# Summary of Evidence to Recommendations Frameworks for Use of JYNNEOS®

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## Advisory Committee on Immunization Practices

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# Reminder: 5 PICO questions

- 1 and 2: **Primary vaccination** with JYNNEOS® in at-risk populations
- 3 and 4: **Booster** after primary JYNNEOS® series in person with continued* occupational risk
- 5: **Change from booster with ACAM2000 to booster with JYNNEOS®** for those who received ACAM2000 primary series

* Continued risk refers to persistent risk due to occupational work performed. Designated public health and healthcare worker response teams approved by public health authorities are not at "continued risk" because they are vaccinated for the purposes of preparedness

# Evidence to Recommendations (EtR) Frameworks 1 and 2: Primary vaccination with JYNNEOS®

# Problem:  Primary vaccination

- Orthopoxvirus infections cause morbidity and mortality

- Several populations are at occupational risk
  - Research laboratory personnel
  - Clinical laboratory personnel performing diagnostic testing for orthopoxviruses
  - Designated response team members
  - Select healthcare personnel who administer ACAM2000 or care for patients infected with replication competent orthopoxviruses

- ACAM2000 is currently recommended by the ACIP
  - Benefits to having more than one effective vaccine
  - Provides options

# PICO #1

| | Policy question: Should JYNNEOS® be recommended for research laboratory personnel*, clinical laboratory personnel performing diagnostic testing for orthopoxviruses†, and designated response team members§ at risk for occupational exposure to orthopoxviruses? |
|---|---|
| **Population** | Clinical laboratory personnel performing diagnostic testing for orthopoxviruses and designated response teams |
| **Intervention** | Vaccination with JYNNEOS® |
| **Comparison** | Vaccination with ACAM2000 |
| **Outcome** | a) Prevention of disease<br>b) Severity of disease<br>c) Serious adverse events<br>d) Myo-/ peri- carditis |

*Research laboratory personnel are those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola).

†Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect or confirmed patients with Orthopoxvirus infections, are not included in this recommendation as their risk for exposure is very low

§Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against Orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak)

# PICO #1

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|---|---|
| **Population** | Clinical laboratory personnel performing diagnostic testing for orthopoxviruses and designated response teams |
| **Intervention** | Vaccination with JYNNEOS® |
| **Comparison** | Vaccination with ACAM2000 |
| **Outcome** | a) Prevention of disease ← Assesses efficacy<br>b) Severity of disease<br>c) Serious adverse events ← Assesses safety<br>d) Myo-/ peri- carditis ← Assesses safety |

*Research laboratory personnel are those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola).

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§Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against Orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak)

# Domain: Benefits and harms

- How substantial are the desirable anticipated effects
- How substantial are the undesirable anticipated effects
- Do the desirable effects outweigh the undesirable effects?
- What is the overall certainty of the evidence for the outcomes?

# Benefits

| How substantial are the desirable anticipated effects? |
| --- |
| ☐ Minimal ☒ Small ☐ Moderate ☐ Large ☐ Don't know ☐ Varies |

- JYNNEOS®  is not a replicating virus so there is no potential spread to others
- FDA found JYNNEOS® to be non-inferior to ACAM2000 for immunogenicity
- Evidence table for outcome A, prevention of disease, suggests there may be a small benefit of JYNNEOS® compared to replicating orthopoxvirus vaccines

# Outcome A: Prevention of disease

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS OPXV vaccine primary series | ACAM2000 OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | | |
| **A. Prevention of disease (assessed with: geometric mean titer)** | | | | | | | | | | | | |
| **2** [1,2,3,4,5,6] | randomized trials | not serious | not serious | serious [a,b] | not serious | none | 213 | 199 | - | MD 1.62 titer units higher (1.32 higher to 1.99 higher) [c] | Level 2<br>MODERATE | CRITICAL |
| **A. Prevention of disease (assessed with: seroconversion rate)** | | | | | | | | | | | | |
| **2** [1,2,3,4,5,6] | randomized trials | not serious | not serious | serious [b,d] | serious [e] | none | 213/213 (100.0%) | 192/199 (96.5%) | RR 1.02 (0.99 to 1.05) | 19 more per 1,000 (from 10 fewer to 48 more) | Level 3<br>LOW | CRITICAL |

a. Geometric mean titer is an indirect measure of efficacy.

b. Frey study used Dryvax in the comparison group. For the immunogenicity outcomes we do not feel there would be a significant difference between the two live vaccines.

c. In order to calculate a mean difference and 95% CI, geometric mean data were transformed to arithmetic mean. The effect estimate was then transformed to geometric mean difference, which you see here.

d. Seroconversion rate is an indirect measure of efficacy.

e. 95% CI includes the potential for both meaningful benefit as well as meaningful harm.

