Policy questions for Evidence to Recommendations framework and plan for next steps

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Poxvirus and Rabies Branch

ACIP Orthopoxvirus WG
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Proposed policy question #1

Should persons who are at occupational risk for orthopoxviruses be offered JYNNEOS® as a vaccination option
**Policy question #1**

<table>
<thead>
<tr>
<th>Population</th>
<th>Persons who are at risk for occupational exposure to orthopoxviruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Vaccination with JYNNEOS®</td>
</tr>
<tr>
<td>Comparison</td>
<td>Vaccination with ACAM2000</td>
</tr>
<tr>
<td>Outcome</td>
<td>1) Prevention of disease</td>
</tr>
<tr>
<td></td>
<td>2) Severity of disease</td>
</tr>
<tr>
<td></td>
<td>3) Severe adverse events</td>
</tr>
<tr>
<td></td>
<td>4) Myo-/ peri-carditis</td>
</tr>
</tbody>
</table>

Policy question: Should JYNNEOS® be recommended for persons who are at risk for occupational exposure to orthopoxviruses?
Booster doses

- ACAM2000 licensed for smallpox
  - Revaccination recommendations for every 3 years in that population
- JYNNEOS licensed for smallpox and for monkeypox
  - No re-vaccination recommendations

- ACIP recommendations for ACAM2000 boosters
  - Made through extrapolation of data for Dryvax

Figures: Screenshots from ACAM2000 package inserts (accessed 2/20/2021)
Policy questions developed since October ACIP meeting

- Recommendations about booster doses
  - Persons who are at continued risk for occupational exposure to more virulent orthopoxviruses like smallpox or monkeypox
  - Persons who are at continued risk for occupational exposure to replication competent orthopoxviruses like vaccinia or cowpox

TABLE 1. Recommendations for revaccination of laboratory and health care personnel at risk for occupational exposure to orthopoxviruses

<table>
<thead>
<tr>
<th>Orthopoxvirus</th>
<th>Revaccination schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replication-competent vaccinia viruses and recombinant viruses developed from replication-competent vaccinia viruses</td>
<td>At least every 10 years</td>
</tr>
<tr>
<td>More virulent orthopoxviruses (e.g., variola, monkeypox)</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>Replication-deficient vaccinia viruses and recombinant viruses developed from replication-deficient vaccinia viruses*</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

* Laboratories that use both replication-competent and replication-deficient vaccinia virus strains but where working areas for these viruses cannot be clearly segregated should follow increased biosafety precautions because laboratory infections due to contamination have previously been documented. Sources: MacNeil A, Reynolds MG, Damon IK. Risks associated with vaccinia virus in the laboratory. Virology 2009;385:1–4; Chasewood LC, Wilson DE. CDC; National Institutes of Health. Biosafety in microbiological and biomedical laboratories. 5th ed. Washington, DC: US Department of Health and Human Services, Public Health Service, CDC, National Institutes of Health, 2009.
Proposed policy question #2

Should persons who are at continued risk for occupational exposure to more virulent orthopoxviruses such as smallpox or monkeypox receive a booster dose of JYNNEOS® two years after the primary JYNNEOS series?

- Population
  - CDC laboratorians who work with smallpox or monkeypox
  - Research laboratorians who work with monkeypox
  - Laboratory Response Network (LRN) laboratorians at state health departments who are designated to test for smallpox
Policy question #2

<table>
<thead>
<tr>
<th>Population</th>
<th>Persons who are at risk for occupational exposure to smallpox or monkeypox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Booster with JYNNEOS® 2 years after primary series</td>
</tr>
<tr>
<td>Comparison</td>
<td>No vaccine booster after JYNNEOS primary series</td>
</tr>
</tbody>
</table>
| Outcome             | 1) Prevention of disease  
                      | 2) Severity of disease  
                      | 3) Severe adverse events  
                      | 4) Myo-/ peri- carditis  |
Proposed policy question #3

Should persons who are at continued risk for occupational exposure to replication competent orthopoxviruses like vaccinia or cowpox receive a booster dose of JYNNEOS® after the primary JYNNEOS series?

- Population
  - Biomedical research laboratorians who work with vaccinia vectors
  - Any other persons who work exclusively with replication competent orthopoxviruses like vaccinia or cowpox
**Policy question #3**

<table>
<thead>
<tr>
<th>Population</th>
<th>Persons who are at risk for occupational exposure to replication competent orthopoxviruses like vaccinia or cowpox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Booster with JYNNEOS®</td>
</tr>
<tr>
<td>Comparison</td>
<td>No booster</td>
</tr>
</tbody>
</table>
| Outcome | 1) Prevention of disease  
2) Severity of disease  
3) Severe adverse events  
4) Myo-/ peri- carditis |
Proposed policy question #4

Should persons who are at continued risk for occupational exposure to orthopoxviruses, and who received an ACAM2000 primary vaccination, receive a booster dose of JYNNEOS® as an option to a booster dose of ACAM2000?
JYNNEOS® after ACAM2000

ACAM2000 primary vaccination

Time (years)
JYNNEOS® after ACAM2000

ACAM2000 primary vaccination

ACAM2000 boosters per ACIP recommendations

Time (years)
JYNNEOS® after ACAM2000

ACAM2000 primary vaccination

ACAM2000 boosters per ACIP recommendations

JYNNEOS® booster?

