COVID-19
October 8, Update

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Durability of immune responses to the BNT162b2 mRNA vaccine

Methods

- Analysis of antibody responses to the homologous Wu strain as well as several variants of concern and T cell responses at six months after the second dose.

Results

- Substantial waning of antibody responses and T cell immunity to SARS-CoV-2 and its variants

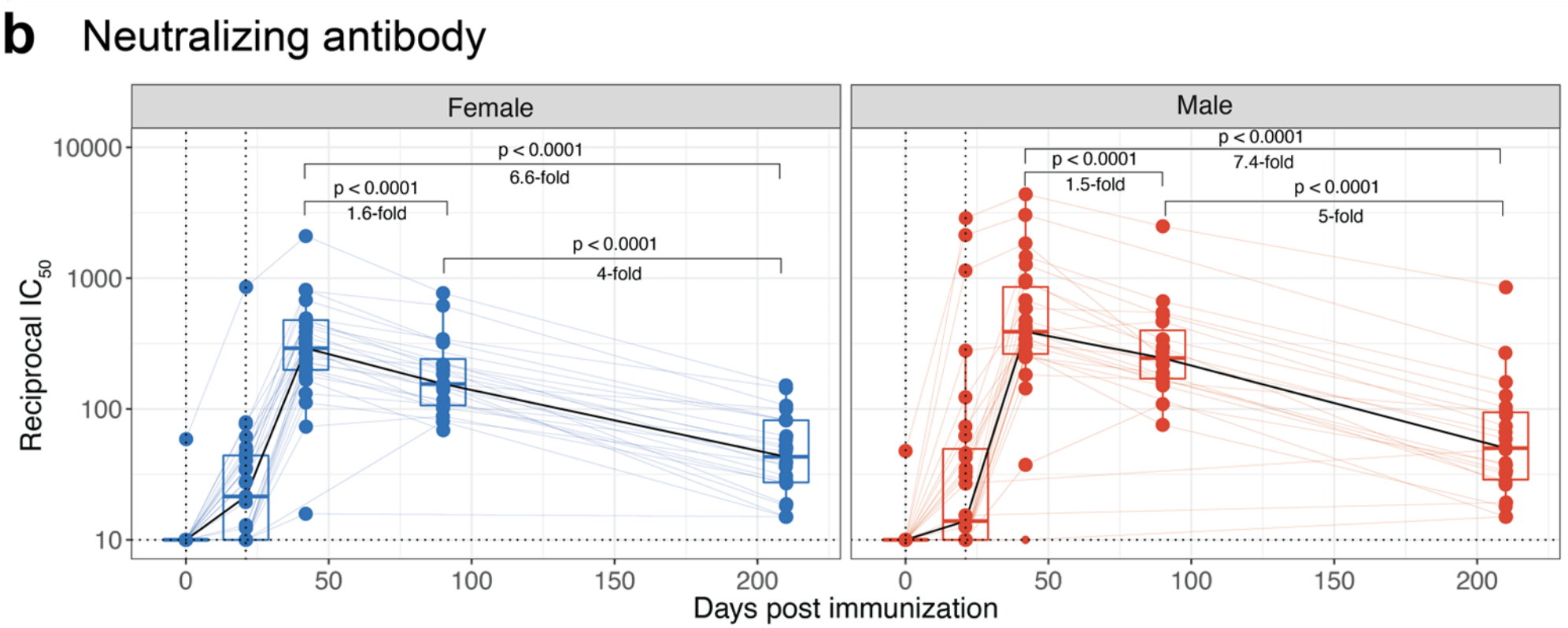
Conclusions

- This data suggest a 3rd booster immunization might be warranted to enhance the antibody titers and T cell responses.

Suthar1 MS, Arunachalam PS, Hu M, et al. doi: https://doi.org/10.1101/2021.09.30.462488This article is a preprint and has not been certified by peer review

Durability of antibody following the Pfizer-BioNTech mRNA vaccination

Kinetics of authentic live virus neutralizing antibody response against the homologous USA/WA1 strain (N = 46, 24 females and 22 males on day 210). Data of day 0, 21 and 90 were obtained from our previously published study6. Day 42 samples were re-assayed with day 210 samples by the FRNT assay.