# Harms

| How substantial are the undesirable anticipated effects? | | | | | |
|---|---|---|---|---|---|
| [X] Minimal | [ ] Small | [ ] Moderate | [ ] Large | [ ] Don't know | [ ] Varies |

- JYNNEOS® is a non-replicating virus; serious adverse events reported from ACAM2000 have been attributed to uncontrolled replication
- There are fewer contraindications to JYNNEOS ® compared to ACAM2000
- Evidence tables
  - Randomized controlled trials (RCTs) and pooled observational data indicate fewer adverse events with JYNNEOS
  - Too few subjects enrolled in the RCTs to adequately assess
  - Pooled observational data was reassuring and included many more subjects

# Summary of outcome C: Serious Adverse Events

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS® OPXV vaccine primary series | ACAM2000 OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | | |
| **C. Serious adverse events (SAE) (assessed with: vaccine associated SAE rate)** | | | | | | | | | | | | |
| **3** [1,2,3,4,5,6,7] | randomized trials | not serious | not serious | not serious | very serious [j] | none | 0/269 (0.0%) | 1/245 (0.4%) [k] | RR 0.33 (0.01 to 7.70) | 3 fewer per 1,000 (from 4 fewer to 27 more) | Level 3<br>LOW | CRITICAL |
| **C. Serious adverse events (SAE) (assessed with: vaccine related SAE rate)** | | | | | | | | | | | | |
| **15** [8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40] | observational studies | serious [l] | not serious | serious [m] | serious [n] | none | 4/5237 (0.1%) [o,p] | 3/873 (0.3%) [q,r] | RR 0.22 (0.05 to 0.99) | 3 fewer per 1,000 (from 3 fewer to 0 fewer) | Level 4<br>VERY LOW | CRITICAL |

# Outcome D: Myo-/pericarditis

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS OPXV vaccine primary series | ACAM2000 OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | | |
| **D. Myo-/pericarditis (assessed with: CDC definition of myocarditis event rate)** | | | | | | | | | | | | |
| **3** [1,2,3,4,5,6,7] | randomized trials | not serious | not serious | not serious | very serious [s] | none | 0/269 (0.0%) | 0/245 (0.0%) | not estimable | | Level 3 LOW | CRITICAL |
| **D. Myo-/pericarditis (assessed with: myo-/pericarditis event rate)** | | | | | | | | | | | | |
| **12** [14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39] | observational studies | serious [l] | not serious | serious [m] | not serious | none | 1/4938 (0.0%) [t] | 5/875 (0.6%) [u] | RR 0.040 (0.004 to 0.310) [v] | 5 fewer per 1,000 (from 6 fewer to 4 fewer) | Level 4 VERY LOW | CRITICAL |

See extra slides for footnotes

# Benefit/Harm ratio

| **Do the desirable effects outweigh the undesirable effects?** |
| --- |
| [X] Favors intervention [ ] Favors comparison [ ] Favors both [ ] Favors neither [ ] Unclear |

- Benefits small but harms are minimal
- The desirable effects therefore outweigh the undesirable effects
- The intervention is favored

# Benefits and Harms

| What is the overall certainty of this evidence for the critical outcomes? |
| --- |
| Effectiveness of the intervention |

☐ No studies found ☐ 4 (very low) ☐ 3 (low) ☒ 2 (moderate) ☐ 1 (high)

- Prevention of disease is the only critical outcome that assessed effectiveness of the intervention
- After considering GMT and SCR data together, we have moderate certainty that there is a small increase in disease prevention provided by JYNNEOS® compared to ACAM2000

# Outcome A: Prevention of disease

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS OPXV vaccine primary series | ACAM2000 OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | | |
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d. Seroconversion rate is an indirect measure of efficacy.

e. 95% CI includes the potential for both meaningful benefit as well as meaningful harm.

# Benefits and Harms

**What is the overall certainty of this evidence for the critical outcomes?**

Safety of the intervention

| | | | | |
|---|---|---|---|---|
| ☐ No studies found | ☐ 4 (very low) | ☒ 3 (low) | ☐ 2 (moderate) | ☐ 1 (high) |

- Evidence table indicated fewer serious adverse events and cases of myocarditis after JYNNEOS® primary series vs. ACAM2000 primary series

- However, there is low certainty in these estimates

# Summary of outcome C: Serious Adverse Events

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS® OPXV vaccine primary series | ACAM2000 OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | | |
| **C. Serious adverse events (SAE) (assessed with: vaccine associated SAE rate)** | | | | | | | | | | | | |
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| **C. Serious adverse events (SAE) (assessed with: vaccine related SAE rate)** | | | | | | | | | | | | |
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# Outcome D: Myo-/pericarditis

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
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See extra slides for footnotes

# Domain:  Values

- Does target population feel that the desirable effects are large relative to undesirable effects?
- Is there important uncertainty about or variability in how much people value the main outcomes?

