Overview of data to inform recommendations for booster doses of COVID-19 vaccines

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ACIP Meeting
June 23, 2021
Policy questions:
Recommendations for booster doses of COVID-19 vaccines

- **Main policy question**: Are booster doses of COVID-19 vaccines needed for those previously vaccinated with a primary series?

- **Other questions:**
  - Are booster doses needed for all persons or only in specific populations?
  - What is the optimal timing of booster doses after primary series?
  - Can these be given as a ‘mixed dose’ or do they need to be matched to a primary series?

**Note**: Decisions around strains for vaccine production likely to be made separately.
Policy questions:
Recommendations for booster doses of COVID-19 vaccines

- Policy on booster doses coordinated with FDA for possible amendments to EUA, and ACIP for recommendations around use in specific populations
  - Both will require data on safety, immunogenicity and public health need

- "Booster dose": Vaccine doses after primary (1 or 2-dose) series that are needed to increase immunity after waning of initial immune response
  Some individuals may not have mounted sufficient immune response after primary series and could need an additional dose to reach protective immunity
Initial doses of COVID-19 vaccines: Data to inform recommendations

- LTCF residents
- Persons ≥65 years
- Persons 16–64 with high-risk medical conditions

- Risk of COVID-19 complications
- Risk of COVID-19 exposure

- Health care personnel
- Frontline Essential Workers
- Other Essential Workers

LTCF = Long Term Care Facility
Booster doses of COVID-19 vaccines: Data to inform recommendations

- Risk of COVID-19 complications
- Risk of COVID-19 exposure
- Risk of waning immunity
- Risk of COVID-19 variants
Booster doses of COVID-19 vaccines: Data to inform recommendations

COVID-19 epidemiology
Cases, hospitalizations, deaths by age, setting, and medical condition

- Risk of COVID-19 complications
- Risk of COVID-19 exposure
- Risk of waning immunity
- Risk of COVID-19 variants
Booster doses of COVID-19 vaccines:
Data to inform recommendations

- Risk of COVID-19 complications
- Risk of COVID-19 exposure
- Risk of waning immunity
- Risk of COVID-19 variants

Duration of protection (antibodies, VE) after primary series
Ability to ‘boost’ with additional doses

VE= Vaccine efficacy/effectiveness
Booster doses of COVID-19 vaccines: Data to inform recommendations

- Risk of COVID-19 complications
- Risk of COVID-19 exposure
- Risk of waning immunity
- Risk of COVID-19 variants

Vaccine effectiveness studies & assessment of vaccine breakthrough cases
Time since vaccination, age, setting, medical condition
Booster doses of COVID-19 vaccines: Data to inform recommendations

- Risk of COVID-19 complications
- Risk of COVID-19 exposure
- Risk of waning immunity
- Risk of COVID-19 variants

Correlates of Protection
Booster doses of COVID-19 vaccines: Data to inform recommendations

- Risk of COVID-19 complications
- Risk of COVID-19 exposure
- Risk of waning immunity
- Risk of COVID-19 variants

Variant proportions, antibody response, and effectiveness for each variant and vaccine
Booster doses of COVID-19 vaccines: What do we know now?
COVID-19 vaccines administered

As of June 21, 2021

Total Vaccine Doses Administered: 318,576,441

% of Population With At Least 1 Dose:

- ≥12 years of age: 62.5%
- ≥18 years of age: 65.4%
- ≥65 years of age: 87.3%

CDC: https://covid.cdc.gov/covid-data-tracker
Booster doses of COVID-19 vaccines: Immunogenicity and antibody response

- **Correlates of protection:**
  - Immune response that allows prediction of the degree of protection against infection or disease
  - Work ongoing, no correlate established yet

- **Duration of protection:**
  - Monitor kinetics of antibody response, efficacy from early phase clinical trials

- **Antibody response to variant-specific boosters**
Robust correlation between vaccine efficacy against symptomatic disease and mean neutralizing antibody titer: Two studies

Earle et al. medRxiv preprint (Mar 20 2021)
Robust correlation between vaccine efficacy against symptomatic disease and mean neutralizing antibody titer: Two studies