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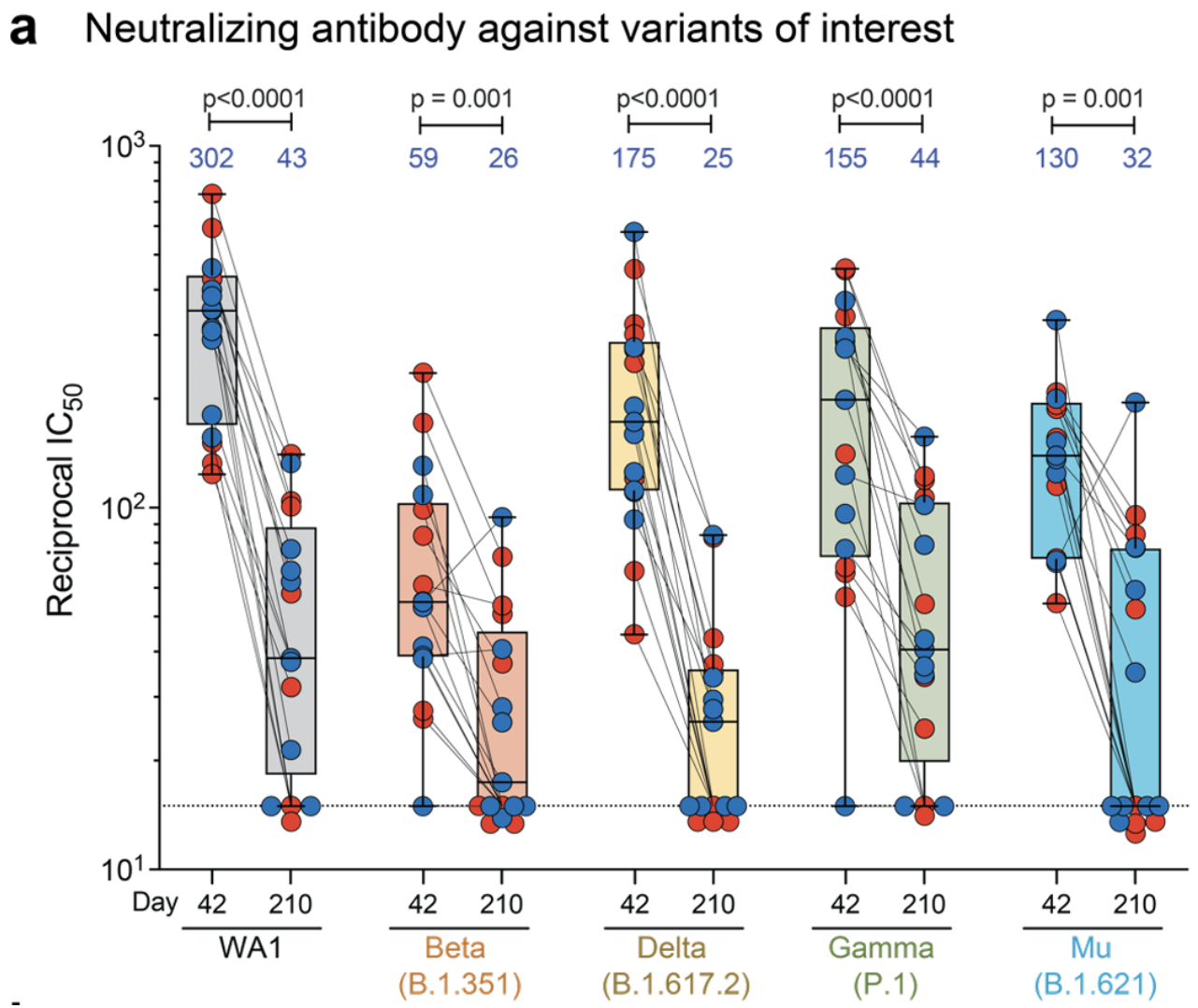
Durability of antibody following the Pfizer-BioNTech mRNA vaccination

- Durability of cross-neutralizing antibody responses following the Pfizer-BioNTech mRNA vaccination. a, Authentic live virus neutralizing antibody responses against the homologous USA/WA1 strain and the variants of concerns B.1.351 (Beta), B.1.617.2 (Delta), P.1 (Gamma) and B.1.621 (Mu) (N=17). The numbers in blue indicate geometric mean titers.



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Safety Monitoring of an Additional Dose of COVID-19 Vaccine – United States, August 12–September 19, 2021

What is already known about this topic?

- Among 306 Pfizer-BioNTech clinical trial participants, adverse reactions after dose 3 were similar to those after dose 2

What is added by this report?

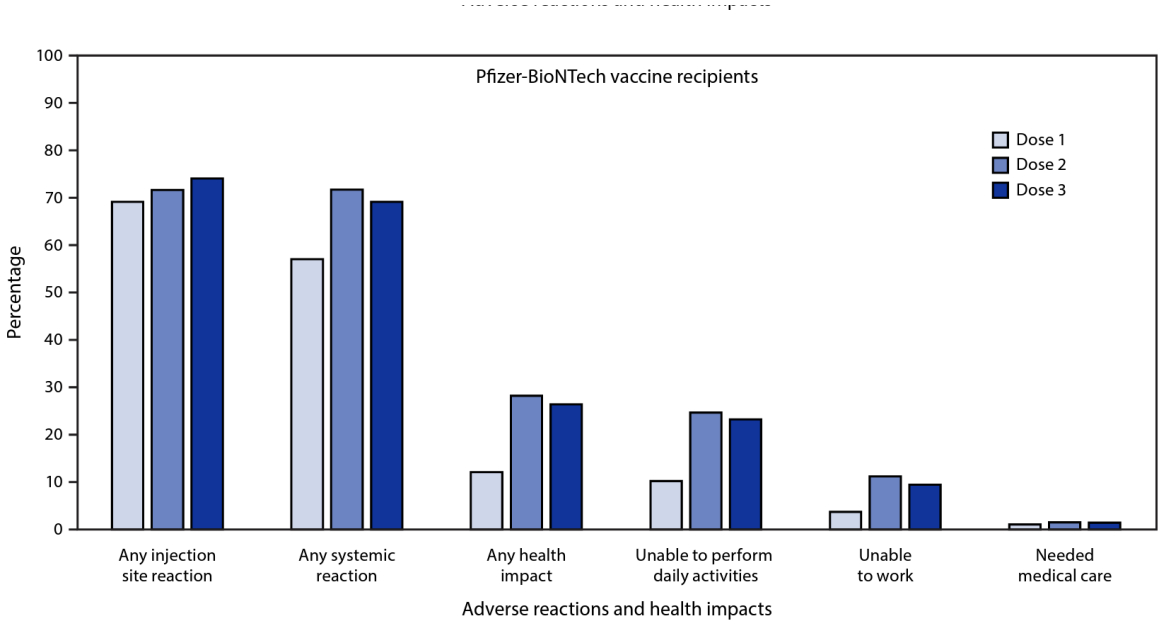
- During August 12–September 19, 2021, among 12,591 v-safe registrants who completed a health check-in survey after all 3 doses of an mRNA COVID-19 vaccine:
- 79.4% and 74.1% reported local or systemic reactions, respectively, after the third dose;
- 77.6% and 76.5% reported local or systemic reactions after the second dose,

