Objectives

- Summarize efficacy for the currently authorized COVID-19 vaccines
- Describe rare adverse events with COVID-19 vaccines
- Review what is known about COVID-19 vaccines in people with HIV

Note: Vaccines discussed are not yet approved
Outline

• How well do the currently authorized vaccines work?
• Do vaccines prevent asymptomatic infection and transmission?
• What about the effect of variants on vaccines?
• What about rare side effects of the vaccines?
• What do we know about COVID vaccines in people with HIV?
• FAQ
BNT162b2 (Pfizer-BioNTech)

- mRNA encoding the spike protein
- Participants ≥ 16 yrs (N = 43,448)
- Two doses of BNT162b2 or placebo 21 days apart
- Vaccine efficacy: 95%
- Efficacy against severe infection: 100%
- No difference in efficacy by age, sex, race/ethnicity
BNT162b2 (*Pfizer-BioNTech*): Continued Efficacy Six Months Following Second Dose

- Efficacy against symptomatic COVID: 91.3%
  - 850 cases in placebo, 77 in vaccine group

- Efficacy against severe disease: 100%
  - 32 cases in placebo group, 0 in vaccine group

Pfizer Vaccine Authorized in Adolescents/Children

- 2229 adolescents 12-15 years old
- Vaccine efficacy: 100%
  - 18 cases (placebo), 0 cases (vaccine)
- Strong antibody responses
  - Geometric mean titer: 1239 vs 705 in those 16-25 years
- Studies in younger children initiated

https://www.fda.gov/media/144413/download
mRNA-1273 (Moderna)

- mRNA encoding spike protein
- Participants ≥ 18 yrs (N = 30,351)
- 2 doses mRNA-1273 or placebo 28 d apart
- Vaccine efficacy: 95%
- Efficacy against severe disease: 97%
- Vaccine induced antibodies persist for at least 6 months

Baden L et al NEJM, 2021; Doria-Rose N et al, NEJM, 2021
Ad26.COV2.S (Janssen)

  - Adults >18 years of age (N=39,321): single Ad26.COV2.S or placebo
  - Vaccine Efficacy (at least 28 days after administration):
    - Against mod/severe disease: 66%
    - Against severe/crit disease: 85%
    - Against hospitalization: 100%

Cumulative Incidence of COVID-19 with Onset at least 1 day after vaccination

Sadoff J et al, NEJM, April 21, 2021
Efficacy of Ad26.COV2.S (Janssen) Vaccine in South Africa

Severe/Critical COVID-19 in South Africa

- B.1.351: 94.5% of sequences
- Vaccine efficacy: 81.7% against severe/critical COVID-19
- 0 hospitalizations in vaccine group, 6 in placebo group
Do COVID-19 Vaccines Prevent Asymptomatic Infection and Transmission?
Real-World COVID-19 Vaccine Effectiveness

• Prospective cohort
  • Female (62%), aged 18-49 (72%), no chronic medical conditions (69%)

• Tested for SARS CoV-2 weekly

• Vaccine effectiveness
  • 90% for those fully vaccinated (including asymptomatic infections)

https://www.cdc.gov/mmwr/volumes/70/wr/mm7013e3.htm
Prevention of Asymptomatic Infection

• Moderna vaccine: 67% reduction
  • Among people who received 1\textsuperscript{st} dose, number of asymptomatic people who tested positive at their 2\textsuperscript{nd} dose appointment: 0.1% (vaccine) vs. 0.3% (placebo)

• Janssen vaccine: 66% reduction in asymptomatic seroconversion

• Mayo Clinic: 80% reduction
  • Retrospective cohort of individuals (n=48,333) having pre-procedural tests
  • Positive results: 1.4% (vaccinated), 3.2% (unvaccinated)

• Israel: 91.5% reduction

Sadoff J et al, NEJM, April 21, 2021; Haas E et al, Lancet 2021
Lower Viral Load in Infections Occurring 12 days or Longer after 1st dose of Vaccine