- Suggests 54 IU/ml as correlate of protection (20% of mean convalescent titer)
- Threshold of protection against severe disease is lower (3% of mean convalescent titer), less affected by vaccine differences
- For variants, 5-fold lower neutralizing titer predicted to reduce efficacy from 95% to 77% in high efficacy vaccine, or from 70% to 32% for lower efficacy vaccine

Predicted duration of immunity varies with initial vaccine efficacy

- Initial efficacy may be useful in predicting time until boosting may be needed

- Vaccine starting with initial efficacy of 95% expected to maintain high efficacy (77%) after 250 days

- Vaccine starting with initial efficacy of 70% may result in drop to lower efficacy (33%) after 250 days

- Model assumes **neutralization** is major mechanism of protection

*Khoury et al. Nature Medicine (2021)*
Protection from severe infection predicted to persist longer than protection against mild infection

- After initial exponential decay, antibody half-lives generally stabilize to ≥10 years (linear decline)
- Depending on when transition occurs, proportion of individuals predicted to be protected against severe disease long-term, even without boosters, but may be susceptible to mild infection

Duration of immunity

- To date, antibody persistence demonstrated for up to 8 months after COVID-19 infection and up to 6 months after the 2nd mRNA vaccine dose

- Two studies, 6 months after receiving Moderna vaccine: Lower neutralizing titers & higher proportions (~50%) with undetectable titers against B.1.351 and P.1, compared with ancestral strain
  - Third modeling study makes similar conclusions

- Many studies have shown larger reductions in variant neutralization for convalescent sera than post-vaccine sera

Dan, J. M. et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 371, eabf4063 (2021)
Variant-specific booster
Preliminary analysis of safety and immunogenicity of a SARS-CoV-2 variant vaccine booster

- Two weeks after booster vaccination, titers against wild-type original strain, B.1.351 and P.1 variants increased to levels similar to or higher than peak titers after the primary series vaccinations

https://www.medrxiv.org/content/10.1101/2021.05.05.21256716v1
Variant-specific booster
Preliminary analysis of safety and immunogenicity of a SARS-CoV-2 variant vaccine booster

- Both vaccines demonstrated broad antibody boosting

50 µg booster dose of mRNA-1273

50 µg booster dose of mRNA-1273.351

https://www.medrxiv.org/content/10.1101/2021.05.05.21256716v1
Booster doses of COVID-19 vaccines:
Vaccine effectiveness

- Overall “real world” vaccine effectiveness
- Efficacy/effectiveness against variants
- Effectiveness in specific populations
“Real world” vaccine effectiveness:
VE in **fully vaccinated** adult population

Fully vaccinated against COVID-19: ≥2 weeks after receipt of 2nd dose in a 2-dose series (Pfizer and Moderna) or ≥2 weeks after receipt of the single dose of the Janssen vaccine

See reference list at end
Reduced antibody neutralization activity of vaccine sera relative to wildtype/dominant strain by study (n=48)

Median: 7.5 3.0 2.8 1.9 2.0

Studies by vaccine
- mRNA
- AstraZeneca
- Novavax
- Janssen

No effect = 1
**“Real world” vaccine effectiveness:**
Studies to inform VE against variants of concern

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine</th>
<th>Dominant strain(s)</th>
<th>Fully vaccinated VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel, Europe &amp; U.K</td>
<td>Pfizer</td>
<td>B.1.1.7 (Alpha)</td>
<td>&gt;85%</td>
</tr>
<tr>
<td>Canada</td>
<td>mRNA</td>
<td>B.1.1.7, P.1 (Alpha, Gamma)</td>
<td>79% (65%–88%)</td>
</tr>
<tr>
<td>Canada</td>
<td>mRNA</td>
<td>P.1/B.1.351 (Gamma/Beta)</td>
<td>88% (61%–96%)*</td>
</tr>
<tr>
<td>Qatar</td>
<td>Pfizer</td>
<td>B.1.1.7 (Alpha)</td>
<td>90% (86%–92%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B.1.351 (Beta)</td>
<td>75% (71%–79%)*</td>
</tr>
<tr>
<td>South Africa</td>
<td>Janssen</td>
<td>B.1.351 (Beta)</td>
<td>52% (30%–67%)</td>
</tr>
</tbody>
</table>