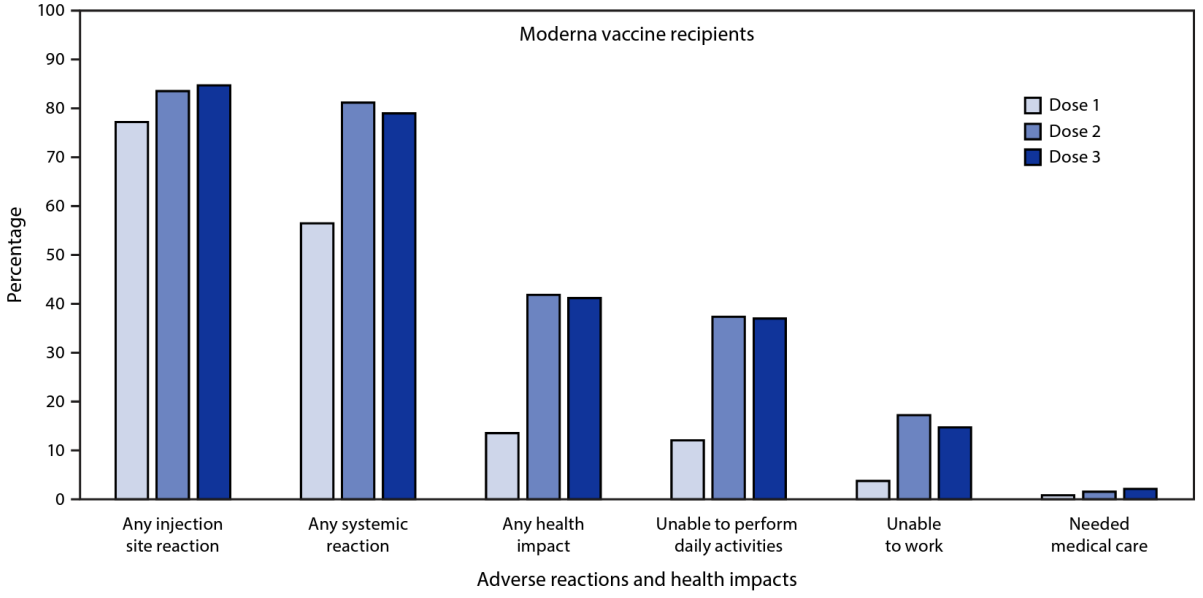
What are the implications for public health practice?

- Voluntary reports to v-safe found no unexpected patterns of adverse reactions after an additional dose of COVID-19 vaccine.

MMWR September 2021

Adverse reactions and health impacts reported by persons who received 3 doses* of Moderna (N = 6,283) or Pfizer-BioNTech (N = 6,308) COVID-19 vaccine and completed at least one v-safe health check-in survey on days 0–7 after each dose, by dose number United States, August 12–September 19, 2021





MMWR September 2021

COVID-19 Messenger RNA Vaccination and Myocarditis
A Rare and Mostly Mild Adverse Effect

Several recent case series have described acute myocarditis after COVID-19 messenger RNA (mRNA) vaccination.[1]

- This study examined the incidence and outcomes of acute myocarditis following COVID-19 mRNA vaccination in a large community health system.
- The study population was 54.0% women and 31.2% White, 6.7% Black, 37.8% Hispanic, and 14.3% Asian individuals.

During the 6 months of follow-up, there were 15 cases of myocarditis among the 2 392 924 Kaiser Permanente Southern California members who received at least 1 dose of the Pfizer and Moderna vaccines

- 1 case per 172 414 fully vaccinated individuals
- This represents a relative ratio of 2.7 compared with unvaccinated individuals.
- Affected patients were all men younger than 40 years with no prior cardiac history and were discharged within a week of conservative management.