Retrospective analysis of PCR cycle threshold (Ct) values among post-vaccination positive tests in Israel (Dec 21, 2020 to Feb 11, 2021) (n=4938)

- Compared to matched unvaccinated controls, Ct differences of 2.8 to 4.5-fold in viral load in vaccinated individuals
- Lower viral load may predict less transmission

COVID Vaccine Breakthroughs Exceedingly Rare

- Breakthrough: + RNA or antigen test ≥14 days after completing vaccine series
- Dec 2020 to April 13, 2021: >75 million people in US fully vaccinated
- CDC has received reports of about 5800 vaccine breakthroughs (0.008%)
  - 1,695 (29%) were reported as asymptomatic
  - 396 (7%) hospitalized
    - 34% were reported as asymptomatic or hospitalized for reason not due to COVID
  - 74 (1%) died
    - 12% reported as asymptomatic or patient died due to a cause not related to COVID
- Sequencing of breakthrough infections is ongoing

https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html
Variants and Vaccines
SARS CoV-2 Variants

Variant of interest:
- Genetic markers associated with change to receptor binding; reduced antibody neutralization; reduced treatment efficacy; potential diagnostic impact; predicted increase in transmissibility or disease severity. B.1.526, P.2

Variant of concern (VOC):
- Evidence of increased transmissibility, more severe disease, significant reduction in antibody neutralization, reduced effectiveness of treatments or vaccines, or diagnostic detection failures. B.1.1.7, B.1.351, P.1, B.1.427, B.1.429.

Variant of high consequence:
- Clear evidence that prevention measures/medical countermeasures have significantly reduced effectiveness. Examples: none
Reduced Neutralization Activity of Vaccine Sera Relative to Wildtype/Dominant Strain, by Study (n=31)

No effect = 1

Studies by vaccine:
- mRNA
- AstraZeneca
- Novavax
B.1.617

- Sub-lineages: B.1.617.1, B.1.617.2, B.1.617.3
- B.1.617.2: declared variant of concern by Public Health England: “at least equivalent transmissibility to B.1.1.7 based on available data”
- B.1.617 declared variant of concern by WHO

<table>
<thead>
<tr>
<th>B.1.617.1</th>
<th>B.1.617.2</th>
<th>B.1.617.3</th>
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<tbody>
<tr>
<td>India</td>
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<tr>
<td>7-8</td>
<td>9-10</td>
<td>7</td>
</tr>
<tr>
<td>L452R</td>
<td>L452R</td>
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<tr>
<td>E484Q</td>
<td>T478K</td>
<td>E484Q</td>
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</table>

B.1.617: Limited Effect on Neutralization by Post-Vaccination Sera

- Selected preliminary non-peer reviewed pre-prints
  - Yadav PD et al: sera from 28 BBV152 (Covaxin) vaccinated individuals: neutralization of B.1.617 within 2-fold of prototype strain B1 (D614G)
  - Hoffmann M et al (pseudovirus assay): plasma from 15 BNT162b2 (Pfizer) vaccinees: 3-fold reduction compared to wild-type spike protein

Note: Preliminary, non-peer reviewed studies. Correlation between lab results and vaccine effectiveness not known.

## Vaccine Efficacy or Effectiveness (VE) Against Variants

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Study type</th>
<th>VE</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Post-EUA</td>
<td>• 90% against B.1.1.7 in Qatar*</td>
<td>100% for severe/critical disease</td>
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<tr>
<td></td>
<td></td>
<td>• 75% against B.1.351 in Qatar</td>
<td></td>
</tr>
<tr>
<td>Janssen</td>
<td>Pre-EUA</td>
<td>• 74% in U.S.</td>
<td>73-82% for severe/critical disease in each country</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 66% in Brazil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 52% in S. Africa</td>
<td></td>
</tr>
<tr>
<td>Novavax</td>
<td>Pre-EUA</td>
<td>• 96% against non-B.1.1.7 in UK</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 86% against B.1.1.7 in UK</td>
<td></td>
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<tr>
<td></td>
<td>Pre-EUA</td>
<td>• 51% against B.1.351 in S. Africa</td>
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<tr>
<td>AstraZeneca</td>
<td>Pre-EUA</td>
<td>• 84% against non-B.1.1.7 in UK</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• 75% against B.1.1.7 in UK</td>
<td></td>
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<tr>
<td></td>
<td>Pre-EUA</td>
<td>• 10% against B.1.351 in S. Africa</td>
<td></td>
</tr>
</tbody>
</table>