* Variant-specific VE

For B.1.351 (Beta), VE shown to be higher for prevention of severe disease

Abu-Radad and Butt, NEJM (2021); Sandoff et al, NEJM (2021); Chung et al, medRxiv preprint (May 28 2021); Yassi et al, medRxiv preprint (May 25 2021)
Vaccines & new variant of concern: Delta B.1.617.2

B.1.617.2-specific VE

- **PCR-confirmed infection:** Scotland, 2 doses Pfizer vaccine: 79% (vs. 92% for B.1.1.7)
- **Symptomatic infection:** England, 2 doses Pfizer vaccine: 88% (vs. 93% for B.1.1.7)
- **Hospitalization:** England, 2 doses Pfizer vaccine: 96% (similar to B.1.1.7)

B.1.617.2 antibody neutralization studies

- 4 studies, 2 doses Pfizer vaccine: 1.4, 2.5, 3, and 5.8-fold reduction (vs. wild-type)

Recent study in UK showing resurgence driven by replacement of B.1.1.7 with B.1.617.2, which has higher transmission rate, and infections in unvaccinated children and young adults

Sheikh et al. Lancet (2021): [https://doi.org/10.1016/S0140-6736(21)01358-1](https://doi.org/10.1016/S0140-6736(21)01358-1); Lopez Bernal et al. medRxiv preprint (May 26 2021); [https://doi.org/10.1101/2021.05.22.21257658](https://doi.org/10.1101/2021.05.22.21257658)


Riley et al. medRxiv (June 21 2021): [https://doi.org/10.1101/2021.06.17.21259103](https://doi.org/10.1101/2021.06.17.21259103); Liu et al. Nature (2021); [https://doi.org/10.1038/s41586-021-03693-y](https://doi.org/10.1038/s41586-021-03693-y)
Booster doses of COVID-19 vaccines: Specific populations

- Need for booster doses of COVID-19 vaccines may only be demonstrated in some populations
- Populations to closely monitor:
  - Residents of long-term care facilities
  - adults ≥65 years of age
  - healthcare personnel
  - immunocompromised persons
Two-dose mRNA vaccine effectiveness against SARS-CoV-2 infection in older adults (60+ years) & residents in long-term care facilities

Residents in long-term care facilities
- Cabezas et al.
- Emborg et al.
- Cavanaugh et al.
- Mousten-Helms et al.

Adults ≥60 years of age
- Dagan et al.
- PHE (5.20.21)
- Lopez-Bernal et al.
- Aran
- Mason et al.

% Vaccine Efficacy

Fully vaccinated against COVID-19: ≥2 weeks after receipt of 2nd dose in a 2-dose series (Pfizer and Moderna)

See reference list at end
“Real world” vaccine effectiveness

Healthcare personnel

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<td>United States</td>
<td>Pfizer</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>Moderna</td>
<td>99%</td>
</tr>
<tr>
<td>United States</td>
<td>Pfizer or Moderna</td>
<td>90%</td>
</tr>
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<td>Pfizer</td>
<td>96%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Pfizer or AstraZeneca</td>
<td>90%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Pfizer</td>
<td>86%</td>
</tr>
<tr>
<td>United Kingdom (Scotland)</td>
<td>Pfizer or AstraZeneca</td>
<td>92%</td>
</tr>
<tr>
<td>Italy</td>
<td>Pfizer</td>
<td>95%</td>
</tr>
<tr>
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</tr>
<tr>
<td>Israel</td>
<td>Pfizer</td>
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</tr>
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</table>

People with clinically or therapeutically suppressed immunity

- Represent ≥2.7% of U.S. adults\(^1\), including people living with rheumatologic conditions, organ transplants, HIV, leukemia, on cancer treatment, etc.
- More likely to get severely ill from COVID-19\(^2\)
- Might be at higher risk for:
  - Prolonged SARS-CoV-2 infection\(^3-7\)
  - Viral evolution during infection and treatment\(^3,6,8-10\)
  - Susceptibility to infection with SARS-CoV-2 variants\(^12\)
- Might more frequently transmit SARS-CoV-2 to household contacts\(^11\)

References:
Factors that may decrease vaccine response among immunocompromised populations

- Older age
- Primary immunodeficiency
- Lower lymphocyte count*
- Decreased kidney function
- Immunosuppressive drugs**
- High-dose corticosteroids
- Current or recent (<6 mos) cancer treatment***