JAMA Intern Med. Published online October 4, 2021. doi:10.1001/jamainternmed.2021.5634

COVID-19 Messenger RNA Vaccination and Myocarditis
A Rare and Mostly Mild Adverse Effect

Overall, vaccination-related myocarditis:

- Are rare and mostly mild adverse event.
- Data from the Vaccine Adverse Event Reporting System indicate that it is not unique to just the COVID-19 mRNA
- Up to 28% of patients with COVID-19 infection showed signs of myocardial

Randomized clinical trials show that COVID-19 mRNA vaccines represent a safe and effective method of preventing infection

- The identification of rare myocarditis does not change clinical decision-making.

JAMA Intern Med. Published online October 4, 2021. doi:10.1001/jamainternmed.2021.5634

Booster Dose of BNT162b2 (Pfizer COVID-19 Vaccine)

In the United States, the US Food and Drug Administration has authorized and the Centers for Disease Control (CDC) recommends a booster dose of BNT162b2 (Pfizer COVID-19 vaccine),

- To be given six months after the last dose of the primary BNT162b2 series
- For certain high-risk adults, including adults ≥65 years
- Adults ≥50 years who have comorbidities that increase the risk of severe COVID-19
- Adults <50 years with such comorbidities
- Adults who are at risk for exposure because of occupation or congregate living situations are also eligible for a booster dose.

Booster doses for individuals who received other COVID-19 vaccines have not yet been authorized

CDC.gov

Established, probable, and possible risk factors

(comorbidities that have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review in observational studies, or in case series)

- Cancer
- Neurologic conditions, including dementia
- Obesity* (BMI ≥30 kg/m^2) and overweight (BMI 25 to 29 kg/m^2)
- Pregnancy
- Smoking* (current and former)
- Sickle cell disease or thalassemia
- Solid organ or blood stem cell transplantation
- Substance use disorders
- Use of corticosteroids or other immunosuppressive medications
- HIV
- Cerebrovascular disease
- Children with certain underlying conditions
- Chronic kidney disease
- COPD* and other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension, cystic fibrosis)
- Diabetes mellitus, type 1* and type 2
- Down syndrome
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)

Possible risk factors but evidence is mixed

(comorbidities have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review, but other studies had reached different conclusions)

- Asthma
- Hypertension
- Immune deficiencies
- Liver disease

TO BOOST OR NOT TO BOOST

THAT IS THE QUESTION

Considerations in boosting COVID-19 vaccine immune responses

What is the Problem?

- Delta variant has led to consideration of the potential need for booster doses for vaccinated populations.

The Idea

- Reducing the number of COVID-19 cases by enhancing immunity in vaccinated people

What should be done

- The decision should be evidence-based and consider the benefits and risks for individuals and society.
- These decisions should be informed by reliable science more than by politics.

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine: What do we know from observational studies

COVID-19 vaccines continue to be effective against severe disease

- Including that caused by the delta variant

Most of the observational studies on which this is based are:

- Preliminary
- Difficult to interpret

Even if boosting were eventually shown to decrease the medium-term risk of serious disease:

- Current vaccine supplies could save more lives if used in previously unvaccinated populations than if used as boosters in vaccinated populations.

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine immune responses

PROs

Boosting May be Needed

For individuals in whom the primary vaccination might not have induced adequate protection

- Low efficacy vaccines
- Immunocompromised individuals
- Age

In the general population

- Because of waning immunity to the primary vaccination
- Because the original vaccine no longer protects adequately against currently circulating viruses.

CONs

Boosting May be a Problem

People who did not respond robustly to the primary vaccination

- Might also not respond well to a booster

It is not known what is more beneficial

- An additional dose of the same vaccine or a different vaccine

Even if humoral immunity appears to wane

- Reductions in neutralizing antibody titer do not necessarily predict reductions in vaccine efficacy over time

