Evidence to Recommendation Framework:

An Additional Dose of mRNA COVID-19 Vaccine Following a Primary Series in Immunocompromised People

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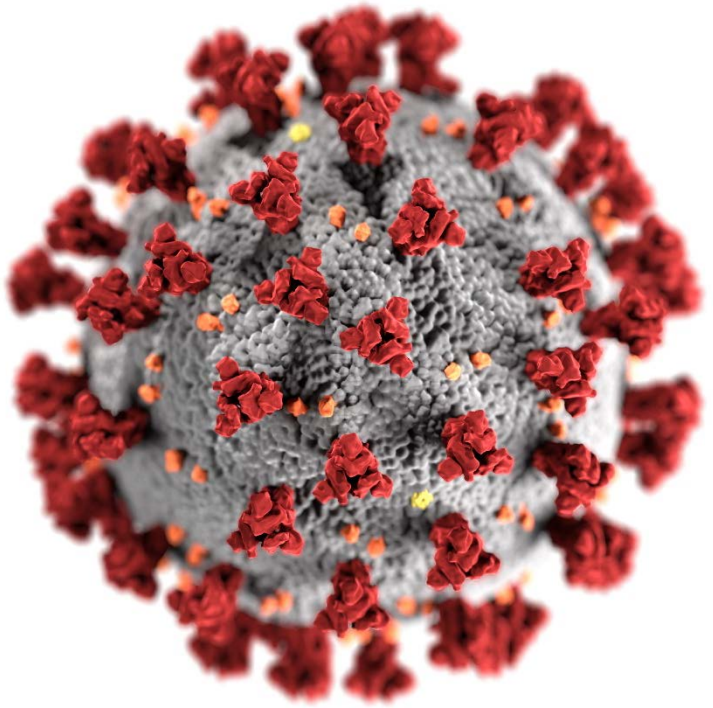
Advisory Committee on Immunization Practices
August 13, 2021



cdc.gov/coronavirus

FDA: Emergency Use Authorization (EUA) Amendment

- **August 12, 2021**: FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals*
  - Other fully vaccinated individuals do not need an additional dose right now
  - Amendment applies to:
  - **Pfizer-BioNTech** COVID-19 vaccine (BNT162b2) (≥12 years old)
  - **Moderna** COVID-19 vaccine (mRNA-1273) (≥18 years old)

- Due to insufficient data, the EUA amendment for an additional dose does not apply to Janssen COVID-19 vaccine or to individuals who received Janssen COVID-19 as a primary series. CDC and FDA are actively engaged to ensure that immunocompromised recipients of Janssen COVID-19 vaccine have optimal vaccine protection

*https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised

Evidence to Recommendations Framework

Evidence to Recommendations (EtR) Framework

- Structure to describe information considered in moving from evidence to ACIP vaccine **recommendations**

- Provide **transparency** around the impact of additional factors on deliberations when considering a recommendation

Evidence to Recommendations (EtR) Framework
Policy Question

- Should ACIP recommend vaccination with an additional dose of Pfizer-BioNTech or Moderna COVID-19 vaccine (mRNA vaccines) following a primary series in immunocompromised people, under an Emergency Use Authorization?

Population: Immunocompromised People

People with medical conditions or people receiving treatments that are associated with moderate to severe immune compromise.[1]

- Active or recent treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ or recent hematopoietic stem cell transplants
- Severe primary immunodeficiency
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory
- Chronic medical conditions such as asplenia and chronic renal disease may be associated with varying degrees of immune deficit

1. Additional information about the level of immune suppression associated with a range of medical conditions and treatments can be found in general best practices for vaccination of people with altered immunocompetence, the CDC Yellow Book, and the Infectious Diseases Society of America policy statement, 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

Intervention: An Additional Dose of mRNA COVID-19 Vaccine

- An additional dose of
  - **Pfizer-BioNTech** COVID-19 vaccine (BNT162b2) (≥18 years old)
  - **Moderna** COVID-19 vaccine (mRNA-1273) (≥18 years old)

  after an initial 2-dose primary series of mRNA COVID-19 vaccine, in immunocompromised people
- Attempts should be made to match the additional dose type to the mRNA primary series, however if that is not feasible, a **heterologous additional dose is permitted**
- The additional dose of mRNA COVID-19 vaccine should be administered **at least 28 days** after completion of the primary mRNA COVID-19 vaccine series

Importance of infection prevention measures

- Immunocompromised people, including those who receive an additional mRNA dose, should continue to follow prevention measures*
  - Wear a mask
  - Stay 6 feet apart from others they don't live with
  - Avoid crowds and poorly ventilated indoor spaces until advised otherwise by their healthcare provider

- Close contacts of immunocompromised people should be strongly encouraged to be vaccinated against COVID-19

* https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

Evidence to Recommendations (EtR) Framework

EtR Domain	Question
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?
Feasibility	• Is the intervention feasible to implement?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?

Evidence to Recommendations (EtR) Framework

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Equity	• What would be the impact of the intervention on health equity?

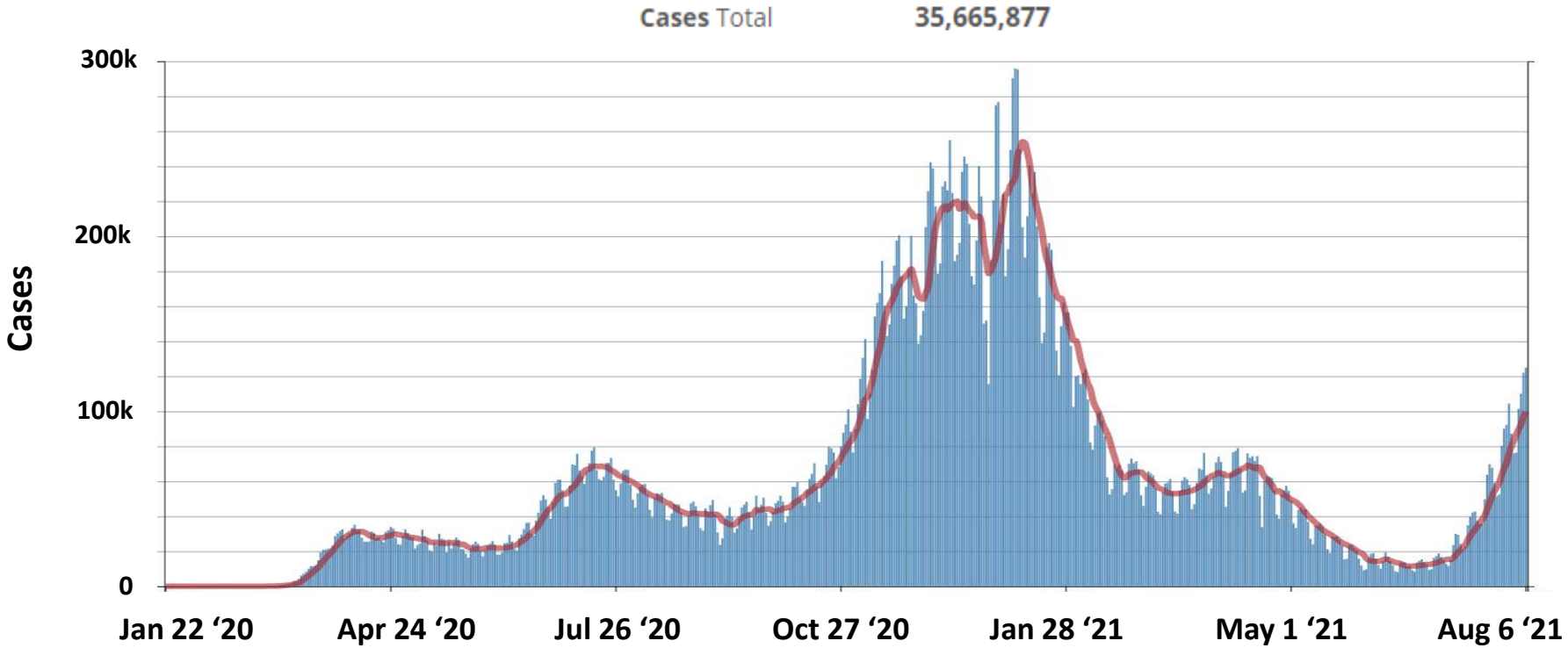
"**The problem**" = COVID-19 among immunocompromised persons

"**The intervention**" = an additional dose of mRNA COVID-19 vaccine in immunocompromised people who have received a primary series of an mRNA COVID-19 vaccine