* Including lower CD4 count for people living with HIV
** Immunosuppressive drugs include methotrexate, mycophenolate, rituximab, infliximab, calcineurin-inhibitors
*** BTK inhibitors, anti-CD20 and anti-CD38 therapies, chemotherapy
mRNA vaccine effectiveness studies of COVID-19 infection among immunocompromised populations

- **71%** effective against **SARS-CoV-2 infection** from 7-27 days after 2nd Pfizer dose among immunocompromised* people vs. **90%** overall
  - **75%** protection against **symptomatic COVID-19** among immunosuppressed vs. **94%** overall
  - Lower protection with increasing age group

- **80%** effective against **SARS-CoV-2 infection** from 7 days after 2nd mRNA dose among people with inflammatory bowel disease on various immunosuppressive medications
  - One mRNA dose: **25%** effective
  - No difference in effectiveness noted between Pfizer and Moderna

*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)

Chodick et al. *Clinical Infectious Diseases*, ciab438, https://doi.org/10.1093/cid/ciab438
Percent antibody response after two mRNA vaccine doses by immunocompromised condition and study (n=40)

- Studies that compared response after 1\textsuperscript{st} and 2\textsuperscript{nd} 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\%

See reference list at end
Fold-reduction in antibody titers after two mRNA vaccine doses among immunocompromised populations vs. healthy controls

- **Cancer**: Darker blue color is hematologic cancers
- **Hemodialysis**
- **Organ Transplant**
- **Immunosuppressive Therapies**

See reference list at end
Evidence on providing 3\textsuperscript{rd} COVID-19 vaccine dose to immunosuppressed people with suboptimal response

- Solid organ transplant recipients (n=30) who had suboptimal response to standard vaccination and subsequently received 3\textsuperscript{rd} dose of vaccine
  - 57% received Pfizer series; 43% received Moderna series
  - 24 (80%) had negative antibody titers; 6 (20%) ‘low-positive’ after primary series
  - Received 3\textsuperscript{rd} dose median of 67 days after 2\textsuperscript{nd} dose: Janssen (n=15), Moderna (n=9), Pfizer (n=6)
  - After 3\textsuperscript{rd} dose: 14 (47%) responded, including all low-positives; 16 (53%) remained negative

- People on hemodialysis (n=77, no COVID-19 history) vaccinated with up to 3 Pfizer doses
  - 64 (83%) seroconverted after 2\textsuperscript{nd} dose
  - Of those negative after 2\textsuperscript{nd} dose:
    - 5 (41%) of 12 people given 3\textsuperscript{rd} dose seroconverted; 7 (59%) remained negative

- At least one clinical trial pending of 3\textsuperscript{rd} dose of Moderna vaccine in transplant recipients

Longlune et al. Nephrology Dialysis Transplantation, gfab193, [https://doi.org/10.1093/ndt/gfab193](https://doi.org/10.1093/ndt/gfab193)
[https://clinicaltrials.gov/ct2/show/NCT04885907](https://clinicaltrials.gov/ct2/show/NCT04885907)
Considerations for specific populations

LTCF residents, adults ≥65 years of age
- Initial VE encouraging
- Vaccinated in early phase of COVID-19 vaccine roll-out
- Needed special considerations for other vaccines (boosters, higher-dose vaccines)

Healthcare personnel
- Vaccinated in early phase of COVID-19 vaccine roll-out
- Continued exposure to SARS-CoV-2, even as rates of community transmission improve

Immunocompromised persons
- Emerging literature suggesting a reduced antibody response after primary series
- By definition, population with an impaired immune response
- Concern for ability to mount an immune response after additional vaccine doses: consider if other prevention measures needed (monoclonal antibodies, etc.)
Mix-and-match:
Heterologous primary series and booster vaccine

- Recent studies from Europe have assessed heterologous primary series with Pfizer and Astra Zeneca with reassuring results
- Evidence is needed regarding the ability to use a different vaccine as a booster than what was used in the primary series
  - Studies specific to U.S. authorized vaccines

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
Booster doses of COVID-19 vaccines: Timing of additional data
Upcoming studies:
NIH or manufacturer studies

Data from Phase I/II/III trials
- Monitor kinetics of antibody response, efficacy from early phase clinical trials
- BLA submission: Include efficacy for ~6 months

