIII).
- The Panel **recommends against** the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication (AIIb).

For Patients Who Are at High Risk of Progressing to Severe COVID-19[b]

Preferred therapies. Listed in order of preference:

- **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] (AIIa)
- **Remdesivir**[d,e] (BIIa)

Alternative therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:

- **Bebtelovimab**[f] (CIII)
- ~~**Molnupiravir**[d,g,h] (CIIa)~~

Per NIH - Molnupirivir: Not recommended in pregnancy unless there are no other options and therapy is clearly indicated

Rating of Recommendations: A = Strong; B = Moderate; C = Weak; **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Ritonavir-boosted nirmatrelvir (Paxlovid): Data from the EPIC-HR Study

2,246 subjects were randomized to receive either PAXLOVID or placebo

	PAXLOVID (N=1,039)	**Placebo** (N=1,046)
COVID-19 related hospitalization or death from any cause through Day 28		
n (%)	8 (0.8%)	66 (6.3%)
Reduction relative to placebo[a] [95% CI], %	-5.62 (-7.21, -4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval.

88% Relative Risk Reduction in Hospitalization or Death

https://www.covid19oralrx-patient.com/files/Fact_Sheet_HCP.pdf

Nirmatrelvir 300mg/ritonavir 100mg (Paxlovid)

First-line Preferred Regimen

Authorization:

- Emergency use only, not FDA approved
- Mild to moderate illness only – not for hospitalized persons
- Treatment only – not for pre- or post-exposure

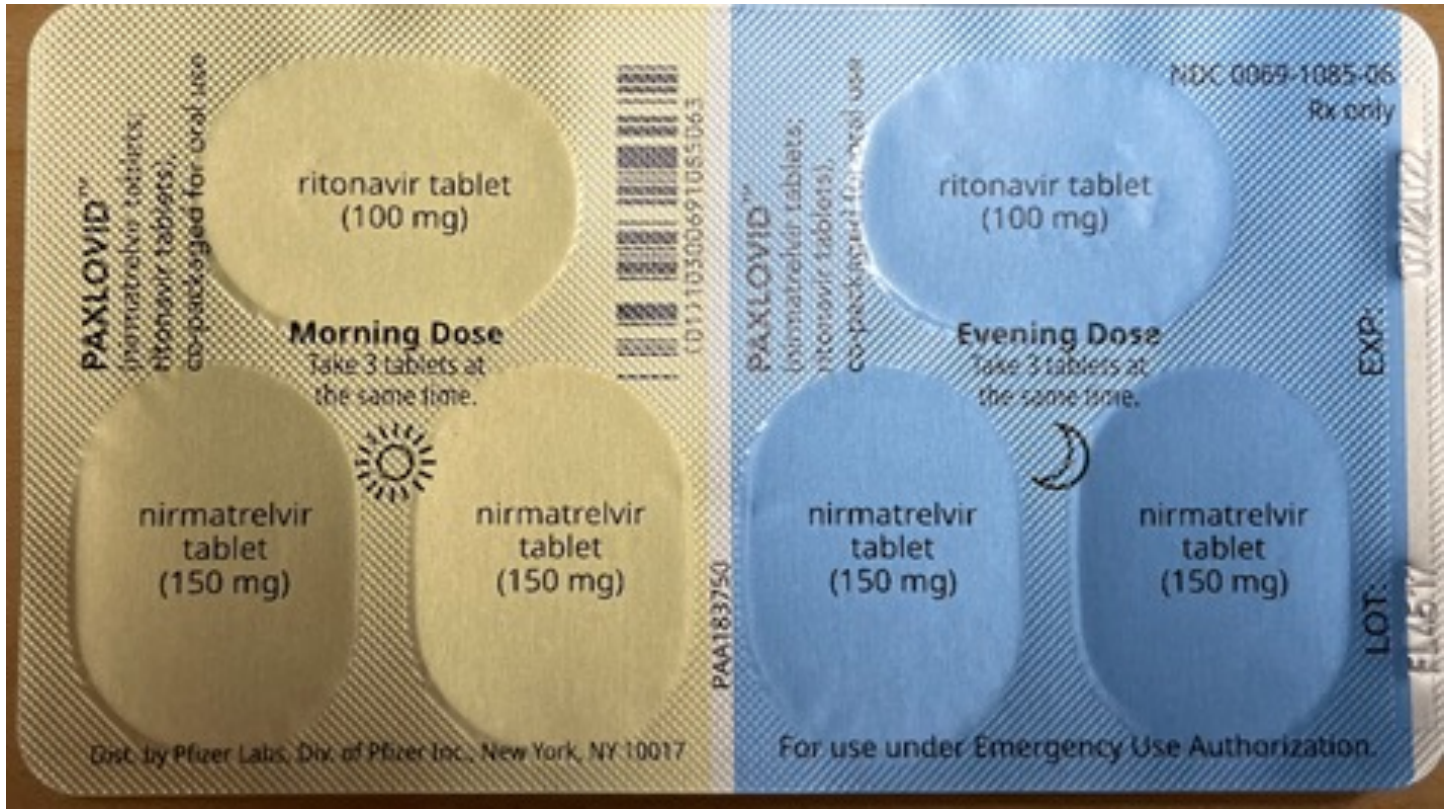
Dosing:

- 300mg nirmatrelvir (two 150mg tablets) with 100mg ritonavir (one 100mg tablet), with all 3 tablets taken together twice daily for 5 days
  - **Renal dosing:** Dose reductions must be made for patients with eGFR ≥ 30 to <60; if eGFR <30, not recommended
- For those aged ≥12 years and weighing ≥40 kg

Timing:

- Start Paxlovid within 5 days of symptom onset
- Better outcomes if started within 3 days of symptom onset
- Reduces risk of hospitalization/death
- Has significant/complex drug-drug interactions

Nirmatrelvir 300mg/ritonavir 100mg (Paxlovid)



Nirmatrelvir 300mg/ritonavir 100mg (Paxlovid): Adverse Effects

Allergic Reactions – hives, trouble breathing or swallowing, swelling, throat tightness, hoarseness, skin rash

Liver problems – loss of appetite, jaundice, dark-colored urine, pale-colored stools and pruitis, or abdominal pain

Resistance to HIV Medications – may lead to some HIV medicines not working as well in the future if needed

Other reported side effects – **metallic taste** or other altered taste (COMMON), diarrhea, high blood pressure, muscle aches

Drug Interactions: Nirmatrelvir/ritonavir

Contraindicated Medications		
•**Anticonvulsants** •Carbamazepine •Phenobarbital •Phenytoin •Primidone •**Immunosuppressants** •Voclosporin •**Pulmonary hypertension** •Sildenafil •Tadalafil •Vardenafil	•**Miscellaneous** •Bosentan •Certain chemotherapeutic agents •Ergot derivatives •Lumacaftor/ivacaftor •St. John's wort •Tolvaptan •**Anti-infectives** •Glecaprevir/pibrentasvir •Rifampin •Rifapentine	•**Cardiovascular** •Amiodarone •Clopidogrel •Disopyramide •Dofetilide •Dronedarone •Eplerenone •Flecainide •Ivabradine •Propafenone •Quinidine •**Neuropsychiatric** •Clozapine •Lurasidone •Midazolam (oral) •Pimozide

Considerations in Pregnancy: Nirmatrelvir/ritonavir

- EPIC-HR trial excluded pregnant and lactating individuals
- Ritonavir has been used extensively during pregnancy in people with HIV and has a favorable safety profile during pregnancy
- The mechanisms of action and the results of animal studies suggest that this regimen can be used safely in pregnant and lactating individuals
- Should be offered to pregnant and recently pregnant patients based on risk-benefit assessment

Remdesivir

Authorization:

- Fully FDA approved
- Can be used for outpatients with mild to moderate illness or for hospitalized persons (duration differs)
- Treatment only – not for pre- or post-exposure

Dosing:

- 200mg IV once on day 1, then 100mg IV daily on days 2 and 3
  - Renal dosing: No dosage adjustment necessary if eGFR >30
- Children weighing ≥40 kg – same as adult dosing above
- Infants/Children >3kg to <40kg: Lyophilized powder only: IV: Loading dose: 5 mg/kg/dose on day 1, followed by 2.5 mg/kg/dose once daily on days 2 and 3

Timing:

- Initiate as soon as possible after diagnosis of symptomatic COVID-19 and within 7 days of symptom onset
- Better outcomes if started early
- Administer as an IV infusion over 30 to 120 minutes - Patients should be observed for ≥1 hour after infusion as clinically appropriate.

