Data and clinical considerations for additional doses in immunocompromised people

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ACIP Meeting
July 22, 2021

cdc.gov/coronavirus
Outline

1) COVID-19 vaccine response among immunocompromised people

2) Response to an additional dose of COVID-19 vaccine among immunocompromised people

3) Frequently asked questions about vaccination of immunocompromised people
Additional doses in immunocompromised people

**Review data:**
Assess safety, immunogenicity, and implementation

**FDA**
- **Regulatory allowance:**
  EUA amendment would allow recommendations under EUA
  BLA would allow for ‘off label’ recommendations

**CDC/ACIP**
- **Clinical update:**
  Clinical considerations/recommendations for use

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COVID-19 vaccine response in immunocompromised people: What do we know now?
Immunocompromised people and SARS-CoV-2 infection

- Immunocompromised people comprise ~2.7% of U.S. adults\(^1\)
  - Solid tumor and hematologic malignancies
  - Receipt of solid-organ or hematopoietic stem cell transplant
  - Severe primary immunodeficiencies
  - Persons living with HIV
  - Treatment with immunosuppressive medications such as cancer chemotherapeutic agents, TNF blockers, certain biologic agents (e.g., rituximab), and high-dose corticosteroids

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Immunocompromised people and SARS-CoV-2 infection

- 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)\(^3,6,8-10,14,17\)
  - Low antibody/neutralization titers to SARS-CoV-2 variants\(^12\)
- More likely to transmit SARS-CoV-2 to household contacts\(^11\)
- More likely to have breakthrough infection:
  - 44\% of hospitalized breakthrough cases are immunocompromised people in US study\(^13\)
  - 40\% of hospitalized breakthrough cases are immunocompromised people in Israeli study\(^18\)

See reference slide at end
mRNA vaccine effectiveness (VE) studies among immunocompromised populations

- **VE: 7-27 days after 2nd dose of Pfizer-BioNTech vaccine**
  - 71% (CI 37-87%) among immunosuppressed* people vs. 90% (CI 83-96%) overall: **SARS-CoV-2 infection**
  - 75% (CI 44-88%) among immunosuppressed people vs. 94% (CI 87-97%) overall: **symptomatic COVID-19**

- **VE: ≥7 days after 2nd dose of mRNA vaccine**
  - 80% among people with inflammatory bowel disease on immunosuppressive meds: **SARS-CoV-2 infection**
  - VE of 25% was noted after 1st dose of mRNA vaccine for **SARS-CoV-2 infection**

- **VE: ≥14 days after 2nd dose of mRNA vaccine**
  - 59% (CI 12-81%) among immunocompromised people vs. 91% (CI 86-95%) without immunocompromise: **COVID-19 hospitalization**

*Immunocompromised conditions (e.g., recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome)

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

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

Darker blue color is hematologic cancers

Healthy Controls: 95%–100%
Response to an additional dose of COVID-19 vaccine in immunocompromised people:

The emerging data
### Comparing evidence 3rd mRNA COVID-19 vaccine dose in immunosuppressed people with seropositive response

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>2nd Dose</th>
<th>3rd Dose Seronegative after 2nd dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sample Size</td>
<td>Seronegative N (%)</td>
</tr>
<tr>
<td>Kamar et al.</td>
<td>Recipients of solid-organ transplant</td>
<td>99</td>
<td>59 (60)</td>
</tr>
<tr>
<td></td>
<td>Recipients of solid-organ transplant</td>
<td>30</td>
<td>24 (80)</td>
</tr>
<tr>
<td>Werbel et al.*</td>
<td>Patients on hemodialysis</td>
<td>82</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Longlune et al.</td>
<td>Patients on hemodialysis</td>
<td>106</td>
<td>66 (62)</td>
</tr>
</tbody>
</table>

* Recipients received homologous mRNA prime followed by either a single Moderna, Pfizer, or Janssen boost.

- Among those who had **no detectable antibody** response to an initial mRNA vaccine series, **33-50% developed an antibody response to an additional dose**
Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients

• No serious adverse events were reported after administration of the 3rd dose, and no acute rejection episodes occurred (n=99)

Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)
No patients developed critical side effects requiring hospitalization

Symptoms reported were consistent with previous doses and the intensity of the symptoms was mostly mild or moderate

Reactogenicity of 3rd mRNA vaccine dose in cohort of patients on hemodialysis (n=63*)

*Sample included patients who had an optimal and suboptimal antibody response to primary mRNA series and chose to receive a 3rd dose

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

- **United Kingdom**\(^2\) (Announced July 1, 2021)
  - Proposal for an additional dose for immunocompromised people ≥16 years (among others), to be implemented between 6 September and 17 December 2021
  - Decision pending

- **Israel**\(^3\) (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

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Summary

- Immunocompromised people are at increased risk of poor outcomes from COVID-19
- Studies indicate a reduced antibody response in immunocompromised people following a primary vaccine series, compared to healthy vaccine recipients
- Emerging data suggest that an additional COVID-19 vaccine dose in immunocompromised people enhances antibody response and increases the proportion who respond
- In small studies, the reactogenicity of the 3rd dose of mRNA vaccine was similar to prior doses
Frequently asked questions about vaccination of immunocompromised people
Which immunocompromised groups should be considered for an additional dose as allowed by regulatory mechanisms?