Heterologous boost
- Primary series followed by different boost vaccine
- NIH-sponsored study: 150 individuals, 12-20 weeks following initial series (any series)
  Results expected late summer 2021

Booster studies
- Moderna: Preliminary results for mRNA-1273 (50µg) published May 2021;
  Additional data on mRNA-1273 and other variants as boosters expected July-Sept 2021
- Pfizer: Data on BNT162b2 (30µg) and variant booster studies expected July-Sept 2021

Upcoming studies:
CDC studies

Vaccine breakthrough cases
- Track breakthrough infections
- Monitor severity of disease and genomic sequence (specifically for variants of concern)

Vaccine effectiveness studies
- Continue to monitor VE studies over time:
  - Stratify by age, time since vaccination, setting and medical condition
- Ability to track any waning VE could be impacted by declining incidence, changes in variant prevalence
- Over time, individuals who are vaccinated may become increasingly less comparable to the unvaccinated population
Vaccine effectiveness: Select upcoming studies

HEROES-RECOVER Cohort
- Following ~5,000 essential workers with weekly SARS-CoV-2 testing and quarterly serology
- To date, fully vaccinated populations followed for ~130 days (~4 months) post-vaccination
- Assess neutralizing antibodies 6-months post-vaccination

VISION VE Network
- Multi-state network of 8 integrated care systems and research centers; assess COVID-19 confirmed by molecular assays and vaccination documented by EHR and registries
- Network assesses waning effectiveness using test-negative VE design

IVY VE Network
- Collaborative of hospital-based investigators, through 18 tertiary academic medical centers in 16 states
- Plans to assess duration of protection by adapting prior methods used for influenza

EHR=Electronic Health Registries
Timeline for additional data

**Summer:** July-September
- **Manufacturer data**
  Safety and Immunogenicity of booster doses
- **Mix-and-match studies**
  Heterologous prime-boost

**Early Fall:** September-October
- **COVID-19 epi**
  Incidence of cases, hospitalizations, deaths
- **COVID-19 variants**
  Variant proportions, VE by variant
- **VE studies**
  VE by age, setting, time since vaccination
- **Breakthrough cases**
  Comparison of variants and clinical outcomes
Timeline for additional data

**Summer:**
July-September

- **Manufacturer data**
  Safety and Immunogenicity of booster doses

- **Manufacturer data**
  Phase I/II/III follow-up

- **Mix-and-match studies**
  Heterologous prime-boost

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**ACIP meetings**
Continue to provide updates. Vote could occur whenever data support updating policy
Booster doses of COVID-19 vaccines:
Work Group interpretation

- Work Group felt that recommendation for booster doses would only occur after:
  1. Evidence of declining protection against illness, such as declines in vaccine effectiveness, not only waning antibody response
  2. An escape variant (variant of concern substantially impacting vaccine protection)

- No data to support recommendations for booster doses currently, but will continue to monitor

- Global vaccine availability should be considered in discussions as well
Questions for ACIP

1. What does ACIP feel would be needed to move forward with booster recommendations?

2. Is the risk of disease enough to warrant a recommendation for boosters, before additional data may be available?
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- Nicole Reisman
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- Danielle Moulia
- Mary Chamberland
- Eddie Shanley
- Hannah Rosenblum
- Vaccine Task Force
- Epi Task Force
- Respiratory Viruses Branch
References
References for Slide 22 (VE in General Adult Population)

References for Slide 27 (VE in Older Adults)

- Cabezas et al., Effects of BNT162b2 mRNA Vaccination on COVID-19 Disease, Hospitalisation and Mortality in Nursing Homes and Healthcare Workers: A Prospective Cohort Study Including 28,594 Nursing Home Residents, 26,238 Nursing Home Staff, and 61,951 Healthcare Workers in Catalonia. Available at SSRN: https://ssrn.com/abstract=3815682 or http://dx.doi.org/10.2139/ssrn.3815682
References for Slides 32 & 33 (Immunocompromised Populations) [1]

References for Slides 32 & 33 (Immunocompromised Populations) [2]

- Nathalie 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 32 & 33 (Immunocompromised Populations) [3]

References for slide 23 (variant neutralization) [1]

References for slide 23 (variant neutralization) [2]

References for slide 23 (variant neutralization) [3]


References in bold are not included in the most recent update of the CDC Science Brief: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html
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