Emary et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): The Lancet. **mild/moderate illness**
Rare Adverse Events
Allergic Reactions to mRNA Vaccines

- Anaphylaxis rate: about 4-5 per million doses (90% within recommended 15 min observation period)
  - Similar anaphylaxis rate as with other vaccines; much lower than to penicillin (1-5/10,000)

- Cutaneous reactions: urticaria, erythema, induration
  - Delayed large local reactions (median onset 8 days after 1st dose)
  - Majority do not have recurrence after dose 2
  - Not a contraindication to 2nd dose

Thrombotic Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattor, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

FDA STATEMENT

Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine

April 13, 2021: 6 cases of cerebral venous sinus thrombosis (CVST) in combination with thrombocytopenia in women between ages of 18 and 48 years

Thrombosis with Thrombocytopenia Syndrome after Janssen vaccine

- N=15
- Median age 37 years (range 18–59)
- Median time to symptom onset 8 days (range 6–15 days)
- All cases occurred in females
- 12 cases: cerebral venous sinus thrombosis (CVST)
- Risk factors for thrombosis include oral contraceptive (n=2), obesity (n=7); none had personal or family history of coagulation disorder; none were pregnant or post-partum

Thrombosis with Thrombocytopenia Syndrome (TTS)

Diagnosis (must meet all four criteria):

- COVID vaccine (J & J/AstraZeneca) 4 to 30 days previously
- Venous or arterial thrombosis (often cerebral or abdominal)
- Thrombocytopenia
- Positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA

- Mechanism appears to be similar to autoimmune heparin-induced thrombocytopenia

https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia
MMWR, April 27, 2021
## Reporting rates of TTS after Janssen Vaccine: 2 per million

<table>
<thead>
<tr>
<th>Age Group</th>
<th>TTS Cases</th>
<th>Doses Admin</th>
<th>Reporting Rate</th>
<th>TTS Cases</th>
<th>Doses Admin</th>
<th>Reporting Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49 yo</td>
<td>13</td>
<td>1,866,294</td>
<td><strong>7 per million</strong></td>
<td>0</td>
<td>1,977,330</td>
<td><strong>0 per million</strong></td>
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<tr>
<td>50+ yo</td>
<td>2</td>
<td>2,125,239</td>
<td><strong>0.9 per million</strong></td>
<td>0</td>
<td>2,010,144</td>
<td><strong>0 per million</strong></td>
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Individual-level Estimated Benefits and Harms from Resuming Vaccinations for 1 month

<table>
<thead>
<tr>
<th>Benefits and harms from resuming vaccinations</th>
<th>No. per million vaccine doses administered</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Benefits</td>
<td>18-49 yr</td>
</tr>
<tr>
<td>Hospitalization prevented</td>
<td>297</td>
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<tr>
<td>ICU admissions prevented</td>
<td>56</td>
</tr>
<tr>
<td>Deaths prevented</td>
<td>6</td>
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<tr>
<td>Harms</td>
<td></td>
</tr>
<tr>
<td>TTS Cases Expected</td>
<td>7</td>
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</tbody>
</table>
CDC Recommendations for Janssen Vaccine

• Women aged <50 years can receive any FDA-authorized COVID-19 vaccine but should be aware of rare risk of TTS and availability of mRNA vaccines

• Persons with history of heparin-induced thrombocytopenia should receive mRNA vaccine (instead of Janssen) if ≤90 days since their illness resolved.