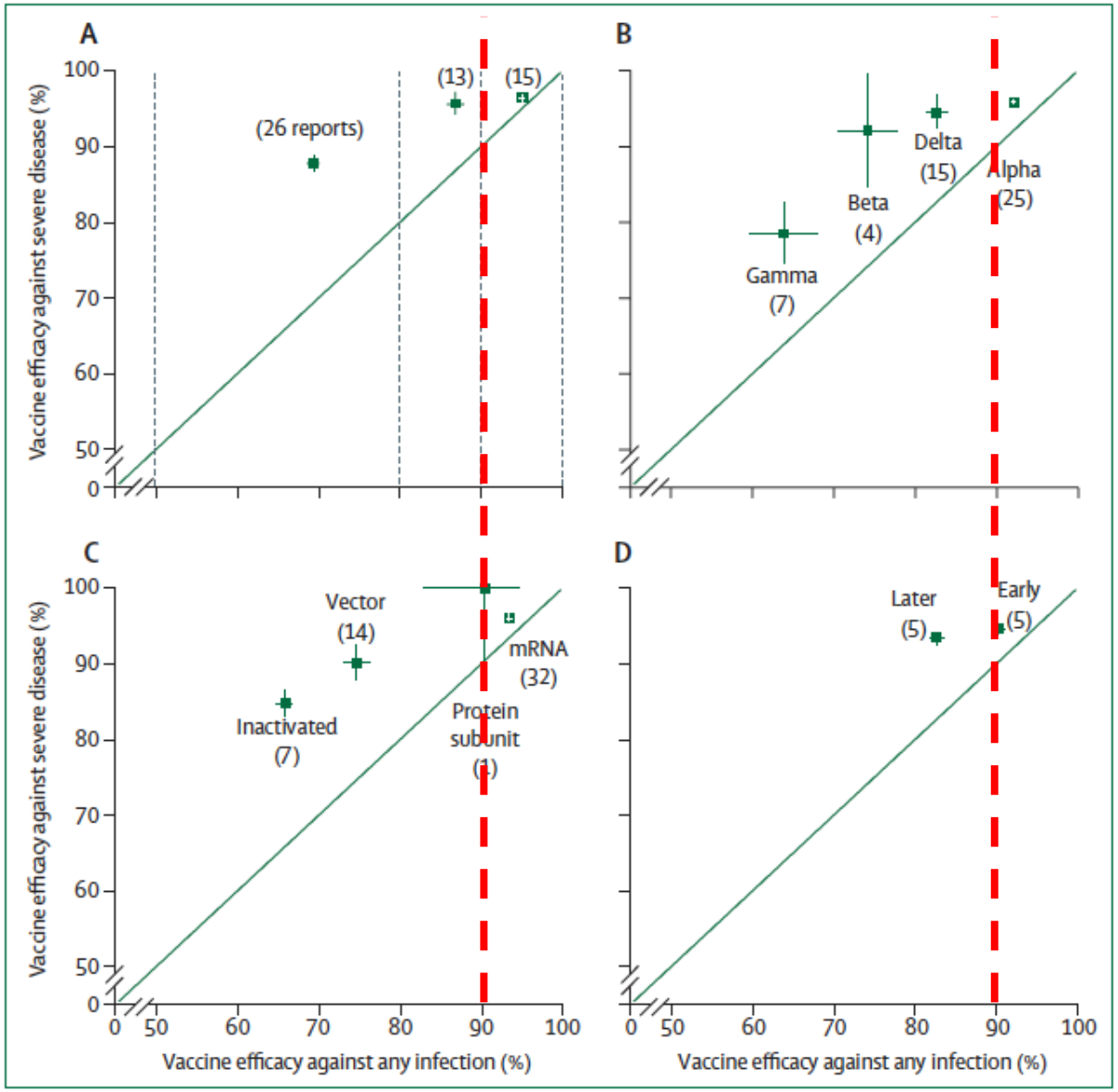
We don't know if benefits outweigh the risks for boosters

- Myocarditis, more common after the second dose of some mRNA vaccines
- Guillain-Barre syndrome, associated with adenovirus-vectored vaccines

If unnecessary boosting causes significant adverse reactions, there could be implications for vaccine acceptance that go beyond COVID-19 vaccines.

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

The figure summarizes the reports that estimated vaccine efficacy separately for severe disease (variously defined) and for any confirmed SARS-CoV-2 infection, plotting one against the other



Review of published or informal reports of vaccine efficacy (with a 95% CI) in observational or in randomised studies (appendix pp 3–4) that gave results both for severe disease and for any infection. Plotted are inverse variance-weighted means (and 95% CIs) of the reported vaccine efficacy (giving the number of studies contributing to that mean), subdivided by

(A) Vaccine efficacy against any infection (50% to <80%, 80% to <90%, ≥90%).

(B) Viral variant.

(C) Type of vaccine (viral vector, inactivated SARS-CoV-2, adjuvanted protein subunit, or mRNA).

(D) Studies reporting vaccine efficacy early (more recently relative to vaccination) or later (less recently relative to vaccination) during the follow-up of the same observational study.

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Considerations in boosting COVID-19 vaccine immune responses: What do we know?

Findings from randomized trials

- Have reliably shown the high initial efficacy of several vaccines
- There are no results from randomized trials looking at the efficacy of booster doses yet

Observational studies have attempted to assess the effects on variants or the durability of vaccine efficacy

- Some are peer-reviewed publications, but some are not, and there is a risk of unduly selective emphasis on particular results.

What have these observational studies shown:

- Vaccine efficacy is substantially greater against severe disease than against any infection
- Vaccination appears to be substantially protective against severe disease from all the main viral variants.
- There is still high vaccine efficacy against both symptomatic and severe disease due to the delta variant.

Current evidence does not appear to show a need for boosting in the general population

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine Problems with Observational Studies

Estimating vaccine efficacy from randomized trials are relatively easy to interpret those form observational studies are not

In observational studies since estimates may be confounded both by patient characteristics at the start of vaccine roll-out and by time-varying factors that are missed by electronic health records.

- Those classified as unvaccinated might include some who were vaccinated, or who are protected because of previous infection, or some whose vaccination was deferred because of COVID-19 symptoms.
- Apparently reduced efficacy among people immunized at the beginning of the pandemic could arise because individuals at high risk of exposure or complications were prioritized
- Among vaccinated people, more of the severe disease could be in immunocompromised individuals, who are more likely to be offered vaccination even though its efficacy is lower

Vaccination status may influence the probability that individuals with asymptomatic or mild COVID-19 infection will seek testing

- Outcomes may be affected over time by varying stress on health-care facilities.