EtR Domain: Public Health Problem

Daily Trends in Number of COVID-19 Cases in the US

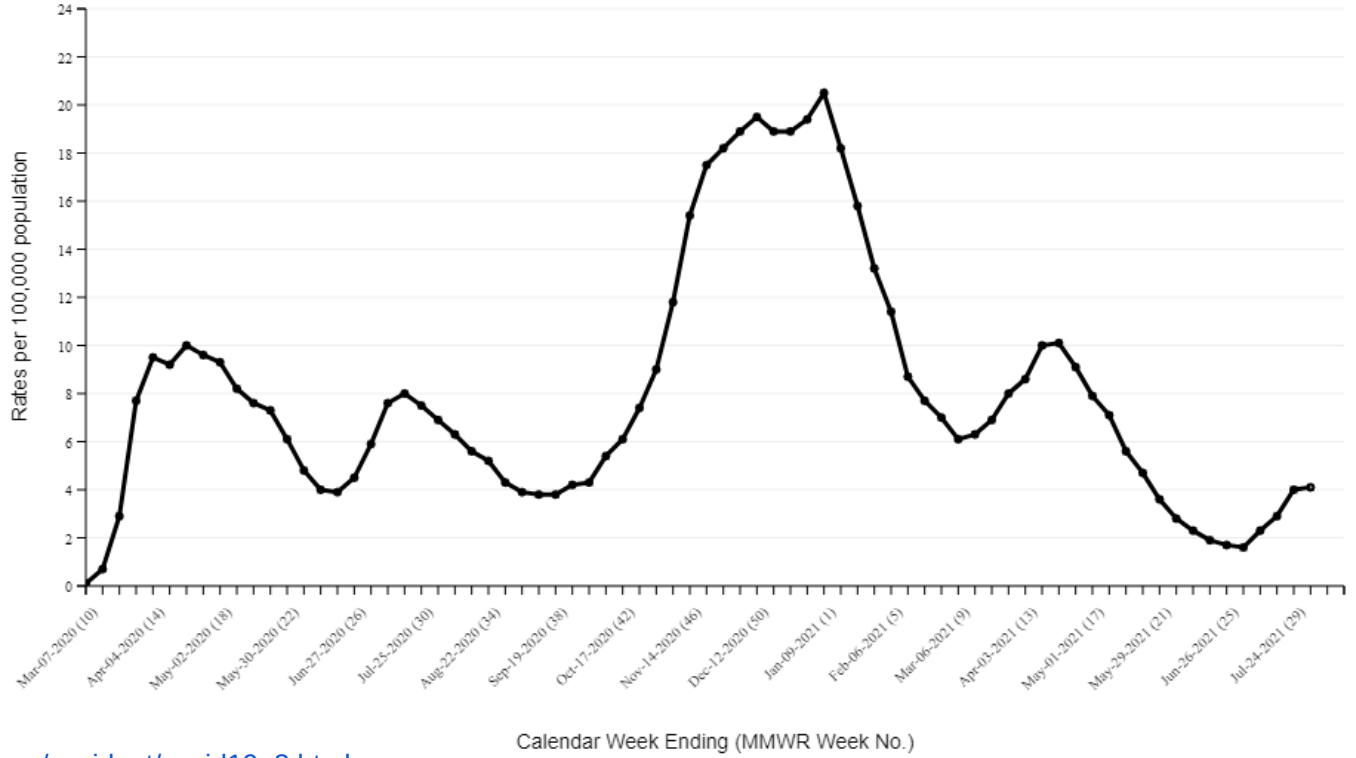
January 22, 2020 – Aug 9, 2021



https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

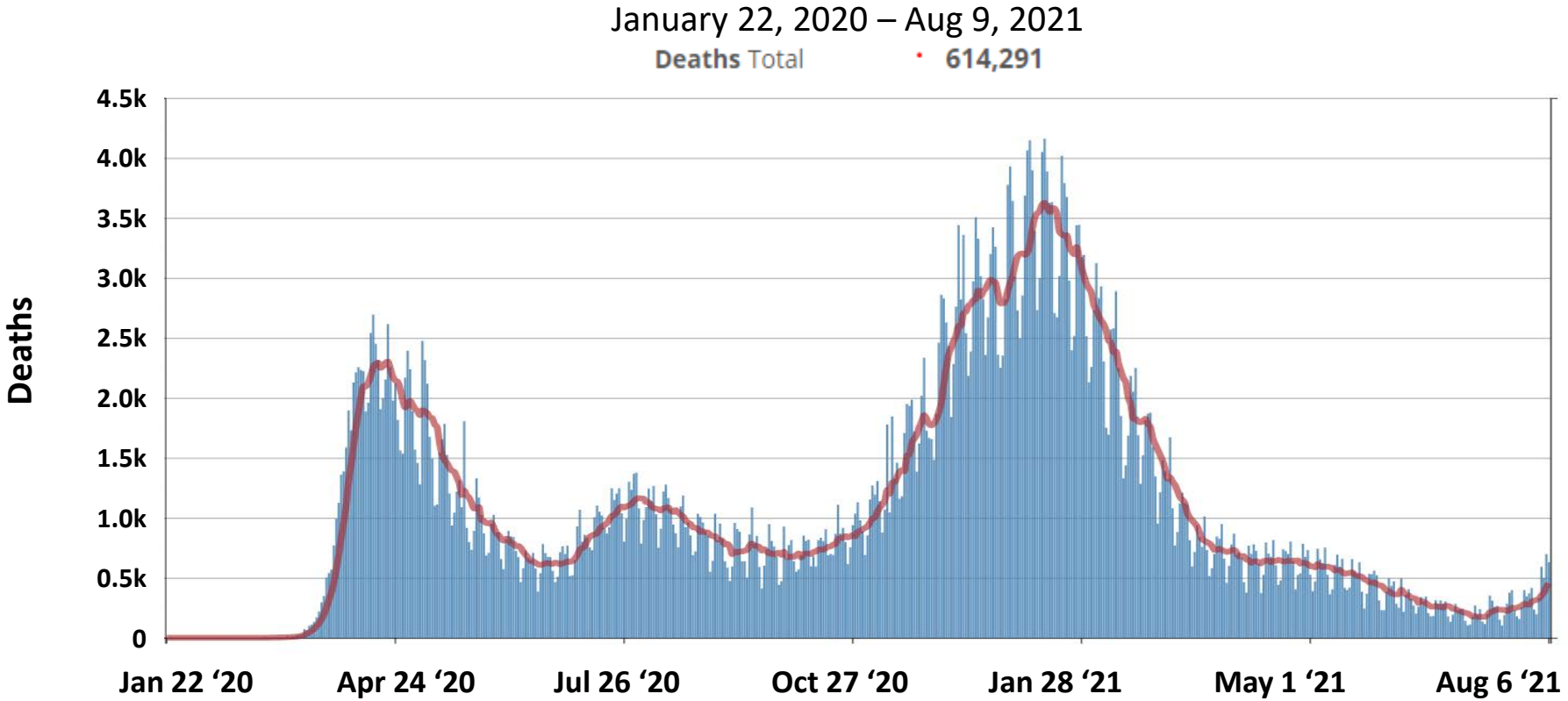
Weekly Trends in COVID-19 Associated Hospitalization Rates in the US

March 7, 2020 – Aug 7, 2021



https://gis.cdc.gov/grasp/covidnet/covid19_3.html

Daily Trends in Number of COVID-19 Deaths in the US



https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

Immunocompromised People and SARS-CoV-2 Infection

- Immunocompromised people comprise ~2.7% of U.S. adults (~7 million adults)[1]
- More likely to get severely ill from COVID-19[1,2]
- Higher risk for:
  - Prolonged SARS-CoV-2 infection and shedding[3-7, 14-16]
  - Viral evolution during infection and treatment (hospitalized patients)[3,6,8-10,14,17]
- Lower antibody/neutralization titers to SARS-CoV-2 variants compared to non-immunocompromised people [12]
- More likely to transmit SARS-CoV-2 to household contacts[11]