Remdesivir

87% Relative Risk Reduction in Hospitalization/Death

Remdesivir: Adverse Effects

- Gastrointestinal symptoms (Nausea)
- Elevated liver enzymes
- Increase in prothrombin time (PT) without change in the international normalized ratio (INR)
- Hypersensitivity reactions

Considerations in Pregnancy: Remdesivir

- Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19
- Subsequent reports on the use of remdesivir in pregnant patients have been reassuring
- Systematic review of 13 observational studies that included 113 pregnant people reported few adverse effects in pregnant patients with COVID-19
  - It was used for moderate to severe illness
- Most common adverse advent was a mild elevation in transaminase levels

Bebtelovimab

- EUA only – not FDA approved
- For nonhospitalized adults aged ≥18 years with mild to moderate COVID-19 and high risk of progressing to severe disease
- **An alternative therapy <u>ONLY</u>** when both ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate
- Treatment should be initiated as soon as possible and within 7 days of symptom onset
- 175mg IV push over 30+ seconds
- Patients should be monitored for at least 1 hour after administration

Considerations in Pregnancy: Bebtelovimab

- Can be a treatment option for pregnant people with COVID-19, especially those who have additional risk factors for severe disease
- There are no pregnancy-specific data on the use of bebtelovimab; however, other IgG products have been safely used in pregnant people when indicated
- Authorized anti-SARS-CoV-2 mAbs should not be withheld during pregnancy

Antithrombotic Therapy

- Pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications after they receive a diagnosis of COVID-19
- A prophylactic dose of anticoagulation is recommendation for pregnant patients **who are hospitalized** for manifestations of COVID-19, unless a contraindication exists
- There is insufficient evidence to recommend either for or against the use of therapeutic anticoagulation in pregnant patients with COVID-19 who do not have evidence of venous thromboembolism

Summary

- Pregnancy places an individual at higher risk for experiencing severe COVID-19
- Pregnant women with COVID-19 are more likely to be hospitalized, mechanically ventilated, and die
- Preterm labor is more common in pregnant women with COVID-19
- Preventing COVID-19 and decreasing its severity is crucial and can be accomplished with vaccination in pregnant people and women of childbearing potential
- Treatment is available and should be offered if appropriate

References

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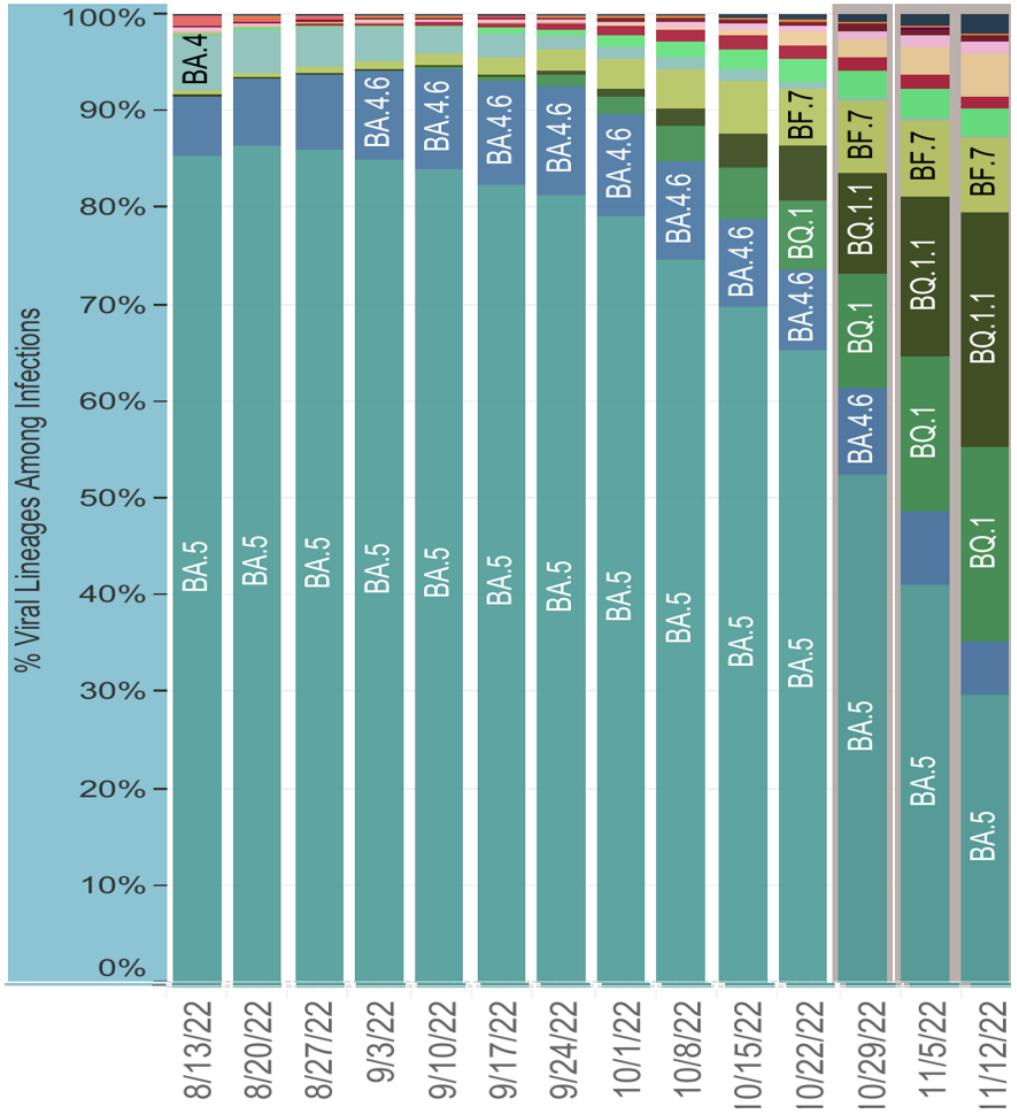
6. Schell RC, Macias DA, Garner WH, White AM, McIntire DD, Pruszynski J, Adhikari EH. Examining the impact of trimester of diagnosis on COVID-19 disease progression in pregnancy. Am J Obstet Gynecol MFM. 2022 Aug 20;4(6):100728. doi: 10.1016/j.ajogmf.2022.100728. Epub ahead of print. PMID: 35995369; PMCID: PMC9391234.