Observational studies that examine efficacy against severe disease are useful and less likely to be affected by diagnosis-dependent biases

To date, none of these studies has provided credible evidence of substantially declining protection against severe disease, even when there appear to be declines over time in vaccine efficacy against symptomatic disease

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine immune responses

In a study in Minnesota, efficacy of mRNA vaccines against hospitalization appeared lower in July, 2021, than in the previous 6 months

- But these estimates had wide confidence intervals .

Reported effectiveness against severe disease in Israel was lower among people vaccinated either in January or April than in those vaccinated in February or March

- Exemplifying the difficulty of interpreting such data.

A report from Israel during August 2021, just after booster doses deployed widely, has suggested efficacy of a third dose (relative to two doses).

- Mean follow-up was, however, only about 7 person-days (less than expected based on the apparent study design
- A very short-term protective effect would not necessarily imply worthwhile long-term benefit

In the USA reports of large studies (US CDC's COVID-NET13 and two from major health maintenance organization)

- Demonstrate the continued high efficacy of full vaccination against severe disease or hospitalization.

Although vaccines are less effective against asymptomatic disease or against transmission than against severe disease

- The unvaccinated are still the major drivers of transmission and are themselves at the highest risk of serious disease.

If new variants that can escape the current vaccines are going to evolve then :

- They are most likely to do so from strains that had already become widely prevalent.
- The effectiveness of boosting against the main variants now circulating and against even newer variants could be greater and longer lived if the booster vaccine antigen is devised to match the main circulating variants
- There is an opportunity now to study variant-based boosters before there is widespread need for them.
- A similar strategy is used for influenza vaccines, for which each annual vaccine is based on the most current data about circulating strains

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine immune responses

The message that boosting might soon be needed, if not justified by robust data and analysis, could adversely affect confidence in vaccines and undermine messaging about the value of primary vaccination.

Public health authorities should also carefully consider the consequences for primary vaccination campaigns of endorsing boosters only for selected vaccines.

- Booster programmes that affect some but not all vaccinees may be difficult to implement
- It will be important to base recommendations on complete data about all vaccines available in a country, to consider the logistics of vaccination, and to develop clear public health messaging before boosting is widely recommended.

If boosters are ultimately to be used, there will be a need to identify specific circumstances in which the direct and indirect benefits of doing so are, on balance, clearly beneficial.

- It needs to be defined if boosters should be with original antigens or variant antigens
- Additional research could help to define such circumstances.
- Given the robust booster responses reported for some vaccines, adequate booster responses might be achieved at lower doses, maybe with reduced safety concerns.

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Considerations in boosting COVID-19 vaccine immune responses

The vaccines that are currently available are safe, effective, and save lives

- The limited supply of these vaccines will save the most lives if made available to people who are at appreciable risk of serious disease and have not yet received any vaccine.
- Even if some gain can ultimately be obtained from boosting, it will not outweigh the benefits of providing initial protection to the unvaccinated.
- If vaccines are deployed where they would do the most good, they could hasten the end of the pandemic by inhibiting further evolution of variants.

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TO BOOST OR NOT TO BOOST

THAT IS THE QUESTION

Anti COVID-19 Monoclonal Antibodies

COVID-19 Monoclonal Antibodies Available

Drug	Setting	Route	Treatment High-Risk Symptomatic Patients	Post Exposure Prophylaxis	Target
Bamlanivimab/ Etezevimab	Outpatient	IV	X		Spike Protein
Casirivimab/ Indevimab	Outpatient	IV/SQ	X	X	Spike Protein
Sotrovimab	Outpatient	IV	X		Spike Protein
Tocilizumab	Inpatient	IV	X		IL-6

Casirivimab/Indevimab: Indications

Outpatient setting to treat mild to moderate COVID-19 in adults with high risk for progressing to severe COVID-19 and/or hospitalization.

High risk is defined as patients who meet at least one of the following criteria:

- BMI greater than 25
- Chronic kidney disease
- Pregnancy
- Diabetes
- Immunosuppressive disease
- Currently receiving immunosuppressive treatment
- 65 years or older
- Cardiovascular disease (including congenital heart disease)
- Hypertension
- Chronic Obstructive Pulmonary Disease/other chronic respiratory disease (asthma [moderate-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension
- Sickle cell disease
- Neurodevelopmental disorders (Cerebral palsy) or other conditions that confer medical complexity (genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19)

Monoclonal Antibody Therapy: Indications

Eligibility is not limited to the conditions listed on prior slide.

- Other factors, such as **race or ethnicity**, are associated with increased risk for progression to severe COVID-19.

For example

- Patients of color or from Tribal communities are most harmed by health inequities
- The risks of hospitalization and death for are greater than those of white patients.
- These patients may face higher risk than white patients, due to longstanding societal injustices including racism, discrimination, colonization, etc., which have and continue to negatively impact health outcomes.

Who should Not Receive Monoclonal Antibody Therapy?