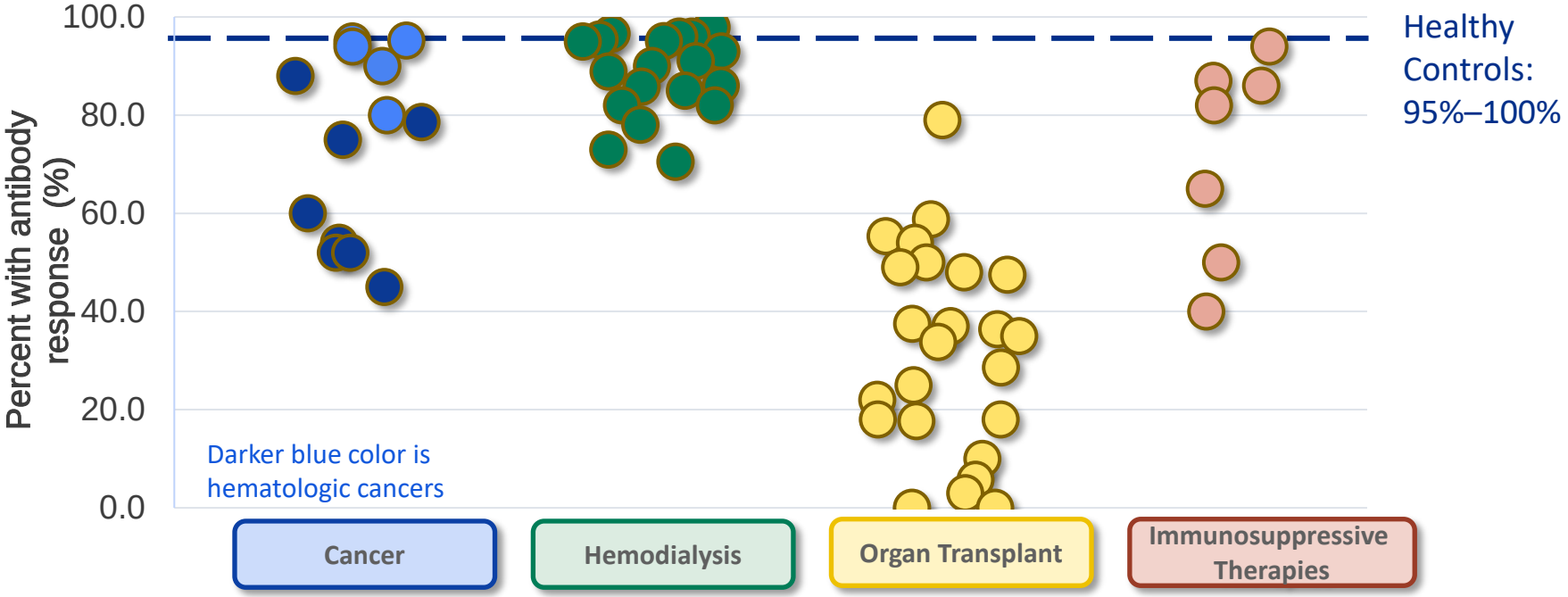
See reference slide at end

Immunocompromised People and Vaccine Breakthrough Infection

- More likely to have breakthrough infection
  - 40-44% of hospitalized breakthrough cases are immunocompromised people in US study[1-2]
- Lower vaccine effectiveness
  - 59--72% VE among immunocompromised people vs. 90--94% among non-immunocompromised people after 2nd dose[1, 3-5]

See reference slide at end

Percent of subjects with antibody response after two mRNA COVID-19 vaccine doses by immunocompromising condition and study (n=63)



- Studies that compared response after 1st and 2nd dose demonstrated less robust response after dose 1
- Antibody measurement and threshold levels vary by study protocol

See reference slide at end

International policies on additional doses for immunocompromised people

- France[1] (Announced April 11, 2021)
  - 3rd dose 4 weeks after the 2nd dose for patients who are “severely immunocompromised”
  - Could be extended at a later date to include a larger immunocompromised population
- Israel[2] (Announced July 11, 2021)
  - People living with organ or stem cell transplants, blood cancer, autoimmune disease and treatment with specific immunosuppressive medications
  - People with breast, lung, or colon cancer do not qualify
- United Kingdom[3] (Announced July 1, 2021)
  - Additional dose for immunocompromised people ≥16 years (among others), to be implemented in September
- Germany[4] (Announced August 2, 2021)
  - Immunocompromised persons (among others)

1. dgs_urgent_n43_vaccination_modalites_d_administration_des_rappels.pdf (solidarites-sante.gouv.fr),
2. https://govextra.gov.il/media/30095/meeting-summary-15122020.pdf
3. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1009174/COVID-19_vaccination_programme_guidance_for_healthcare_workers_6_August_2021_v3.10.pdf
4. https://www.reuters.com/world/europe/french-president-macron-third-covid-vaccine-doses-likely-elderly-vulnerable-2021-08-05/

Public Health Problem

Is COVID-19 disease among immunocompromised people of public health importance?

- Are the consequences of COVID-19 serious in this population?
- Is COVID-19 urgent?
- Are a large number of immunocompromised people affected by COVID-19?
- Are there populations disproportionally affected by COVID-19?

O **No**	O **Probably no**	O **Probably yes**	O **Yes**	O **Varies**	O **Don't know**

EtR Domain: Benefits and Harms

Benefits and Harms

How substantial are the desirable anticipated effects?

- How substantial are the anticipated effect for each main outcome for which there is a desirable effect?

O Minimal	O Small	O Moderate	O Large	O Varies	O Don't know

Benefits and Harms

How substantial are the undesirable anticipated effects?

- How substantial are the anticipated effect for each main outcome for which there is a undesirable effect?

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Benefits and Harms

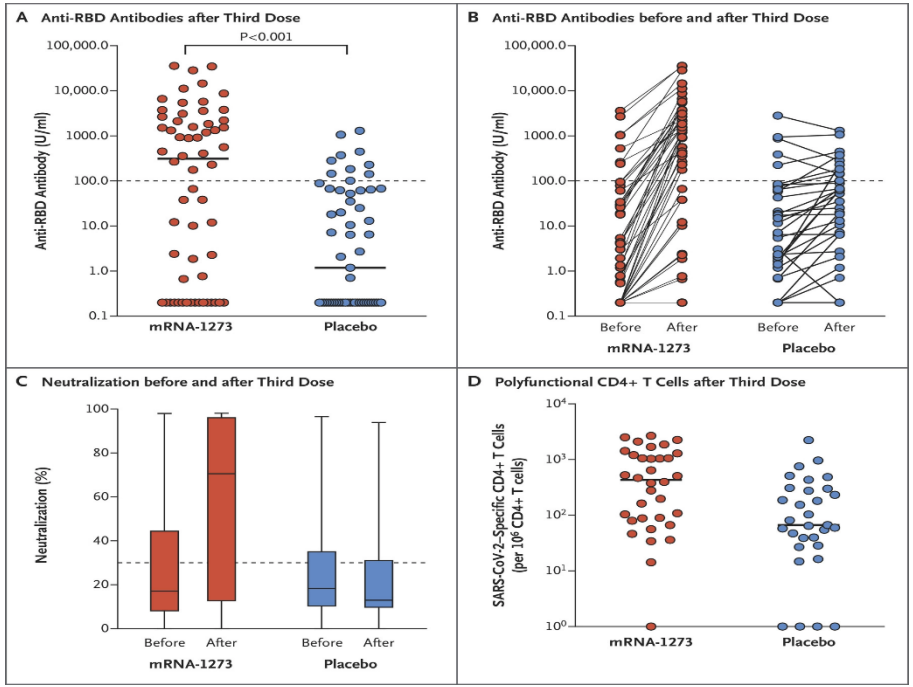
Do the desirable effects outweigh the undesirable effects?

- What is the balance between the desirable effects relative to the undesirable effects?

O Favors intervention (An additional dose of mRNA vaccine in IC people)
O Favors comparison (no additional COVID-19 vaccine doses)
O Favors both
O Favors neither
O Unclear

Benefits:

Randomized Trial of a 3rd Dose of Moderna Vaccine in Transplant Recipients (n=120)



RBD antibody (≥100 U/ml)
1 month post dose 3:

33 of 60 patients
(55%) vaccine group
vs.
10 of 57 patients
(18%) placebo group

Hall et al. (2021) NEJM. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. DOI: 10.1056/NEJMc2111462

Benefits:

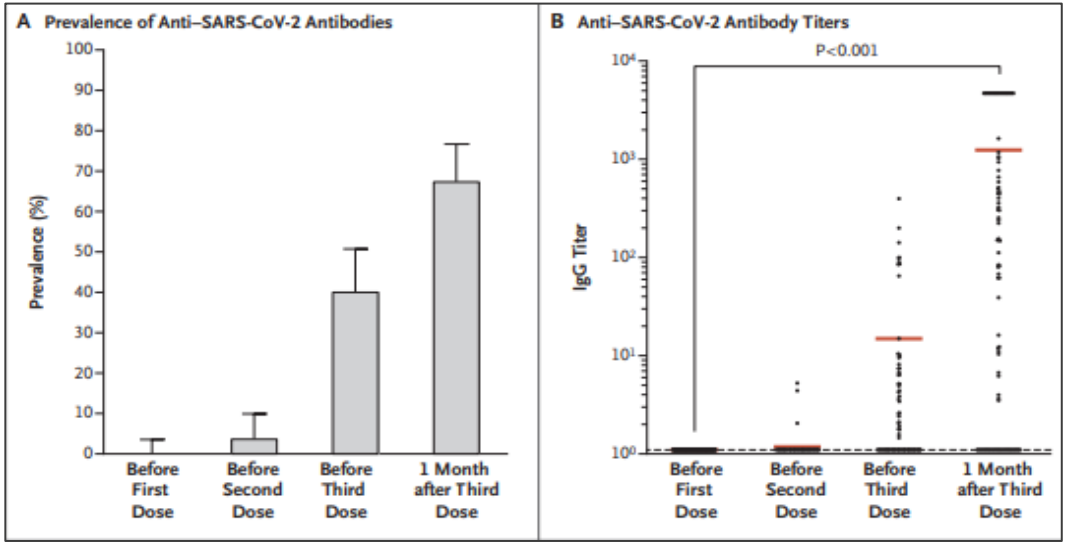
Study	Patient Population	2nd Dose			3rd Dose Seronegative after 2 nd dose		
		Sample Size	Seronegative N (%)	Seropositive N (%)	Sample Size	Seronegative N (%)	Seropositive N (%)
Kamar et al.	Recipients of solidorgan transplant	99	59 (60)	40 (40)	59	33 (56)	**26 (44)**
Werbel et al.	Recipients of solidorgan transplant	30	24 (80)	6 (20)	24	16 (67)	**8 (33)**
Longlune et al.	Patients on hemodialysis	82	13 (16)	69 (84)	12	7 (58)	**5 (42)**
Epsiet al.	Patients on hemodialysis	106	66 (62)	40 (38)	12	6 (50)	**6 (50)**
Ducloux et al.	Patients on hemodialysis	45	5 (11)	40 (89)	5	3 (60)	**2 (40)**

- Among those who had **no detectable antibody** response to an initial mRNA vaccine series,

33-50% developed an antibody response to an additional dose

See reference slide at end

Benefits and Harms:

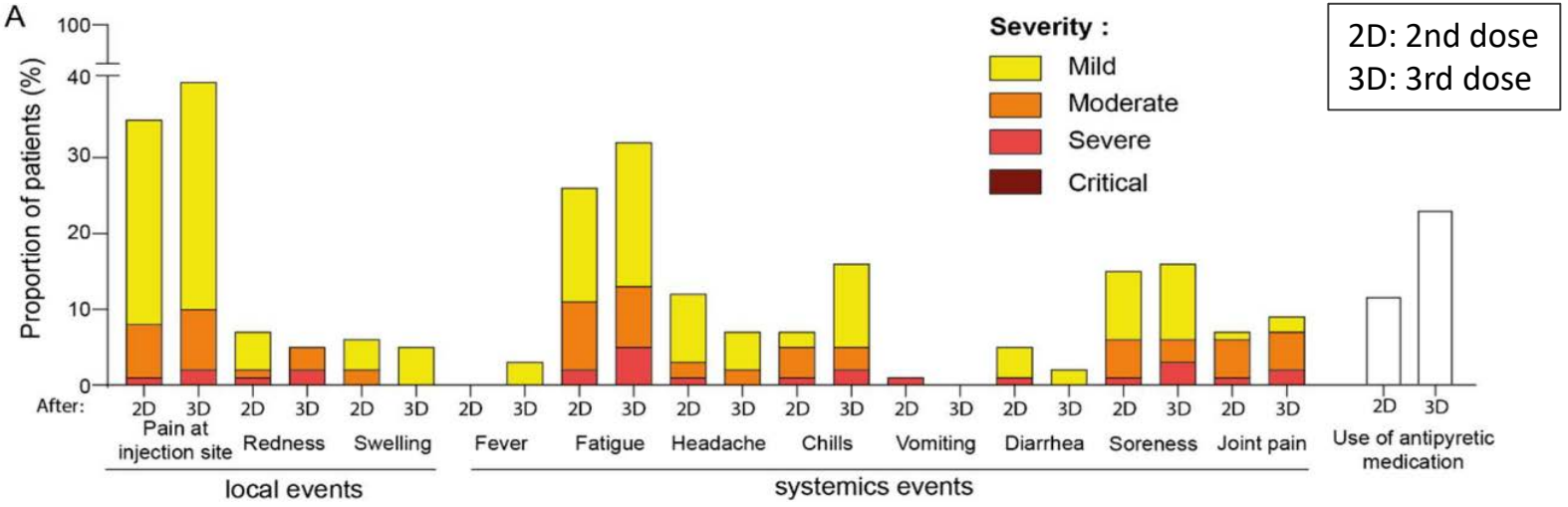


- The proportion of the group who are seropositive increase after each dose: **40%** post dose 2 and **68%** post dose 3
- Average antibody titre increased after each dose
- No serious adverse events were reported after administration of the 3rd dose, and no acute rejection episodes occurred (n=99 Solid Organ Transplant Patients)

Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)

Harms:

- No patients developed critical side effects which required hospitalization
- Symptoms reported were consistent with previous doses and the intensity of the symptoms was mostly mild or moderate



Epsi et al. (2021) medRxiv doi: https://doi.org/10.1101/2021.07.02.21259913

Benefits and Harms:
Summary of the Available Evidence

Benefits:

- Emerging experimental and observational data in adults suggest that an additional mRNA COVID-19 vaccine dose in immunocompromised people enhances antibody response and increases the proportion who respond to COVID-19 vaccine
- No efficacy or effectiveness studies of COVID-19 prevention following a 3rd dose

Harms:

- In small studies of an additional dose of mRNA vaccine
  - No serious adverse events were observed
  - Reactogenicity of the 3rd dose of mRNA vaccine was similar to prior doses
- mRNA COVID-19 vaccines are associated with rare but serious adverse events, including anaphylaxis as well as myocarditis and pericarditis in young adults. The impact of immunocompromising conditions on these rare events is unknown.
- There are no safety studies of an additional mRNA dose in immunocompromised adolescents

Benefits and Harms

How substantial are the desirable anticipated effects?

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- O Favors both
- O Favors neither
- O Unclear

EtR Domains: Values & Acceptability

Values

Criteria 1:
Does the target population feel that the desirable effects are large relative to undesirable effects?

- How does the target population view the balance of desirable versus undesirable effects?
- Would patients/caregivers feel that the benefits outweigh the harms and burden?
- Does the immunocompromised population appreciate and value an additional dose of mRNA COVID-19 vaccine?

O **Minimal**	O **Small**	O **Moderate**	O **Large**	O **Varies**	O **Don't know**

Values

Criteria 2:

Is there important uncertainty about, or variability in, how much people value the main outcomes?

- How much do individuals value each outcome in relation to the other outcomes?
- Is there evidence to support those value judgements?
- Is there evidence that the variability is large enough to lead to different decisions?

- O Important uncertainty or variability
- O Probably important uncertainty or variability
- O Probably not important uncertainty or variability
- O No important uncertainty or variability
- O No known undesirable outcomes

Acceptability

Is an additional dose of mRNA COVID-19 vaccines acceptable to key stakeholders?

- Are there key stakeholders that would not accept the distribution of benefits and harms?
- Are there key stakeholders that would not accept the undesirable effects in the short term for the desirable effects (benefits) in the future?

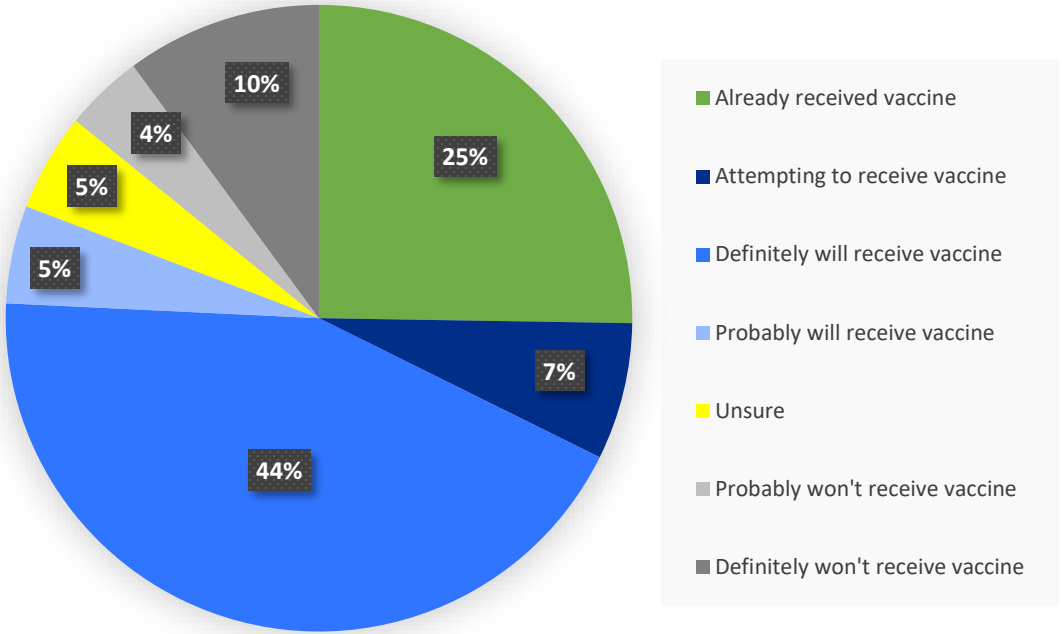
O **No**	O **Probably no**	O **Probably yes**	O **Yes**	O **Varies**	O **Don't know**

