Welcome & Introductions
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Vice President, Clinical Affairs & Guidelines
IDSA

- 75th in a series of weekly calls, initiated by CDC as a forum for information sharing among frontline clinicians caring for patients with COVID-19

- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.

- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.
Vaccine Boosters
Update and Q&A

Understanding adaptive immunity and immune memory to SARS-CoV-2 and COVID-19 vaccines
Shane Crotty, PhD
Professor, Center for Infectious Disease and Vaccine Research
La Jolla Institute for Immunology

Perspectives from the Vaccines and Related Biological Products Advisory Committee (VRBPAC)
Hana M. El Sahly, MD
Professor of Molecular Virology and Microbiology, Baylor College of Medicine
Chair, VRBPAC, U.S. Food and Drug Administration

Archana Chatterjee, MD, PhD
Dean, Chicago Medical School and Vice President for Medical Affairs, Rosalind Franklin University
Member, VRBPAC, U.S. Food and Drug Administration

FDA Update
Peter Marks, MD, PhD
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Overview of CDC’s Interim Recommendation for use of a single Pfizer-BioNTech vaccine booster dose
Erin Tromble, MD
Chief Medical Officer, Vaccine Task Force, CDC COVID-19 Response
Centers for Disease Control and Prevention
Disclosures

• **Shane Crotty, PhD**: None related to this vaccine topic. Dr. Crotty has consulted for GSK, JP Morgan, Citi, Morgan Stanley, Avalia NZ, Roche.

• **Hana M. El Sahly, MD**: Received NIH funding as co-PI of P301, the Phase 3 study evaluating the efficacy of mRNA1273 (Moderna vaccine), NIH funding as co-Investigator of the Phase 3 study evaluating the efficacy of NVX-CoV2373 (Novavax vaccine)

• **Archana Chatterjee, MD, PhD**: Nothing to disclose

• **Peter Marks, MD, PhD**: Nothing to disclose

• **Erin Tromble, MD**: Nothing to disclose

• **Jennifer Layden, MD, PhD**: Nothing to disclose

• **Neela D. Goswami, MD, MPH**: Nothing to disclose
Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button
Understanding adaptive immunity and immune memory to SARS-CoV-2 and COVID-19 vaccines

Shane Crotty, PhD
Professor, Center for Infectious Disease and Vaccine Research
La Jolla Institute for Immunology
Understanding adaptive immunity and immune memory to SARS-CoV-2 and COVID-19 vaccines

Shane Crotty, Ph.D.
Professor, Center for Infectious Disease and Vaccine Research
What are mechanisms of protective immunity against COVID-19?

- The simplest option for any vaccine development is high level, long lasting, neutralizing antibodies.

- Various lines of evidence point to protective contributions of T cells against COVID-19

- It is reasonable to consider that hospitalization-level COVID-19 is prevented by any decent combination of antibody, memory B cells, CD4 T cells, and CD8 T cells.
Anatomy of adaptive immunity to SARS-CoV-2

It is all a race
A race between the virus and your immune system.
Vaccines change the race. You then have the headstart instead of the virus.

Sette and Crotty. Cell 2021
doi: 10.1016/j.cell.2021.01.007
The simplest option for any vaccine development is high level, long lasting, neutralizing antibodies.

- This virus is clearly susceptible to neutralizing antibodies.
- Antibodies can clearly protect against COVID-19 in humans and animal models when present before infection. (Monoclonal antibody studies)
- Antibodies are the only mechanism that can provide truly sterilizing immunity.
- Antibodies correlate with protection from symptomatic COVID-19 in multiple human vaccine studies.
- Antibodies are a correlate of CD4 T cells: Neutralizing antibodies almost always depend on CD4 T cells. Thus, antibodies are usually a surrogate marker of vaccine-specific CD4 T cells, at least T follicular helper (T\textsubscript{FH}) cells.

What are mechanisms of protective immunity against COVID-19?

- Memory B cell
- Antibodies
- CD4+ T cells
- CD8+ T cells
Memory B cells after SARS-CoV-2 infection

Memory B cells are present at substantial frequencies, and actually increase between 1 and 8 months post-infection.

Dan et al., Science. Jan 2021
doi: 10.1126/science.abf4063

Memory B cells after RNA vaccine

Memory B cells after RNA vaccine

Goel et al., pre-print. Aug 2021
doi: 10.1101/2021.08.23.457229
What are mechanisms of protective immunity against COVID-19?