# Values

| **Does the target population feel that the desirable effects are large relative to undesirable effects** | | | | | |
|---|---|---|---|---|---|
| ☐ No | ☐ Probably no | ☐ Uncertain | ☒ Probably yes | ☐ Yes | ☐ Varies |

- In 2015, CDC surveyed 275 healthcare personnel in the Democratic Republic of Congo (DRC) to evaluate the target populations values
  - 99% of respondents had reported having seen a monkeypox case
  - >75% were **not** interested in ACAM2000, many citing adverse events, potential for autoinoculation, and not wanting a vaccine scar
  - 98% **were** interested in JYNNEOS®
- The U.S. target population has made multiple requests for this vaccine

# Values

**Is there important uncertainty about or variability in how much people value the main outcomes**

| Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | No important uncertainty or variability | No known undesirable outcomes |
|---|---|---|---|---|
| ☐ | ☐ | ☒ | ☐ | ☐ |

- No research identified but stakeholders expected to value immunity; 2-dose JYNNEOS® found to be non-inferior to ACAM2000 for immunogenicity by FDA
- Will take longer (from first vaccination) before person given JYNNEOS® is considered fully vaccinated compared to person given ACAM2000; 2-doses of JYNNEOS® administered over 28 days but only one vaccination for ACAM2000

# Domain: Acceptability

| Is the intervention acceptable to key stakeholders | | | | | |
|---|---|---|---|---|---|
| ☐ No | ☐ Probably no | ☐ Uncertain | ☐ Probably yes | ☒ Yes | ☐ Varies |

- Ease of finding provider; no absences from work to travel to provider who can give the vaccine because any many more providers will be comfortable administering a subcutaneous injection
- Non-replicating virus so no risk of transmission to others, particularly to immunocompromised persons and those with eczema
- Adverse events expected to be more rare

# Domain: Resource Use

| Is the intervention a reasonable and efficient allocation of resources | | | | |
|---|---|---|---|---|
| ☐ No | ☐ Probably no | ☐ Uncertain | ☐ Probably yes | ☒ Yes |

- JYNNEOS®, like ACAM2000, would be provided from HHS' Strategic National Stockpile (SNS) free-of-cost
- Even in cases where employers do not cover the cost of clinic appointments, there may be similar clinic costs associated with JYNNEOS® and ACAM2000 vaccinations. This is because in some clinics, patients return for in-person clinic appointments on multiple days after ACAM2000 vaccination (e.g., days 3, 7 and sometimes many times afterwards) to perform dressing changes and assess the "take" site

# Domain: Equity

**What would be the impact on health equity?**

| | | | |
|---|---|---|---|
| ☐ Reduced | ☐ Probably Reduced | ☐ Probably no impact | ☐ Probably increased |
| ☒ Increased | ☐ Varies | ☐ Don't know | |

- For some vaccine recipients, cost of clinic appointments is absorbed by the employer. There would be no change in those costs
- There would be fewer costs and challenges associated with identifying a provider to provide the vaccine which occurs for ACAM2000; some persons needing ACAM2000 currently travel to a provider willing to administer the vaccine and in the process, incur personal expenses for hotel and mileage

# Domain: Feasibility

| Is the intervention feasible to implement | | | | | |
|---|---|---|---|---|---|
| ☐ No | ☐ Probably no | ☐ Uncertain | ☐ Probably yes | ☒ Yes | ☐ Varies |

- Potentially the same number (or possibly fewer) clinic visits with JYNNEOS®
- Less difficulty getting on a vaccination schedule because more providers willing to administer subcutaneous injection
- JYNNEOS®, once thawed/refrigerated, is good for 6 months; thawed ACAM2000 is good for 18 months
- Shipping conditions are the same for both JYNNEOS® and ACAM2000 and the 6 month window allows ample time for providers to schedule vaccinations