Additional doses of COVID-19 vaccines in the general U.S. population

- Approximately 139.5 million individuals completed a 2-dose series of Moderna or Pfizer-BioNTech COVID-19 vaccine
  - ~1.14 million (<1%) received 1 or more additional COVID-19 vaccine doses
- Approximately 12 million individuals received 1 dose of Janssen COVID-19 vaccine
  - ~90,979 (<1%) received 1 or more additional COVID-19 vaccine doses

Values:

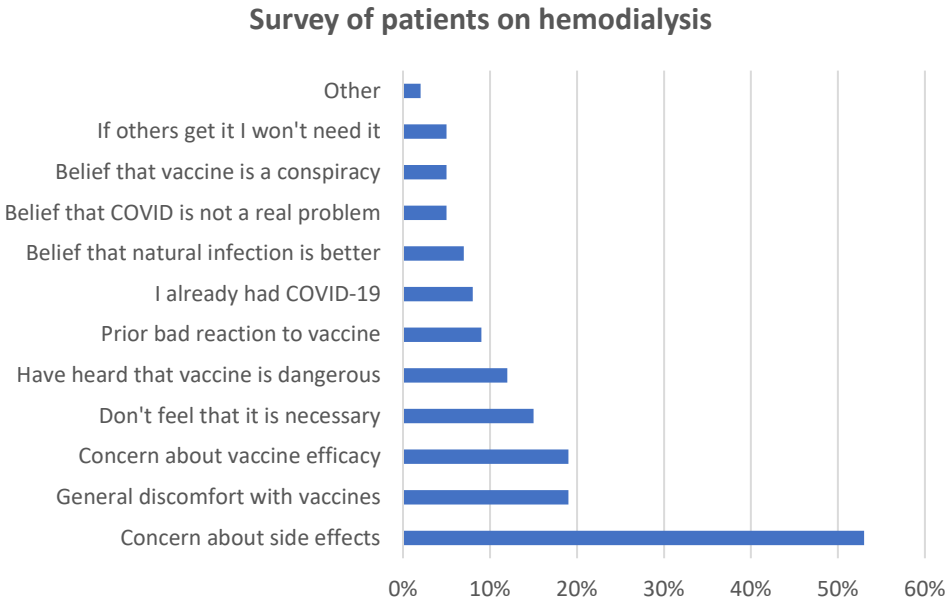
Survey of individuals with cancer, autoimmune diseases, and other serious co-morbid conditions, January 15-February 22, 2021 (n=21,943)

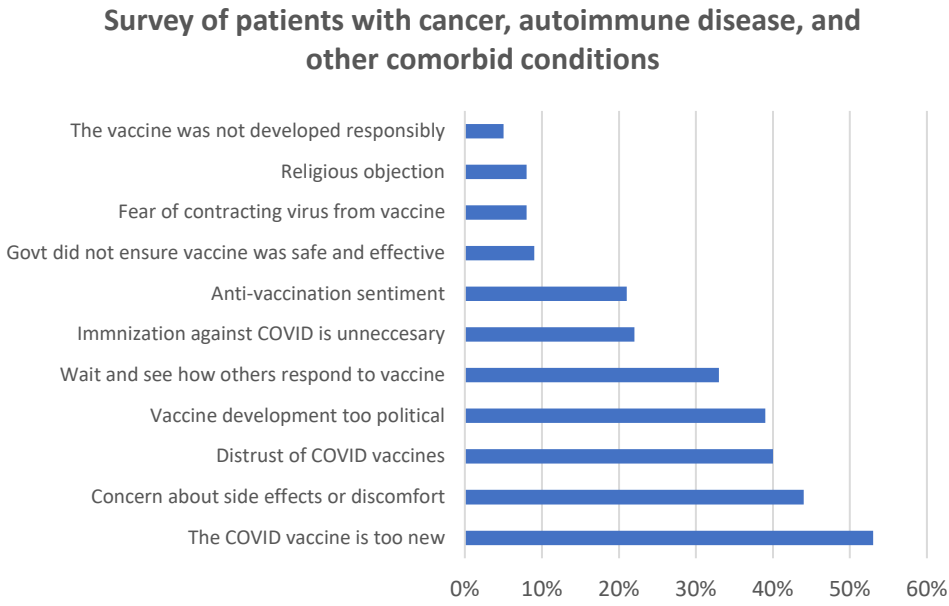


- **Factors associated with vaccine hesitancy**
  - Younger age
  - Female gender
  - Black, Pacific Island, Native American race/ethnicity
  - Less formal education
  - Anti-vaccine sentiment
  - Distrust of media

COVID-19 vaccine hesitancy among individuals with cancer, autoimmune diseases, and other serious comorbid conditions (medrxiv.org)

Values:
Stated reasons for vaccine refusal





1. COVID-19 vaccine hesitancy among individuals with cancer, autoimmune diseases, and other serious comorbid conditions (medrxiv.org)

2. SARS-CoV-2 Vaccine Acceptability in Patients on Hemodialysis: A Nationwide Survey | American Society of Nephrology (asnjournals.org)

Acceptability:

Professional bodies strongly support COVID-19 vaccination and an additional dose

1) Encourage study of safety and efficacy/effectiveness of an additional dose of COVID-19 vaccine in immunocompromised people
2) Support swift action on the part of ACIP to recommend use of an additional dose of COVID-19 vaccine in immunocompromised people

- Infectious Diseases Society of America
- American College of Rheumatology
- American Society of Transplantation
- American Society of Transplant Surgeons
- International Society for Heart and Lung Transplantation
- Pediatric Infectious Diseases Society
- Children's Oncology Group

Acceptability:

Advocacy bodies strongly support COVID-19 vaccination and study of an additional dose

Leukemia and Lymphoma Society **supports**:

- Providing access to doses of COVID-19 vaccine for supplemental vaccination in immunosuppressed patients and urges that these patients have the opportunity to be among the first to receive these additional doses

Values:
Summary of the available evidence

- Overall, initial intent to vaccinate is high among immunocompromised populations
- Concerns about safety and possible side-effect are major reasons for vaccine hesitancy
- Vaccine hesitancy appears to be associated with younger age, female gender, racial/ethnic minorities, and less formal education
- Strong support for an additional dose was expressed by immunocompromised patients via written and oral comment to ACIP meeting July 22, 2021

Acceptability:
Summary of the available evidence

- Professionals who provide healthcare to immunocompromised people recognize their patients are at high risk for severe outcomes from COVID-19 and strongly support a recommendation for an additional dose of COVID vaccine

- Societies that advocate for access to the best quality care for patients with immunocompromising conditions support access to an additional dose of COVID-19 vaccine to increase the chances of vaccine protection

Values

Criteria 1:

Does the target population feel that the desirable effects are large relative to undesirable effects?

- How does the target population view the balance of desirable versus undesirable effects?
- Would patients/caregivers feel that the benefits outweigh the harms and burden?
- Does the immunocompromised population appreciate and value an additional dose of mRNA COVID-19 vaccine?

O **Minimal**	O **Small**	O **Moderate**	O **Large**	O **Varies**	O **Don't know**

Values

Criteria 2:

Is there important uncertainty about, or variability in, how much people value the main outcomes?

- How much do individuals value each outcome in relation to the other outcomes?
- Is there evidence to support those value judgements?
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Acceptability

Is an additional dose of mRNA COVID-19 vaccines acceptable to key stakeholders?

- Are there key stakeholders that would not accept the distribution of benefits and harms?
- Are there key stakeholders that would not accept the undesirable effects in the short term for the desirable effects (benefits) in the future?

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EtR Domain: Feasibility

Feasibility

Is an additional dose of mRNA COVID-19 vaccine feasible to implement among immunocompromised people?

- Is the additional dose of mRNA COVID-19 vaccine sustainable?
- Are there barriers that are likely to limit the feasibility of implementing the additional dose of mRNA COVID-19 vaccine or require considerations when implementing it?
- Is access to an additional dose of mRNA COVID-19 vaccine for immunocompromised people an important concern?