- **Memory B cell**
- **Antibodies**
- **CD4⁺ T cells**
- **CD8⁺ T cells**

**Helpers**
- Critical for antibody responses
- Can have direct antiviral activities

**Killers**
- Important in many viral infections
Various lines of evidence point to protective contributions of T cells

- T cell responses correlate with better outcomes and lower viral loads in SARS-CoV-2 infection
- CD8 T cells provide control in monkeys
- Regeneron and Lilly outpatient and inpatient monoclonal antibody clinical trials. Modest impact on viral loads
- Agammaglobulinemic and B cell depleted individuals
  - moderately increased risk of hospitalization with COVID-19
  - COVID-19 in ocrelizumab-treated people with MS is predominantly mild
- 1-dose of Moderna or Pfizer vaccine provided substantial protection with low or absent neutralizing antibodies in most individuals
- Crossreactive T cells in human may be associated with partial protection
- T cell responses to vaccines in NHPs correlate with better outcomes and lower viral loads
Anatomy of adaptive immunity to SARS-CoV-2

Sette and Crotty. Cell 2021
doi: 10.1016/j.cell.2021.01.007
Low dose Moderna mRNA-1273 COVID-19 vaccine

Mateus et al. Science. Sept 2021
doi: 10.1126/science.abj9853
What are mechanisms of protective immunity against COVID-19?

It is reasonable to consider that hospitalization-level COVID-19 is prevented by any decent combination of antibody, memory B cells, CD4 T cells, and CD8 T cells.
Vaccine protection against SARS-CoV-2

Protection against Detectable Infection

Protection against Hospitalizations & Deaths

Major

Minor

Antibodies + CD4 + CD8

or

or

Memory B cell
Waning protection against Detectable Infection

No waning protection against Hospitalizations & Deaths

Kaiser study. Pre-print. Tartof et al. pre-print Aug 2021
Recent 6 months ago

Unvaccinated
- Asymptomatic
- Pauci-symptomatic
- Cold-like
- Flu-like
- Hospitalized
- Fatal
- ICU

Vaccinated
- Recent
  - No Infection

Vaccinated
- 6 months ago
  - No Infection
  - Asymptomatic
  - Pauci-symptomatic
  - Cold-like
  - Flu-like
  - Hospitalized
Limitations: A working model has been presented here of immunological factors that may contribute to protective immunity in humans, based on a preponderance of data, but these are not proven.
THE TEAM

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La Jolla Institute
Life Without Disease

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La Jolla
UCSD
Mt. Sinai
Perspectives from the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

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Dean, Chicago Medical School
Vice President for Medical Affairs
Rosalind Franklin University
Member, VRBPAC, U.S. Food and Drug Administration
Pfizer-BioNTech’s supplemental BLA for a third dose, or “booster” dose, of Comirnaty in individuals 16 years of age and older

Hana El Sahly, MD and Archana Chatterjee, MD PhD
COVID-19 Epidemiology and COVID-19 Vaccines
Dr. Sara Oliver (CDC)

• Trends in number of COVID-19 cases in the US: delta wave has peaked
• After a rapid rise, there is a decline in weekly of COVID-19 associated hospitalizations.
• As of Sep 14th: 82.5% of elderly population and 63.1% of those 12 years of age and older were fully vaccinated
• After an increase in daily number of new vaccinees in July, a decline began in Sep
• COVID-19 vaccines continue to maintain high protection against severe disease, hospitalization, and death
• Protection against infection lower in recent months: time since primary series versus Delta variant?
Summary of **VE estimates** since introduction of the Delta variant

Adults ≥60 years of age

- Vaccine effectiveness of Pfizer-BioNTech COVID-19 vaccine against symptomatic illness with Delta is similar among those aged ≥60 years compared with younger age groups

- Persistence of vaccine effectiveness against hospitalization remains high
“Real-world” effectiveness of vaccines

Dr. Jonathan Sterne

• Estimated effectiveness of vaccines that is biased, by an unknown amount

• Baseline confounding (presence of characteristics predicting both vaccination and outcome)

• Defining the comparison group: Very rapid rollout of vaccination, so unvaccinated people rapidly become vaccinated. Solution: split follow up time for each individual into unvaccinated and post-vaccination

• Time-varying confounding

• Unmeasured confounding

• Accounting for pandemic waves

• Characterising persistently unvaccinated individuals
“Real-world” effectiveness of vaccines
Dr. Jonathan Sterne

<table>
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<th>Study Location (reference)</th>
<th>Vaccine</th>
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<th>Upper limit of 95% CI</th>
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<td>96</td>
<td>88</td>
<td>99</td>
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</tbody>
</table>
Booster Effectiveness - data from Israel
Drs. S. Alroy-Preis and Dr. R. Milo