Patients hospitalized due to COVID-19*

Patients requiring supplemental oxygen due to COVID-19

Patients on baseline supplemental oxygen due to non COVID-19 chronic condition

- Only if they require increase in baseline supplemental oxygen

*Monoclonal antibodies may be associated with worse clinical outcomes when

- Given to hospitalized COVID-19 patients requiring oxygen or mechanical ventilation.

Casirivimab/Imdevimab: Post Exposure Prophylaxis Indications

REGEN-COV may only be used as post-exposure prophylaxis for:

- Adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, **and**

Not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination

- (for example, people with immunocompromising conditions, including those taking immunosuppressive medications), **and**

Have been exposed to an individual infected with SARS-CoV-2

- Consistent with close contact criteria per Centers for Disease Control and Prevention (CDC), **or**
- Who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes or prisons)
- Can be used for repeat dosing for those with ongoing exposure > 4 weeks (especially in large household or facility-wide outbreaks

Casirivimab/imdevimab: Treatment Outcomes

For Treatment

- Reduced viral load
- 50-70% reduction in medically attended visits/hospitalizations
- NNT = 33-50

For Post Exposure Prophylaxis

- 81% risk reduction in the development of symptomatic laboratory confirmed COVID-19
  - NNT= 15.8
- 66% reduction in development of any laboratory confirmed confirmed COVID-19
  - NNT = 10
- In a sub analysis of patients at high risk for progression, this efficacy to reduce the chances of developing symptomatic COVID-19 was 74%
  - NNT = 20

Outcome Comparison of High-Risk Native American Patients Who Did or Did Not Receive Monoclonal Antibody Treatment for COVID-19

Abbreviations: BiPAP, bilevel positive airway pressure; IQR, interquartile range; mAb, monoclonal antibody; NA, not applicable; NNT, number needed to treat; NRB, nonrebreather; OR, odds ratio. a Number needed to treat to prevent the given medical outcome. Only given if P < .05. b COVID-19–related emergency department visit or hospitalization. c COVID-19–related hospitalization, including local hospitalizations and transfers. d Absolute risk reductions are given as percentages when ORs were not possible. e Among patients with known symptom onset dates (32 mAb-treated patients and 108 nontreated patients)

Table 2. Comparison of 30-Day Outcomes Among Patients Who Did or Did Not Receive Monoclonal Antibody Treatment for COVID-19

Outcome	mAb recipients, No. (%)	Nonrecipients, No. (%)	Point estimate, OR (95% CI)	*P* value	NNT[a]
Among all patients					
No. of patients	201	280			
Acute medical visit[b]	59 (29.4)	136 (48.6)	0.44 (0.29 to 0.66)	<.001	6
Emergency department visit only	24 (11.9)	16 (5.7)	NA	NA	NA
Hospitalization[c]	35 (17.4)	120 (42.9)	0.28 (0.18 to 0.44)	<.001	4
Transfer to outside facility for higher-level care	4 (2.0)	26 (9.3)	0.20 (0.05 to 0.59)	.001	14
Intensive care unit admission	0	12 (4.3)	−4.3 (−6.7 to −1.9)[d]	.003	24
Death	0	8 (2.9)[c]	−2.9 (−4.8 to −0.9)[d]	.008	35
Adverse reaction	1 (0.5)	NA	NA	NA	NA
Among hospitalized patients					
No. of patients	35	120			
Symptom duration at admission, No./total No. (%)					
Asymptomatic	2/35 (6)	5/120 (4)	1.4 (0.13 to 9)	.66	NA
Days, median (IQR)[e]	6 (3-9)	5 (3-8)		.66	NA
Admission in ≤3 d[e]	10/32 (31)	35/108 (32)	0.95 (0.36 to 2.4)	.90	NA
Days in hospital, median (IQR)	4 (3-5)	4 (4-5)		.48	NA
Oxygen requirement, No./total No. (%)	26/35 (74)	91 (76)	0.92 (0.36 to 2.5)	.53	NA
None	9/35 (26)	29/120 (24)	NA	.54	NA
Low flow	25/35 (71)	81/120 (68)			
NRB mask, high flow, or BiPAP	1/35 (3)	4/120 (3)			
Intubation	0/35	6/120 (5)			

Casirivimab/Imdevimab: Administration

There should be immediate access to medication and equipment to treat severe infusion reaction/anaphylaxis.

casirivimab and imdevimab is administered as a single IV infusion **as soon as possible after positive viral test.**