O **No**	O **Probably no**	O **Probably yes**	O **Yes**	O **Varies**	O **Don't know**

Feasibility:

- High levels of interaction between immunocompromised populations and healthcare system provide opportunities for an additional dose to following the primary series
- mRNA COVID-19 vaccine supply in the United States is sufficient to make additional doses for immunocompromised people feasible
- Testing for antibodies following vaccination is not recommended, reducing the complexity of a recommendation for an additional dose

Feasibility

Is an additional dose of mRNA COVID-19 vaccine feasible to implement among immunocompromised people?

- Is the additional dose of mRNA COVID-19 vaccine program sustainable?
- Are there barriers that are likely to limit the feasibility of implementing the additional dose of mRNA COVID-19 vaccine or require considerations when implementing it?
- Is access to an additional dose of mRNA COVID-19 vaccine for immunocompromised people an important concern?

O **No**	O **Probably no**	O **Probably yes**	O **Yes**	O **Varies**	O **Don't know**

EtR Domain: Resource Use

Resource Use

Is an additional dose of mRNA COVID-19 vaccine, given to immunocompromised people, a reasonable and efficient allocation of resources?

- What is the cost-effectiveness of the additional mRNA COVID-19 vaccine dose in this population?
- How does the cost-effectiveness of the additional dose change in response to changes in context, assumptions, etc?

O **No**	O **Probably no**	O **Probably yes**	O **Yes**	O **Varies**	O **Don't know**

Resource Use:
Review of the available evidence

- U.S. Government has purchased 600 million doses of mRNA vaccines[1]
- Vaccine is available at no cost to the recipient
- No studies evaluated cost-effectiveness around the use of COVID-19 vaccines among immunocompromised
  - Immunocompromised patients experience high medical costs at baseline and are at higher risk of hospitalization. The cost of an additional dose of COVID-19 vaccine is small relative to these costs.

[1] https://www.hhs.gov/about/news/2021/02/11/biden-administration-purchases-additional-doses-covid-19-vaccines-from-pfizer-and-moderna.html

Resource Use:
Work Group Interpretation

- Work Group concluded that cost-effectiveness may not be a primary driver for decision-making during a pandemic and for vaccine used under EUA

Resource Use

Is an additional dose of mRNA COVID-19 vaccine, given to immunocompromised people, a reasonable and efficient allocation of resources?

- What is the cost-effectiveness of the additional mRNA COVID-19 vaccine dose in this population?
- How does the cost-effectiveness of the additional dose change in response to changes in context, assumptions, etc?

O **No**	O **Probably no**	O **Probably yes**	O **Yes**	O **Varies**	O **Don't know**

EtR Domain: Equity

Equity

What would be the impact of an additional dose of mRNA COVID-19 vaccine, given to immunocompromised people, on health equity?

- Are there groups or settings that might be disadvantaged in relation to COVID-19 disease burden or receipt of the additional dose?
- Are there considerations that should be made when implementing the additional mRNA COVID-19 vaccine dose program for immunocompromised people to ensure that inequities are reduced whenever possible, and that they are not increased?

O Reduced	O Probably reduced	O Probably no impact	
O Probably increased	O Increased	O Varies	O Don't know

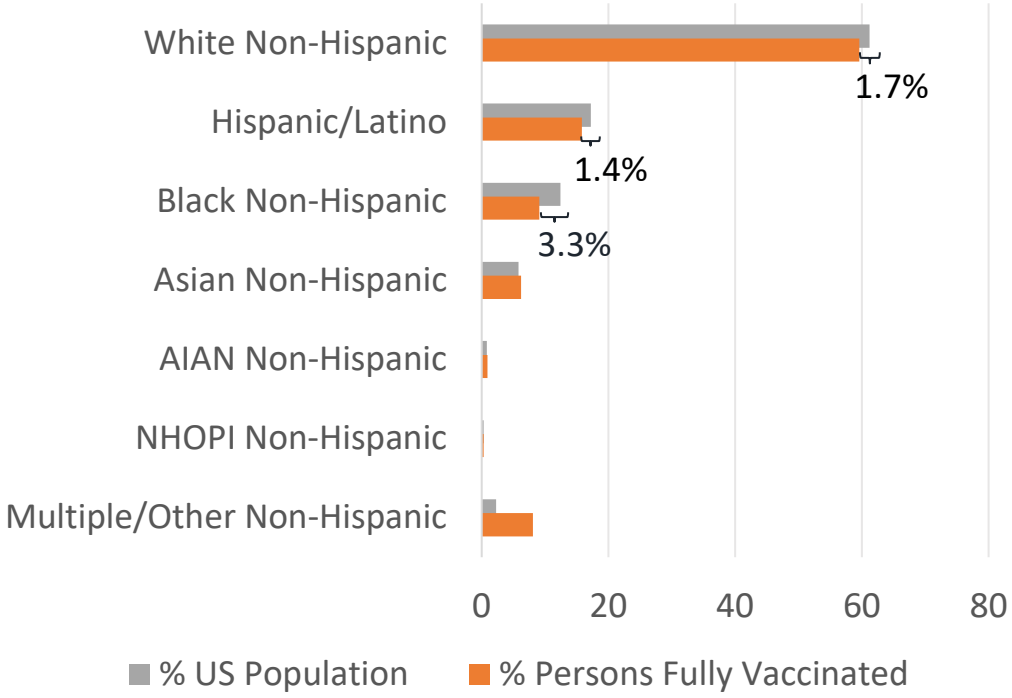
Which immunocompromised groups in the United States could be disadvantaged with respect to an additional mRNA COVID-19 vaccine dose?

- **Place of residence**
  - Living in rural/frontier areas
  - Living in congregate settings (long-term care facilities)
  - Experiencing homelessness
- **Racial and ethnic minority populations**
  - Black, Hispanic or Latino, and Alaskan Native/American Indian
  - Immigration status
- **Socioeconomic status**
  - Poverty
  - High social vulnerability
- **Personal characteristics associated with discrimination**
  - With disabilities
  - Substance use
- **Recipients of Janssen COVID-19 Vaccine**

Equity:

Data on equitable provision of COVID-19 vaccine in adults

- As of August 8, 2021, Black adults had the largest difference in the percentage of fully vaccinated persons compared with the percentage in the overall U.S. population
- May see similar patterns in immunocompromised



CDC. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic as of August 8, 2021, and US Census Bureau National Population Estimates

Equity:

Opportunities to increase equitable access of an additional dose of mRNA COVID-19 vaccine to immunocompromised people

- Multipronged approach to ensure access
  - Primary care providers and specialist clinics serving immunocompromised patients, FQHCs, rural health clinics, community health centers, hospitals, & pharmacies

Equity

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O Probably increased	O Increased	O Varies	O Don't know

Summary

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is COVID-19 disease among immunocompromised people of public health importance?	**Yes**
Benefits and Harms	How substantial are the desirable anticipated effects?	**Large**
	How substantial are the undesirable anticipated effects?	**Minimal**
	Do the desirable effects outweigh the undesirable effects?	**Favors additional dose of mRNA vaccine in immunocompromised people**
	What is the overall certainty of the evidence for the critical outcomes?	**Not GRADED**
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	**Large**
	Is there important variability in how patients value the outcomes?	**Probably not important variability**
Acceptability	Is an additional dose of mRNA COVID-19 vaccines acceptable to key stakeholders?	**Yes**
Feasibility	Is an additional dose of mRNA COVID-19 vaccine feasible to implement among immunocompromised people?	**Yes**
Resource Use	Is an additional dose of mRNA COVID-19 vaccine, given to immunocompromised people, a reasonable and efficient allocation of resources?	**Yes**
Equity	What would be the impact of an additional dose of mRNA COVID-19 vaccine, given to immunocompromised people, on health equity?	**Probably no impact**

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Type of recommendation	We do not recommend the intervention	We recommend the intervention for individuals based on shared clinical decision-making	We recommend the intervention

Questions for ACIP discussion

1) **Intervention**: does ACIP support the intervention of an additional dose of mRNA COVID-19 vaccine following a primary series in immunocompromised people?
2) **Population**: balancing potential benefits and potential harms, what is the optimal lower age threshold for the additional dose intervention in immunocompromised people?