- Vaccinated vs Unvaccinated population Differences
- Brief Duration of follow up
- Severity Criteria Differences
- Epidemiologic Differences
• In another study: 306 participants received a 3rd dose 7 mo post dose 2

• Systemic Events by Maximum Severity within 7 Days of 3rd Dose Similar to Post-dose 2

• Local Reactions by Maximum Severity within 7 Days of 3rd Dose Similar to Post-dose 2
1. Do the safety and effectiveness data from clinical trial C4591001 support approval of a COMIRNATY booster dose administered at least 6 months after completion of the primary series for use in individuals 16 years of age and older?
VRBPAC Deliberations and Concerns

- Is there an unmet need? VE against outcomes of interest (Severe COVID) remains very high in the US.
- Unmet need remains **expanding vaccine coverage**: adults, adolescents and children
- Unclear incremental public health advantage of vaccinating the vaccinated
- Age groups in the Q to the committee not represented in the clinical trial
- Data presented from clinical trials on a very limited # of participants
- The BLA expansion to a booster rests heavily on immunogenicity data in the absence of an antibody threshold for protection
- What is the role of cellular immunity?
Voting Question to the Committee

- Do the safety and effectiveness data from clinical trial C4591001 support approval of a COMIRNATY booster dose administered at least 6 months after completion of the primary series for use in individuals 16 years of age and older?

Please vote Yes or No

16 NO votes vs 2 Yes votes
EUA CRITERIA

• Serious or Life-Threatening Disease or Condition
• Medical products that may be considered for an EUA are those that "may be effective" to prevent serious or life-threatening diseases or conditions
• Known and potential benefits of the product... outweigh the known and potential risks of the product
• No Alternatives
Amended Voting Question to the Committee

• Based on the totality of scientific evidence available, including the safety and effectiveness data from clinical trial C4591001, do the known and potential benefits outweigh the known and potential risks of a Pfizer-BioNTech COVID-19 vaccine booster dose administered at least six months after completion of the primary series for:

  • individuals 65 years of age and older; and

  • individuals at high risk of severe COVID-19.

Please vote Yes or No 18 Yes votes
Polling Question to the Committee

• Should healthcare workers or others at high risk for occupational exposure be included in the EUA?

Please vote Yes or No  

18 Yes votes
FDA Update

Vaccine Boosters and Q&A

Peter Marks, MD, PhD
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Waning immunity in Israel was observed across age groups

Rate of confirmed SARS-CoV-2 infections stratified by vaccination period and age group
Per 1000 persons, during July 11, 2021 and July 31, 2021

Goldberg et al., https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1

Vaccination times (time before study period)
- Jan, 16-31 (=6 months)
- Feb, 1-15 (=5.5 months)
- Feb, 16-28 (=5 months)
- Mar, 1-15 (=4.5 months)
- Mar, 16-31 (=4 months)
- Apr (=3 months)
- May (=2 months)
Waning immunity also observed for severe disease in 60+ group
Per 1000 persons, during July 11, 2021 and July 31, 2021

Goldberg et al.,
https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1
Waning immunity against severe disease may occur also in younger age groups.

Rates of severe COVID-19 stratified by vaccination period and age group per 1000 persons, July 11 – Aug 15, 2021

Few cases (insufficient for statistical analysis)
Booster campaign began in Israel on July 30th

Booster doses

- 60+
- 50-59
- 40-49
- 30-39
- 16-29

≈1M doses
≈500K + 500K doses
≈400K + 400K doses

>2.8 million booster doses to date
Large fraction of the older population received a third dose, leading to a substantial decrease in confirmed infections among people over 60y
Following the third dose, severe cases sharply decreased.
A Pfizer-BioNTech COVID-19 vaccine booster dose administered at least 6 months after completion of the primary series is authorized for use in:

- individuals 65 years of age and older,
- individuals 18 through 64 years of age at high risk of severe COVID-19, and
- individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19
Overview of CDC’s Interim Recommendation for use of a single Pfizer-BioNTech vaccine booster dose

Erin Tromble, MD
Chief Medical Officer, Vaccine Task Force,
CDC COVID-19 Response
Centers for Disease Control and Prevention
Overview of CDC’s Interim Recommendation for use of a single Pfizer-BioNTech vaccine booster dose

Erin Tromble, MD
Chief Medical Officer
Vaccine Task Force, CDC COVID-19 Response

September 25th, 2021
Review of latest data:

- Data from a small clinical trial show that a booster dose of Pfizer-BioNTech COVID-19 vaccine increased immune response in those who completed a primary series six months prior.
- Among adults 65 years and older, data show vaccines remain effective in preventing hospitalization and severe disease, but recent evidence suggests they are less effective in preventing infection or milder symptomatic illness due to waning over time and the Delta variant.
- Emerging evidence show that among healthcare and other frontline essential workers, vaccine effectiveness is waning against COVID-19 infections.
Groups at risk for severe COVID-19 or SAR-CoV-2 infection after primary series vaccination
Age-Based Group: people aged ≥ 65 years

- Increased risk of severe COVID-19 (including hospitalization and death) among this age group of fully vaccinated people compared to younger fully vaccinated people

- Waning of COVID-19 vaccine effectiveness against severe disease has been observed in people aged ≥65yrs
Risk-Based Group: Long Term Care Facility (LTCF) residents

- Residents of LTCFs, aged ≥18 years
- Likely increased risk of severe COVID-19 (including hospitalization and death) among fully vaccinated residents compared to fully vaccinated people living independently
- Some waning of COVID-19 vaccine protection against infection has been observed in LTCF residents
- Congregate living setting associated with increased risk of COVID-19
Risk-Based Group: underlying medical conditions

- Aged ≥18 years
- Fully vaccinated persons with underlying medical conditions may be at risk of severe COVID-19 if they become infected with SARS-CoV-2

Examples:

- Cancer
- Cerebrovascular disease
- Chronic kidney disease
- Chronic obstructive pulmonary disease
- Diabetes mellitus, type 1 and type 2
- Heart conditions
- Obesity (BMI ≥30 kg/m²)
- Pregnancy and recent pregnancy
- Smoking, current and former

Risk-Based Group: occupation or setting

- Aged $\geq 18$ years
- Fully vaccinated persons may be at increased risk of SARS-CoV-2 infection due to occupation or setting
- Absence from occupation due to SARS-CoV-2 infection may hinder societal functions

Interim Recommendations
People 65 years and older and residents in long-term care settings **should** receive a booster shot of Pfizer-BioNTech’s COVID-19 vaccine at least 6 months after their Pfizer-BioNTech primary series.
CDC Interim Recommendations for COVID-19 Pfizer-BioNTech Vaccine Booster Dose:

People aged 50 to 64 with certain underlying medical conditions should receive a booster shot of Pfizer-BioNTech’s COVID-19 vaccine at least 6 months after their Pfizer-BioNTech primary series.
CDC Interim Recommendations for COVID-19 Pfizer-BioNTech Vaccine Booster Dose:

People 18 to 49 who are at high risk for severe COVID-19 due to certain underlying medical conditions may receive a booster shot of Pfizer-BioNTech’s COVID-19 vaccine at least 6 months after their Pfizer-BioNTech primary series, based on their individual benefits and risks.
CDC Interim Recommendations for COVID-19 Pfizer-BioNTech Vaccine Booster Dose:

People aged 18-64 years who are at increased risk for COVID-19 exposure and transmission because of occupational or institutional setting may receive a booster shot of Pfizer-BioNTech’s COVID-19 vaccine at least 6 months after their Pfizer-BioNTech primary series, based on their individual benefits and risks.
Additional Considerations
**Booster dose - Administration**

- Pfizer-BioNTech COVID-Vaccine (BTN162b2), 0.3ml, intramuscular administration
- Timing: ≥6 months after completion of the primary series
  - Immunity wanes gradually over time, therefore a booster may be given at an interval greater than 6 months
- Co-administration: a Pfizer-BioNTech COVID-Vaccine booster dose may be given with other vaccines, without regard to timing. This includes simultaneous administration of COVID-19 and other vaccines on the same day.
Definition of ‘fully vaccinated’ unchanged

- For public health purposes, people who have completed a primary vaccine series (i.e. 2-dose mRNA vaccine series or a single dose of the Janssen vaccine) are considered fully vaccinated ≥2 weeks after completion of the primary series
- The above definition applies to all people including those who receive an additional dose as recommended for moderate to severely immunocompromised people and those who receive a booster dose
Thank you!
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.
Q&A/Discussion
An online community bringing together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.

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CDC-IDSA Partnership: Clinical Management Call Support

FOR WHOM?
- Clinicians who have questions about the clinical management of COVID-19

WHAT?
- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

HOW?
- Clinicians may call the main CDC information line at 800-CDC-INFO (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form
Continue the conversation on Twitter

@RealTimeCOVID19  #RealTimeCOVID19

We want to hear from you!
Please complete the post-call survey.

Next Call:
Saturday, Oct. 9th

A recording of this call will be posted at
www.idsociey.org/cliniciancalls
-- library of all past calls now available --

Contact Us:
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Deirdre Lewis (dlewis@idsociety.org)