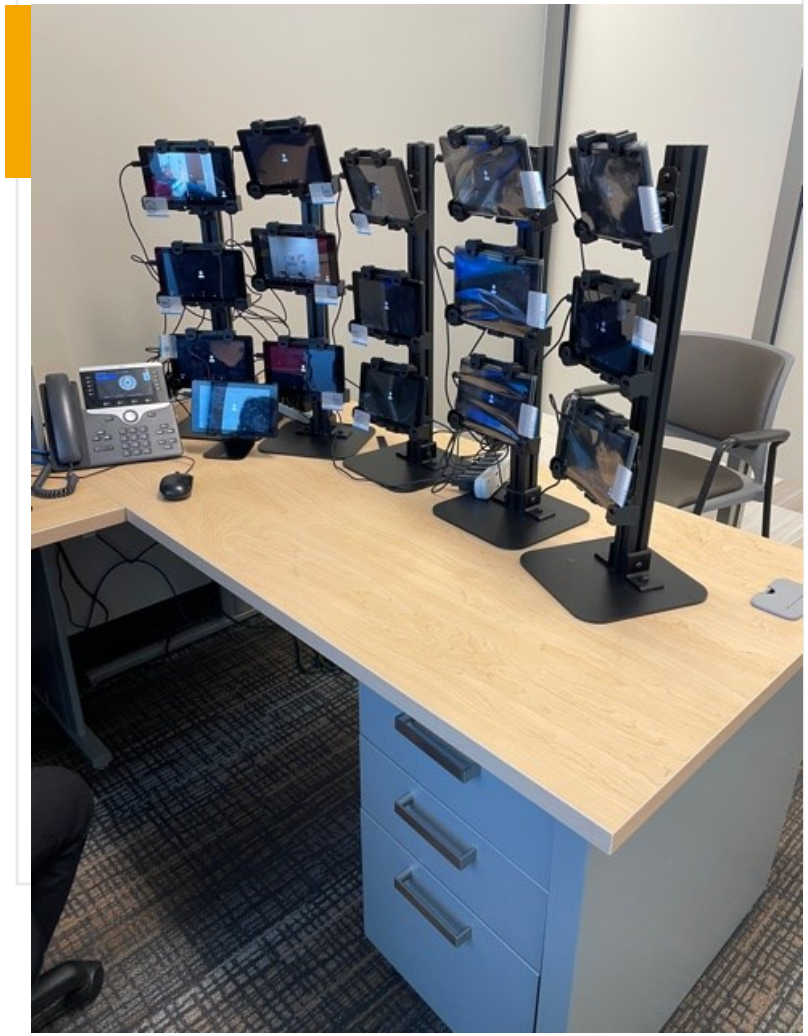
REGEN-COV is to be administered within 10 days of symptom onset; use later in disease may lead to worse outcomes

REGEN-COV is available as two separate vials **or** in a co-formulated single vial

REGEN-COV is administered as a single 100 mL infusion diluted in normal saline

REGEN-COV is administered over 21 minutes (and up to 50 minutes if needed)

Casirivimab/Imdevimab: Administration



Patients are to be **monitored during the infusion and for at least one hour after the infusion is complete.**

Staff are to wear appropriate PPE (Airborne Precautions) while caring for patients receiving REGEN-COV (casirivimab and imdevimab).

Monitoring during and after infusion is to include

Vital signs	Signs and/or symptoms of infusion-related reactions

Casirivimab/Imdevimab:Adverse Events

There is potential for serious hypersensitivity reactions, including anaphylaxis.

If signs and/or symptoms of clinically significant hypersensitivity reaction or anaphylaxis occur,

- Immediately discontinue administration
- Initiate appropriate medications and/or supportive care

- Infusion-related reactions to Casirivimab/ imdevimab can include:
  - Fever
  - Chills
  - Nausea
  - Headache
  - Bronchospasm
  - Hypotension
  - Angioedema
  - Throat irrigation
  - Rash, including urticaria, and/or pruritus
  - Myalgia
  - Dizziness

Mandatory Requirements under the EUA:

Use casirivimab/ imdevimab

- Only in authorized patient populations described

Communicate to patients or parents/caregivers:

- Information consistent with the “Fact Sheet for Patients, Parents and Caregivers” prior to receiving Casirivimab/ imdevimab.

Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in medical record that the patient/caregiver has been:

- Given the “Fact Sheet for Patients, Parents and Caregivers”
- Informed of alternatives to receiving authorized Casirivimab/imdevimab
- Informed that Casirivimab/imdevimab are not approved and authorized for use under this EUA.

Patients with known hypersensitivity to any ingredient of Casirivimab/imdevimab

- Must not receive Casirivimab/imdevimab.

The prescriber is responsible for mandatory reporting of all drug errors and SAEs potentially related to treatment

- Within 7 calendar days from onset of event.

Casirivimab/Imdevimab: Administration Highlights

Diluted into 100 mL of total volume with normal saline

Infuse over 21 minutes (up to 50 minutes if needed)

Use in-line or add-on 0.2 micron polyethersulfone (PES) filter for infusing

Observe patients for one hour after the infusion

Monitor vital signs and for infusion-related reactions during and after infusion

Document infusion times in patient's MAR on day of infusion

Casirivimab/Imdevimab: In Summary

1. Determine the use for REGEN-COV (treatment or post-exposure prophylaxis), and confirm your patient's eligibility (see below for full authorized use).
2. Confirm that the patient is at high risk, as defined in the Fact Sheet for Healthcare Providers.

   Healthcare providers should consider the benefit-risk for each individual patient.
3. Determine if REGEN-COV will be administered by intravenous (IV) infusion or subcutaneous injection, and write the order for REGEN-COV.[§]
4. If unable to administer the medication, find an administration site near your patient.
5. Share educational resources with your patient so they know what to expect.