• Patients with previous venous thromboembolism or risk factors for VTE (inc. pregnancy, oral contraceptive use, inherited/acquired thrombophilia) may receive Janssen vaccine

• Aspirin or anticoagulation not recommended before vaccination unless a person is on these medicines for other reasons

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#janssen-vaccine-certain-populations
What do we know about COVID Vaccines in People with HIV?
People with HIV (PWH) in FDA authorized COVID-19 vaccine studies

- Participants with stable HIV:
  - Moderna: 176
  - Pfizer: 196
  - J & J: 1218

- No immunogenicity data reported yet
Immune Responses to AstraZeneca Vaccine in people with or without HIV are Comparable

- PWH (n=54)
  - On ART with viral suppression
  - Median CD4 694
- People without HIV (n=50)
- Antibody, T cell responses comparable between people with and without HIV
- Similar results in study of 104 PWH and 70 people without HIV in South Africa after AZ vaccine

SARS CoV-2 anti-spike protein IgG

Frater J et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection. SSRN pre-print, posted online 19 April 2021.
Madhi S et al. ChAdOx1 nCoV-19 (AZD1222) vaccine in people living with and without HIV. Research Square pre-print, posted online 17 March 2021.
COVID-19 Vaccine FAQs
How well do Immunosuppressed Patients Respond to COVID-19 Vaccines?

- Decreased anti-spark antibody (Ab) responses in solid organ transplant (SOT) recipients, immunosuppressed individuals:
  - 658 SOT recipients: 46% did not have antibody responses after mRNA vaccine
  - Other immunosuppressed patients: eg, heme malignancies, immunosuppressive meds: lower Ab responses (B cell depleting therapy, 36-fold; steroids, 10-fold)
- T cells/vaccine effectiveness studies needed
Interim Recommendations

• When feasible, vaccinate before transplantation, immunosuppression
• Vaccinate household members/caregivers and friends to reduce exposures
• Continue protective measures including masking and social distancing regardless of vaccination status: “Get vaccinated but behave as though you’re not” (Dr. Dorlan Kimbrough, a neurologist at Duke)

• CDC:
  • Antibody testing not recommended to assess for immunity following vaccination;
  • Revaccination not recommended after people regain immune competence;
  • Area of active investigation – stay tuned!

COVID-19 Vaccine: FAQ

• Should someone with previous COVID-19 receive the COVID-19 vaccine?
  • Yes, once their symptoms have resolved and they are no longer infectious
  • Reinfection unlikely for at least 3-6 months so vaccine can be delayed if desired
  • Although people with previous COVID-19 respond quickly to first dose of mRNA vaccine, still recommend completing both doses
  • In the blinded Moderna vaccine trial, those with prior COVID-19 did not have more adverse events after vaccination than those without previous COVID-19

COVID-19 Vaccine: FAQ

• When should person who received monoclonal Ab or convalescent plasma for COVID-19 treatment be vaccinated?
  • Wait >90 days to avoid potential for interference with vaccine-induced immune responses

• What is appropriate timing of COVID vaccines in relation to other vaccines?
  • COVID vaccines and other vaccines may now be administered without regard to timing.

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
COVID-19 Vaccine: FAQ

• What should be done for people who have had COVID vaccine not authorized by FDA?
  • If vaccine authorized by WHO (AstraZeneca, Sinopharm)
    • If vaccine series completed, no additional doses
    • If partially vaccinated, offer FDA-authorized vaccine series
  • If vaccine not authorized by WHO: offer FDA-authorized COVID vaccine

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
COVID-19 Vaccines Summary

• COVID-19 vaccines are highly effective in preventing symptomatic COVID-19
• Evidence that vaccines prevent asymptomatic infection, transmission
• SARS CoV-2 variants may affect different vaccines in different ways:
  • Thus far, vaccines prevent severe COVID-19/hospitalization/death
  • Must accelerate global vaccine delivery to forestall new variants, prevent humanitarian catastrophe
• Rare adverse events – including anaphylaxis and thrombosis with thrombocytopenia syndrome – occur but vaccine risks greatly outweighed by benefits
• Immune response data on COVID vaccine in PWH look promising; more data on vaccine effectiveness in immunosuppressed individuals needed