COVID-19 Variants in the United States

- Evusheld not active for:
  - BA4.6, BQ.1, Bq1.1 & BF.7
- Activity of Bebtelovimab against these new variants is also low



WHO label	Lineage #	US Class		%Total	9..
Omicron	BA.5		VOC	85.9%	
	BA.4.6		VOC	7.9%	
	BA.4		VOC	4.1%	
	BF.7		VOC	0.6%	
	BA.2.12.1		VOC	0.4%	
	BA.2.75		VOC	0.3%	
	BA.2		VOC	0.3%	
	BA.2.75.2		VOC	0.1%	
	BA.5.2.6		VOC	0.1%	
	BQ.1		VOC	0.1%	
	BA.1.1	†	VOC	0.0%	
	B.1.1.529	†	VOC	0.0%	
	BN.1	†	VOC	0.0%	
	BQ.1.1	†	VOC	0.0%	
Delta	B.1.617.2	†	VBM	0.0%	
Other	Other*			0.1%	

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
† Estimates are less reliable based on one or more violations of NCHS data presentation standards for proportions: https://www.cdc.gov/nchs/data/series/sr_02/sr02..

A Bivalent Omicron-Containing Booster Vaccine against Covid-19

A Bivalent vaccine (Wuhan-Hu-1 and omicron) was compared with previously authorized mRNA-1273 booster

- Open-label, ongoing phase 2–3 study in adults who had received a two-dose primary series (100 µg) and first booster dose (50 µg) of mRNA-1273 in the COVE trial or under U.S. EUA at least 3 months earlier.
- The bivalent vaccine contained 50-µg (25 µg each of ancestral Wuhan-Hu-1 and omicron B.1.1.529 [BA.1] spike messenger RNAs)

Both vaccines were given as a second booster

- In adults who had previously received a two-dose (100-µg) primary series and first booster (50-µg) dose of mRNA-1273 (≥3 months earlier).
- COVID-19 infection in previous 3 months was an exclusion criteria

The primary objectives were to:

- Assess the safety, reactogenicity, and immunogenicity of mRNA-1273.214 at 28 days after the booster dose.

Horberg MA, Watson E,Bhatia M, et al. Nature Communications | (2022) 13:5822

A Bivalent Omicron-Containing Booster Vaccine against Covid-19

The median time between the first and second boosters was similar for mRNA-1273.214 (136 days) and mRNA-1273 (134 days).

In participants with no previous SARS-CoV-2 infection the geometric mean titers of neutralizing antibodies against the omicron BA.1 variant

- Were 2372.4 (95% CI, 2070.6 to 2718.2) after receipt of the bivalent booster
- Were 1473.5 (95% CI, 1270.8 to 1708.4) after receipt of the mRNA-1273 booster.