- Conditions and treatments associated with moderate to severe immune compromise:
  - Active or recent treatment for solid tumor and hematologic malignancies
  - Receipt of solid-organ or recent hematopoietic stem cell transplant
  - Severe primary immunodeficiency
  - Advanced or untreated HIV infection
  - Treatment with immunosuppressive medications such as cancer chemotherapeutic agents, TNF blockers, certain biologic agents (e.g., rituximab), and high-dose corticosteroids

- Chronic conditions associated with varying degrees of immune deficit, such as asplenia and chronic renal disease:

- Different medical conditions and treatments can result in widely varying degrees of immunosuppression. A patient’s clinical team is best able to assess the degree of altered immunocompetence and optimal timing of vaccination

*General Best Practice Guidelines for Immunization and CDC Yellow Book can be consulted for detailed information*
Should immunocompromised people undergo antibody testing following COVID-19 vaccination?

- Utility of serologic testing or cellular immune testing to assess immune response to COVID-19 vaccination has not been established
- Exact correlation between antibody level and protection from COVID-19 remains unclear
- Commercial antibody and cellular immune testing may not be consistent across laboratories
- Serologic (antibody) testing or cellular immune testing outside of the context of research studies is **not recommended in the United States at this time**
Are there data to support mixed-dose series in immunocompromised people: for example, Janssen followed by mRNA COVID-19 vaccine?

- Studies from Europe have assessed heterologous primary series (AstraZeneca and Pfizer-BioNTech) in the general adult population and found immunogenicity to be at least equivalent to homologous series 1-5
  - Large UK trial (Com-COV) found that one dose of AstraZeneca + one dose of Pfizer-BioNTech resulted in superior immunogenicity compared with two doses of AstraZeneca vaccine but lower antibodies than 2 doses of Pfizer-BioNTech; increase in systemic reactogenicity observed with heterologous schedules5

- Evidence is needed regarding the safety and immunogenicity of using a mixed-dose approach for Janssen (FDA-authorized adenoviral vector vaccine) + mRNA vaccine in immunocompromised people

1. Borobia et al. Reactogenicity and Immunogenicity of BNT162b2 in Subjects Having Received a First Dose of ChAdOx1s: Initial Results of a Randomized, Adaptive, Phase 2 Trial (CombiVacS). Available at SSRN: https://ssrn.com/abstract=3854768
3. Hillus et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunization with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study. medRxiv; 2021. DOI: 10.1101/2021.05.19.21257334
Following COVID-19 vaccination, what infection prevention measures should immunocompromised people maintain?

- Immunocompromised people should be counseled about potential for reduced immune responses to COVID-19 vaccination and need 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 encouraged to be vaccinated against COVID-19

Is there a role for monoclonal antibody use in immunocompromised people?

- Monoclonal antibodies are currently authorized by FDA for emergency use in persons with SARS-CoV-2 infection who are at high risk for progressing to severe COVID-19 and/or hospitalization.

- Monoclonal antibodies are not yet authorized for SARS-CoV-2 infection prevention.

What are the implications of the Emergency Use Authorizations (EUAs) for the COVID-19 vaccines, with respect to considerations for an additional dose in immunocompromised persons?

- FDA has authorized mRNA vaccines as a 2-dose series and Janssen COVID-19 vaccine as a single dose.
- At this time, we are not aware of data submitted to FDA to support an amendment to the EUA for this population.
- CDC/ACIP will closely monitor any updates to data and regulatory mechanisms.

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Now:
Immunocompromised people should continue to follow infection prevention measures:
- Wear a mask, stay 6 feet apart from others, avoid crowds and poorly ventilated spaces

Close contacts (≥12 years) of immunocompromised people should be vaccinated against COVID-19

Early treatment with monoclonal antibodies may be beneficial in this population

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Additional COVID-19 vaccine dose in immunocompromised people: Next steps

- Assess additional studies of safety and immunogenicity of additional dose in immunocompromised people
- Assess additional studies and expert opinion regarding the subpopulations of immunocompromised people who may benefit most from an additional dose
- Determine acceptable intervals and mix and match schedules
- Await regulatory allowance (e.g. FDA amendment of EUA or BLA) for an additional dose of COVID-19 vaccine

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Questions for ACIP
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1. What additional data do ACIP need to inform these discussions?

2. Thoughts on the focus of “moderate to severe” immunocompromised populations, once authorized/approved?
Acknowledgements

- Nicole Reisman
- Mary Chamberland
- Kathleen Dooling
- Jack Gersten
- Heather Scobie
- Kristine Schmit
- Lauri Hicks
- Stephen Hadler
- Jessica MacNeil
- Danielle Moulia
- Eddie Shanley
- Hannah Rosenblum
- Monica Godfrey

- Vaccine Task Force
- Epi Task Force
- Respiratory Viruses Branch
References
References for slide 7: Immunocompromised people and SARS-CoV-2 infection

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
10. Khataimas 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
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/jia075.
References for slides 9: immunocompromised populations [1]

References for slides 9: immunocompromised populations [2]

- 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
References for slides 9: immunocompromised populations [3]

- 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
References for slides 9: immunocompromised populations [4]

References for slides 10: Comparing evidence 3rd for mRNA COVID-19 vaccine dose in immunosuppressed people with suboptimal response

- Longlune et al, High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients, 2021; https://doi.org/10.1093/ndt/gfab193
- Maxime et al. (2021) medRxiv doi: https://doi.org/10.1101/2021.07.02.21259913
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.