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  - DVD Enhanced Surveillance
  - Community Surveillance
  - Seroprevalance
- Data, Analytics and Visualization Task Force
- Respiratory Viruses Branch

References: Immunocompromised people and SARS-CoV-2 infection (Slides 14)

1. Harpaz et al. *Prevalence of Immunosuppression Among US Adults*, 2013. JAMA 2016.
2. Williamson et al. *Factors Associated with COVID-19-related Death Using Open SAFELY*. Nature 2020.
3. Truong et al. *Persistent SARS-CoV-2 Infection and Increasing Viral Variants in Children and Young Adults With Impaired Humoral Immunity*. medRxiv 2021.
4. Hensley et al. *Intractable Coronavirus Disease 2019 (COVID-19) and Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-CoV-2) Replication in Chimeric Antigen Receptor-Modified T-Cell Therapy Recipient: A Case Study*. CID 2021
5. Baang et al. *Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Replication in an immunocompromised Patient*. JID 2021
6. Choi et al. *Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host*. NEJM 2020
7. Helleberg et al. *Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy*. JID 2020
8. Clark et al. *SARS-CoV-2 Evolution in an Immunocompromised Host Reveals Shared Neutralization Escape Mechanism*. Cell 2021
9. Kemp et al. *SARS-CoV-2 Evolution During Treatment of Chronic Infection*. Nature 2021
10. Khatamzas et al. Emergence of Multiple SARS-CoV-2 Mutations in an Immunocompromised Host. medRxiv 2021
11. Lewis et al. *Household Transmission of Severe Acute Respiratory Syndrome Coronavirus-2 in the United States*. CID 2020
12. Stengert et al. *Cellular and Humoral Immunogenicity of a SARS-CoV-2 mRNA Vaccine Inpatients on Hemodialysis*. medRxiv preprint 2021.
13. Tenforde et al. *Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States* (2021) DOI: https://doi.org/10.1101/2021.07.08.21259776
14. Khatamzas et al. *Emergence of Multiple SARS-CoV-2 Mutations in an Immunocompromised Host MedRxiv* preprint doi: https://doi.org/10.1101/2021.01.10.20248871
15. Avanzato et al. *Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer*. doi: 10.1016/j.cell.2020.10.049. Epub 2020 Nov 4. PMID: 33248470; PMCID: PMC7640888.
16. Nakajima, Yukiko et al. *Prolonged viral shedding of SARS-CoV-2 in an immunocompromised patient.* Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy doi:10.1016/j.jiac.2020.12.001
17. Tarhini et al . *Long-Term Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infectiousness Among Three Immunocompromised Patients: From Prolonged Viral Shedding to SARS-CoV-2 Superinfection*. doi: 10.1093/infdis/jiab075.
18. Brosh –Nissimiv et al. *BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel* (2021) https://doi.org/10.1016/j.cmi.2021.06.03

References: Immunocompromised people and SARS-CoV-2 infection (Slides 15)

1. Tenforde et al. *Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States* (2021) DOI: https://doi.org/10.1101/2021.07.08.21259776
2. Brosh –Nissimiv et al. *BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel* (2021) https://doi.org/10.1016/j.cmi.2021.06.03
3. Chodick G et al. The Effectiveness of the Two-Dose BNT162b2 Vaccine: Analysis of Real-World Data. Clinical Infectious Diseases, ciab438. https://doi.org/10.1093/cid/ciab438;
4. Khan N, Mahmud N. Effectiveness of SARS-CoV-2 Vaccination in a Veterans Affairs Cohort of Patients With Inflammatory Bowel Disease With Diverse Exposure to Immunosuppressive Medications. Gastroenterology(2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf
5. Chemaitelly et al. SARS-CoV-2 vaccine effectiveness in immunosuppressed kidney transplant recipients. medRxiv 2021.08.07.21261578; doi: https://doi.org/10.1101/2021.08.07.21261578

References: Percent of subjects with antibody response after two mRNA vaccine doses (Slide 16 - 1)

- Anand, et al. "Antibody Response to COVID-19 vaccination in Patients Receiving Dialysis." Journal of the American Society of Nephrology (2021).
- Attias, Philippe, et al. "Antibody response to BNT162b2 vaccine in maintenance hemodialysis patients." Kidney international (2021).
- Barrière, E. Chamorey, Z. Adjtoutah, O. Castelnau, A. Mahamat, S. Marco, E. Petit, A. Leysalle, V. Raimondi, M. Carles, Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors, Annals of Oncology, 2021, ISSN 0923-7534,https://doi.org/10.1016/j.annonc.2021.04.019. (https://www.sciencedirect.com/science/article/pii/S0923753421011832)
- Benotmane, Ilies, et al. "Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine." Kidney international 99.6 (2021): 1498-1500.
- Bertrand, D., et al. (2021). "Antibody and T Cell Response to SARS-CoV-2 Messenger RNA BNT162b2 Vaccine in Kidney Transplant Recipients and Hemodialysis Patients." Journal of the American Society of Nephrology 10: 10.
- Boyarsky, Brian J., et al. "Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients." Jama (2021).
- Broseta, J. J., et al. (2021). "Humoral and Cellular Responses to mRNA-1273 and BNT162b2 SARS-CoV-2 Vaccines Administered to Hemodialysis Patients." American Journal of Kidney Diseases 23: 23.
- Chan, L., et al. (2021). "Antibody Response to mRNA-1273 SARS-CoV-2 Vaccine in Hemodialysis Patients with and without Prior COVID-19." Clinical journal of the American Society of Nephrology : CJASN. 24.
- Chavarot, Nathalie, et al. "Poor Anti-SARS-CoV-2 Humoral and T-cell Responses After 2 Injections of mRNA Vaccine in Kidney Transplant Recipients Treated with Belatacept." Transplantation (2021).
- Chevallier, P., et al. (2021). "Safety and immunogenicity of a first dose of SARS-CoV-2 mRNA vaccine in allogeneic hematopoietic stem-cells recipients." EJHaem 01: 01.
- Diefenbach C, Caro J, Koide A, et al. Impaired Humoral Immunity to SARS-CoV-2 Vaccination in Non-Hodgkin Lymphoma and CLL Patients. medRxiv; 2021. DOI: 10.1101/2021.06.02.21257804.
- Frantzen, Guilhem Cavaillé, Sandrine Thibeaut, Yohan El-Haik, Efficacy of the BNT162b2 mRNA COVID-19 vaccine in a haemodialysis cohort, Nephrology Dialysis Transplantation, 2021;, gfab165, https://doi.org/10.1093/ndt/gfab165
- Furer, V., et al. (2021). "Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study." Annals of the Rheumatic Diseases 14: 14.
- Gallo, A., et al. (2021). "Preliminary evidence of blunted humoral response to SARS-CoV-2 mRNA vaccine in multiple sclerosis patients treated with ocrelizumab." Neurological Sciences 15: 15.
- Geisen, Ulf M., et al. "Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort." Annals of the rheumatic diseases (2021).

References: Percent of subjects with antibody response after two mRNA vaccine doses (Slide 16 - 2)

- Grupper, Ayelet, et al. "Reduced humoral response to mRNA SARS-Cov-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus." American Journal of Transplantation (2021).
- Haberman, Rebecca H., et al. "Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease." Annals of the Rheumatic Diseases (2021).
- Havlin, J., et al. (2021). "Immunogenicity of BNT162b2 mRNA COVID-19 vaccine and SARS-CoV-2 infection in lung transplant recipients." Journal of Heart & Lung Transplantation 21: 21.
- Herishanu, Yair, et al. "Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia." Blood (2021)
- Holden, I. K., et al. (2021). "Immunogenicity of SARS-CoV-2 mRNA vaccine in solid organ transplant recipients." Journal of Internal Medicine 08: 08.
- Itzhaki Ben Zadok, O., Shaul, A.A., Ben-Avraham, B., Yaari, V., Ben Zvi, H., Shostak, Y., Pertzov, B., Eliakim-Raz, N., Abed, G., Abuhazira, M., Barac, Y.D., Mats, I., Kramer, M.R., Aravot, D., Kornowski, R. and Ben-Gal, T. (2021), Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients – a prospective cohort study. Eur J Heart Fail. https://doi.org/10.1002/ejhf.2199
- Jahn M, Korth J, Dorsch O, Anastasiou OE, Sorge-Hädicke B, Tyczynski B, Gäckler A, Witzke O, Dittmer U, Dolff S, Wilde B, Kribben A. Humoral Response to SARS-CoV-2-Vaccination with BNT162b2 (Pfizer-BioNTech) in Patients on Hemodialysis. Vaccines. 2021; 9(4):360. https://doi.org/10.3390/vaccines9040360
- Kennedy, Nicholas A., et al. "Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD." Gut (2021).
- Korth, Johannes, et al. "Impaired humoral response in renal transplant recipients to SARS-CoV-2 vaccination with BNT162b2 (Pfizer-BioNTech)." Viruses 13.5 (2021): 756.
- Lacson, Eduardo, et al. "Immunogenicity of SARS-CoV-2 Vaccine in Dialysis." medRxiv (2021).
- Longlune, Marie Béatrice Nogier, Marcel Miedougé, Charlotte Gabilan, Charles Cartou, Bruno Seigneuric, Arnaud Del Bello, Olivier Marion, Stanislas Faguer, Jacques Izopet, Nassim Kamar, High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients, Nephrology Dialysis Transplantation, 2021;, gfab193, https://doi.org/10.1093/ndt/gfab193
- Marinaki, S., Adamopoulos, S., Degiannis, D., Roussos, S., Pavlopoulou, I.D., Hatzakis, A. and Boletis, I.N. (2021), Immunogenicity of SARS-CoV-2 BNT162b2 vaccine in solid organ transplant recipients. Am J Transplant. https://doi.org/10.1111/ajt.16607
- Massarweh A, et. al Evaluation of Seropositivity Following BNT162b2 Messenger RNA Vaccination for SARS-CoV-2 in Patients Undergoing Treatment for Cancer. JAMA Oncol. 2021 May 28. doi: 10.1001/jamaoncol.2021.2155. Epub ahead of print. PMID: 34047765.
- Mazzola, A., et al. (2021). "Poor Antibody Response after Two Doses of SARS-CoV-2 vaccine in Transplant Recipients." Clinical Infectious Diseases 24: 24.
- Miele, M., Busà, R., Russelli, G., Sorrentino, M.C., Di Bella, M., Timoneri, F., Mularoni, A., Panarello, G., Vitulo, P., Conaldi, P.G. and Bulati, M. (2021), Impaired anti-SARS-CoV-2 Humoral and Cellular Immune Response induced by Pfizer-BioNTech BNT162b2 mRNA Vaccine in Solid Organ Transplanted Patients. American Journal of Transplantation. Accepted Author Manuscript. https://doi.org/10.1111/ajt.16702