Against the omicron BA.4 and BA.5

- The Bivalent booster elicited geometric mean titers of 727.4 (95% CI, 632.8 to 836.1)
- The mRNA-1273 booster elicited 492.1 (95% CI, 431.1 to 561.9)

The bivalent booster compared to the mRNA-1273 booster

- Elicited higher binding antibody responses against multiple other variants (alpha, beta, gamma, and delta)

N Engl J Med 2022; 387:1279-1291

A Bivalent Omicron-Containing Booster Vaccine against Covid-19

Safety and reactogenicity were similar with the two booster vaccines.

Vaccine effectiveness was not assessed in this study

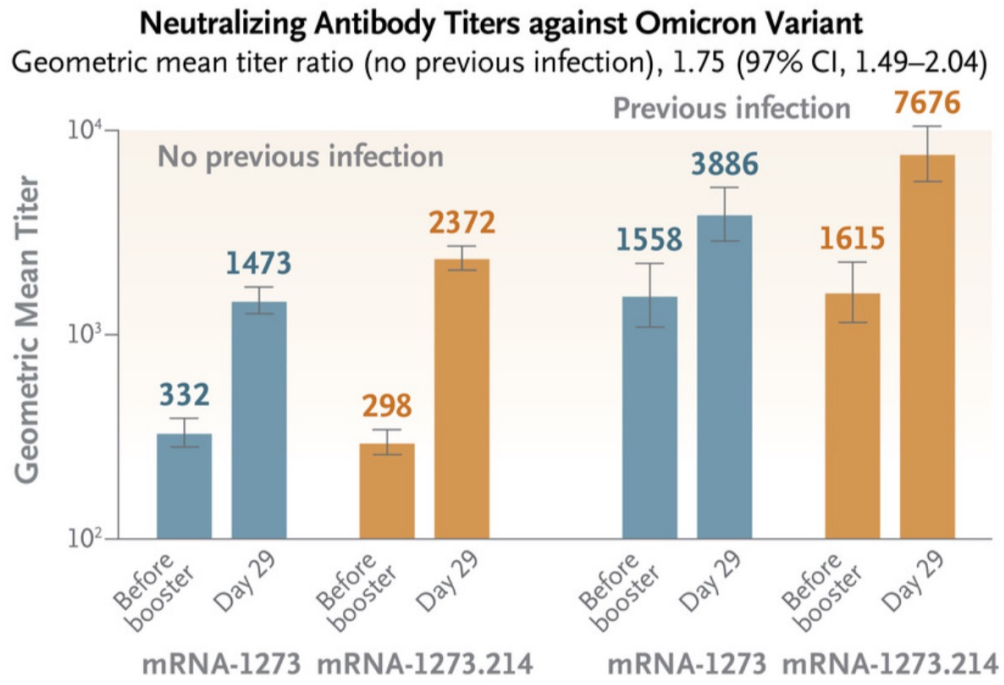
- In an exploratory analysis, SARS-CoV-2 infection occurred in 11 participants after the mRNA-1273.214 booster and in 9 participants after the mRNA-1273 booster.