Time (years)
**Policy question #4**

<table>
<thead>
<tr>
<th><strong>Policy question:</strong> Should persons who are at continued risk for occupational exposure to orthopoxviruses, <em>and who received an ACAM2000 primary vaccination</em>, receive a booster dose of JYNNEOS® as an option to a booster dose of ACAM2000?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
</tr>
</tbody>
</table>
| **Outcome** | 1) Prevention of disease  
2) Severiity of disease  
3) Severe adverse events  
4) Myo-/ peri- carditis  
5) Adverse events due to interaction between JYNNEOS and ACAM2000 |
ACAM2000 After JYNNEOS®

JYNNEOS primary vaccination

ACAM2000 booster?

Time (years)
Progress on systematic review
**Anticipated Timeline**

- **February 2021**: Update ACIP about WG discussions and new policy questions
- **June 2021**: For all policy questions, present:
  - Evidence tables,
  - Evidence to Recommend frameworks
  - Draft recommendations
- **October 2021**: Present clinical guidance and commence ACIP Vote
Systematic Review: Search Terms

- Worked with CDC librarian to draft broad search terms: JYNNEOS, Imvamune, Imvanex, Modified Vaccinia Ankara
- Searched multiple databases and 740 articles identified

- Medline Articles (n=310)
- Embase Articles (n=214)
- Cochrane Articles (n=46)
- CINHAL Articles (n=0)
- NTIS Articles (n=2)
- Scopus Articles (n=21)
- Clinicaltrials.gov Articles (n=83)
- Global Index Medicus Articles (n=64)

Total Citations (n=740)

Hand Searched Articles (n=0)
Systematic Review– Progress

Records identified through database searching (n = 740)

Records after duplicates removed (n = 740)

Records screened (n = 740)

Full-text articles assessed for eligibility (n = 84)

Studies included in qualitative synthesis (n = 45)

Records excluded\(^a\) (n = 649)

Full-text articles excluded\(^b\) (n = 39)

\(^a\) Reasons for exclusion:
- 466 Recombinant MVA study
- 49 Review or policy article
- 22 Non-human subjects
- 18 Vaccine production
- 13 In vitro studies
- 9 No human trial data
- 6 DNA vaccine research
- 6 HIV vaccine research
- 4 Antiviral research
- 2 Cancer research
- 1 Treatment of vaccinia
- 53 Other

\(^b\) Reasons for exclusion:
- 15 No results posted (no data available)
- 6 MVA recombinant
- 6 No clinical data available (review article)
- 4 Erratum no data available
- 3 Animal model data
- 2 Wrong setting
- 2 Wrong study design
- 1 Opinion article (no clinical data available)
Systematic review challenges

- JYNNEOS is unlike ACAM2000 in that there is no vaccine take
- No standardized definition of “seroconversion”
- Follow-up data after JYNNEOS booster generally short, new vaccine
- “Vaccinia-experienced” subject groups in clinical trials may have had variable exposures to vaccinia
  - e.g. previous vaccination with Dryvax, or ACAM2000, or vaccina infection
- Deduplication of data: Clinical trial data may be reported in multiple records
  - E.g. Clinicaltrial.gov record, multiple publications including review publications
WG Considerations for EtR and Clinical Guidance
## Differences between ACIP and JYNNEOS®

<table>
<thead>
<tr>
<th></th>
<th>ACAM2000</th>
<th>JYNNEOS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine virus</strong></td>
<td>Replication-competent vaccinia virus</td>
<td>Replication-deficient MVA</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Administered via multiple puncture technique in a single dose</td>
<td>Administered subcutaneously in 2 doses 28 days apart</td>
</tr>
<tr>
<td><strong>Take</strong></td>
<td>Successful vaccination produces a major cutaneous reaction or “take”</td>
<td>No cutaneous reaction or “take” is produced</td>
</tr>
<tr>
<td><strong>Inadvertent inoculation and autoinoculation</strong></td>
<td>Vaccine site lesion presents a risk of inadvertent inoculation and autoinoculation</td>
<td>No risk of inadvertent inoculation and autoinoculation</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>Risk for serious adverse events secondary to uncontrolled viral replication (e.g., progressive vaccinia and eczema vaccinatum)</td>
<td>No risk for uncontrolled viral replication</td>
</tr>
<tr>
<td><strong>Cardiac adverse events</strong></td>
<td>Suspect cases of myopericarditis observed in up to 5.7 per 1,000 primary vaccinees</td>
<td>No serious cardiac adverse events considered causally related reported to date</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>Effectiveness was assessed by comparing the immunologic response to Dryvax</td>
<td>Effectiveness was assessed by comparing the immunologic response to ACAM2000</td>
</tr>
</tbody>
</table>
Some Considerations for Evidence to Recommend Framework

- Access to providers with training to administer ACAM2000

- No visual evidence of immunogenicity, e.g., “take”

- Two clinic appointments for JYNNEOS®

- Both vaccines would be available from Strategic National Stockpile (free of cost)
Acknowledgements

- Orthopoxvirus WG
- Florence Whitehill, CDC Poxvirus and Rabies Branch
- Doug Campos-Outcalt, GRADE consultant
- Rebecca Morgan, ACIP methodology consultant
- Jessica MacNeil, ACIP
Thank you!
Questions

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.