References: Percent of subjects with antibody response after two mRNA vaccine doses (Slide 16 - 3)

•Monin, Leticia, et al. "Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study." The Lancet Oncology (2021).
•Mounzer Agha, et.al Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients medRxiv 2021.04.06.21254949; doi: https://doi.org/10.1101/2021.04.06.21254949
•Narasimhan, M., et al. (2021). "Serological Response in Lung Transplant Recipients after Two Doses of SARS-CoV-2 mRNA Vaccines." 9(7): 30.
•Olivier, et al. "Safety and Immunogenicity of Anti–SARS-CoV-2 Messenger RNA Vaccines in Recipients of Solid Organ Transplants." Annals of Internal Medicine (2021).
•Ou, M. T., et al. (2021). "Immunogenicity and Reactogenicity After SARS-CoV-2 mRNA Vaccination in Kidney Transplant Recipients Taking Belatacept." Transplantation. 19.
•Parakkal, et al. "Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2." medRxiv (2021).
•Parry, Helen Marie, et al. "Antibody responses after first and second Covid-19 vaccination in patients with chronic lymphocytic leukaemia." (2021).
•Peled, Yael, et al. "BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response." The Journal of Heart and Lung Transplantation (2021).
•Pimpinelli, F., Marchesi, F., Piaggio, G. et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. J Hematol Oncol 14, 81 (2021). https://doi.org/10.1186/s13045-021-01090-6
•Rabinowich, Ayelet Grupper, Roni Baruch, Merav Ben-Yehoyada, Tami Halperin, Dan Turner, Eugene Katchman, Sharon Levi, Inbal Houri, Nir Lubezky, Oren Shibolet, Helena Katchman, Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients, Journal of Hepatology, 2021, ISSN 0168-8278, https://doi.org/10.1016/j.jhep.2021.04.020.
•Rashidi-Alavijeh, et al. (2021). "Humoral Response to SARS-Cov-2 Vaccination in Liver Transplant Recipients–A Single-Center Experience." Vaccines 9(7): 738-738.
•Rincon-Arevalo, H., et al. (2021). "Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients." Science immunology 6(60): 15.
•Roeker, Lindsey E., et al. "COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia." Leukemia (2021): 1-3.
•Rozen-Zvi, Benaya, et al. "Antibody response to mRNA SARS-CoV-2 vaccine among kidney transplant recipients–Prospective cohort study." Clinical Microbiology and Infection (2021).
•Ruddy, J. A., et al. (2021). "High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases." Annals of the Rheumatic Diseases (no pagination).

References: Percent of subjects with antibody response after two mRNA vaccine doses (Slide 16 - 4)

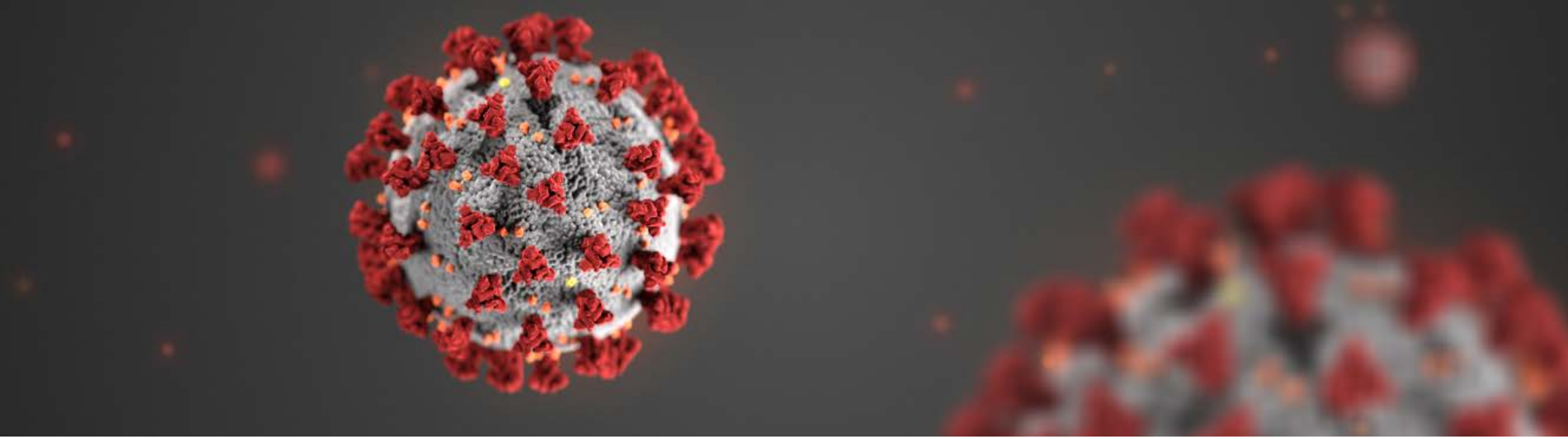
- Rui, A. D., et al. (2021). Humoral Response to BNT162b2 mRNA Covid19 Vaccine in Peritoneal and Hemodialysis Patients: a Comparative Study.

Sattler, Arne, et al. "Impaired Humoral and Cellular Immunity after SARS-CoV2 BNT162b2 (Tozinameran) Prime-Boost Vaccination in Kidney Transplant Recipients." medRxiv (2021).

- Schramm, R., et al. (2021). "Poor humoral and T-cell response to two-dose SARS-CoV-2 messenger RNA vaccine BNT162b2 in cardiothoracic transplant recipients." Clinical Research in Cardiology 09: 09.
- Shostak, Yael, et al. "Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine." The Lancet Respiratory Medicine 9.6 (2021): e52-e53.
- Shroff, Rachna T., et al. "Immune Responses to COVID-19 mRNA Vaccines in Patients with Solid Tumors on Active, Immunosuppressive Cancer Therapy." medRxiv (2021).
- Simon, Benedikt, et al. "Hemodialysis pat
- ients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls." MedRxiv (2021).
- Speer, Claudius, et al. "Early Humoral Responses of Hemodialysis Patients after COVID-19 Vaccination with BNT162b2." Clinical Journal of the American Society of Nephrology (2021).
- Strengert, Monika, et al. "Cellular and humoral immunogenicity of a SARS-CoV-2 mRNA vaccine in patients on hemodialysis." medRxiv (2021).
- Thakkar, A., et al. (2021). "Seroconversion rates following COVID-19 vaccination among patients with cancer." Cancer Cell 05: 05.
- Yanay, Noa Berar, et al. "Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients." Kidney international 99.6 (2021): 1496-1498.
- Yau, Kevin, et al. "The Humoral Response to the BNT162b2 Vaccine in Hemodialysis Patients." medRxiv (2021).
- Zitt, E., et al. (2021). "The Safety and Immunogenicity of the mRNA-BNT162b2 SARS-CoV-2 Vaccine in Hemodialysis Patients." Frontiers in Immunology 12: 704773.

References: Percent of subjects with antibody response after 3 mRNA vaccine doses (Slide 25)

- Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)
- Epsi et al. (2021) medRxiv doi: https://doi.org/10.1101/2021.07.02.21259913
- Ducloux., et al. (2021). Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis.“Kidney Int. 2021 Jun 30m doi: 10.1016/j.kint.2021.06.025 [Epub ahead of print .



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