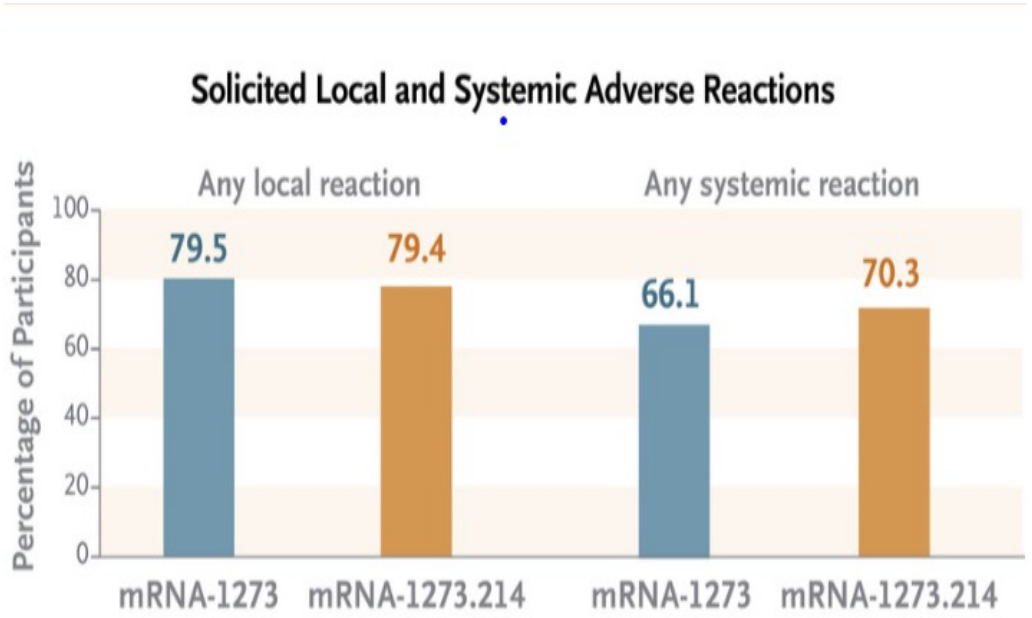
CONCLUSIONS

- The bivalent omicron-containing vaccine mRNA-1273.214 elicited neutralizing antibody responses against omicron that were superior to those with mRNA-1273, without evident safety concerns.

N Engl J Med 2022; 387:1279-1291

A Bivalent Omicron-Containing Booster Vaccine against Covid-19



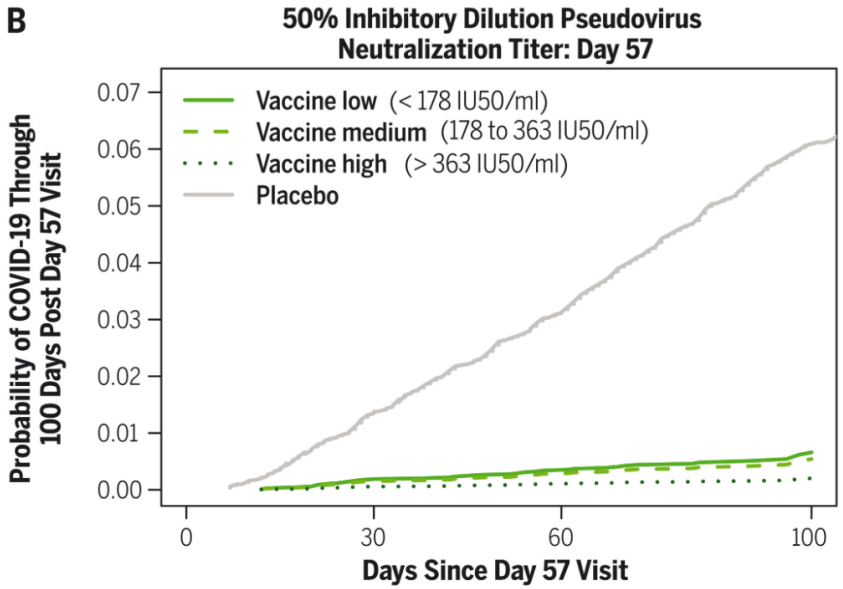


N Engl J Med 2022; 387:1279-1291

Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial

2 dose vaccine assessed
Higher antibody levels associated with less Disease

ID50 nAb Titer	Vaccine Efficacy vs Disease
1:10	78%
1:100	91%
1:1000	96%



IDSA 2022: *SCIENCE*, 23 Nov 2021;Vol 375, Issue 6576pp. 43-50

Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial: **Limitations**

Inability to control for SARS-CoV-2 exposure factors (e.g., virus magnitude)

Lack of data for assessing correlates against other outcomes besides COVID-19

- Such as severe COVID-19, asymptomatic SARS-CoV-2 infection, infection regardless of symptomology, and viral shedding)

Relatively short follow-up time of 4 months that precluded the assessment of immune correlate durability

- Relatively small number of COVID-19 cases

Lack of data for assessing the potential contribution of anamnestic responses to the immune correlates

Almost all COVID-19 cases resulted from infections with viruses with a spike sequence similar to that of the vaccine strain

- This precluded the assessment of robustness of correlates to SARS-CoV-2 variants of concern.

SCIENCE, 23 Nov 2021;Vol 375, Issue 6576pp. 43-50

Serologic Testing
Conclusions and Summary ID Week 2022

Role of SCV2 serologic testing for diagnosis

- Primarily for COVID-19 related sequelae when molecular/Ag tests were negative
- Envelope Ab is due to infection

Status of SCV2 correlation for protection

- Neutralizing and Binding Ab can be used as surrogates for vaccine efficacy but do not have a threshold cutoff
- High assay variety and lack of quantitative standardized assays
- Variability relative to different VOCs

Role of SCV2 to asses "immunity" or protection

- Not recommended for pre or post vaccination testing by any agency
- May be used on a case by case basis on Immunocompromised Hosts at higher risk of severe disease
  - Enhanced personal protective measures
  - Additional booster doses