# Summary of EtR #1

| Domains | | Domains | | Domains | |
|---|---|---|---|---|---|
| Benefits: How substantial are the desired anticipated effects | Small | Values: Does the target population feel desirable effects are large | Yes | Impact on health equity | Increased |
| Harms: How substantial are undesirable anticipated effects? | Minimal | Is there important uncertainty about or variability in values? | Probably not | Feasible to implement? | Yes |
| Benefit / Harm: | Favors intervention | Acceptable to stakeholders? | Yes | Balance of consequences: Desirable consequences probably outweigh undesirable consequences in most settings | |
| Overall certainty of the evidence for the critical outcomes | Effectiveness: moderate<br><br>Safety: low | Reasonable and efficient allocation of resources? | Yes | | |

# Proposed recommendation 1

## The ACIP recommends JYNNEOS® as an alternative to ACAM2000 for research laboratory personnel*, clinical laboratory personnel performing diagnostic testing for orthopoxviruses†, and for designated response team members at risk for occupational exposure to orthopoxviruses§

*Research laboratory personnel are those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola).

†Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect or confirmed patients with Orthopoxvirus infections, are not included in this recommendation as their risk for exposure is very low

§Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against Orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak)

# PICO #2

| | **Policy question: Should JYNNEOS® be recommended for healthcare personnel who 1) administer ACAM2000 or 2) care for patients infected with replication competent orthopoxviruses*** |
|---|---|
| **Population** | Healthcare personnel who administer ACAM2000 or care for patients after vaccination with replication competent orthopoxviruses |
| **Intervention** | Vaccination with JYNNEOS® |
| **Comparison** | Vaccination with ACAM2000 |
| **Outcome** | a) Prevention of disease<br>b) Severity of disease<br>c) Serious adverse events<br>d) Myo-/ peri- carditis |

* For example, those caring for patients enrolled in clinical trials for replication-competent orthopoxvirus vaccines and those caring for persons with suspected or confirmed orthopoxvirus infections (e.g., clinicians and environmental services personnel)

# Benefits and harms: Identical GRADE table as for EtR #1

| Domains | | Explanation |
|---|---|---|
| Benefits: How substantial are the desired anticipated effects | Small | Evidence table for outcome A, prevention of disease, suggests there is a small benefit of JYNNEOS® compared to ACAM2000 for prevention of infection |
| Harms: How substantial are undesirable anticipated effects? | Minimal | Evidence tables for the RCTs could not adequately assess harms because of the small number of persons enrolled in these; however, the observational data is reassuring that there JYNNEOS® is either slightly better or similar to ACAM2000 for harms |
| Benefit / Harm: | Favors intervention | Small benefit and minimal harms favors the intervention, i.e., JYNNEOS® |
| Overall certainty of the evidence for the critical outcomes | Effectiveness: moderate<br><br>Safety: low | Same certainty levels as for EtR #1 because GRADE tables are the same |

# Values

| **Does the target population feel that the desirable effects are large relative to undesirable effects** | | | | | |
|---|---|---|---|---|---|
| ☐ No | ☐ Probably no | ☐ Uncertain | ☒ Probably yes | ☐ Yes | ☐ Varies |

- There is no research data to evaluate this but it is believed that some members of the population will be interested in vaccination or at least, would like the option of being vaccinated even if it is not indicated for the entire population
- In the past, when patients were admitted with adverse events from replicating orthopoxvirus vaccines, some healthcare workers were anxious
- Allowing for these persons to be vaccinated is consistent with the ACIP recommendations for ACAM2000

# Values

| Is there important uncertainty about or variability in how much people value the main outcomes | | | | |
|---|---|---|---|---|
| ☐ Important uncertainty or variability | ☒ Possibly important uncertainty or variability | ☐ Probably no important uncertainty or variability | ☐ No important uncertainty or variability | ☐ No known undesirable outcomes |

- Because of the low risk, many persons within this population may opt to not be vaccinated
- Others, however, may (for the factors previously discussed) opt to be vaccinated
- There is some variability in how much people value this recommendation, potentially indicating it could be recommended by shared clinical decision-making

# Acceptability, impact on health equity, and feasibility

| Domains | | Explanation |
|---|---|---|
| Acceptable to stakeholders? | Yes | Ease of finding provider, no absences from work to travel, no costs incurred by vaccinee |
| Reasonable and efficient allocation of resources? | Yes | • JYNNEOS, like ACAM2000, would be provided from HHS' SNS<br>• Cost of clinic appointments would presumably be covered by employer and supervisors would be supportive |
| Impact on health equity | Increased | Decreased costs and challenges for whose who would otherwise need to travel to receive an orthopoxvirus vaccine |
| Feasible to implement? | Yes | • No research identified but potentially the same number of in-person clinic visits (or possibly fewer) than for ACAM2000<br>• Easier to get on provider schedule for subcutaneous injection |

# Summary of EtR #2

| Domains | | Domains | | Domains | |
|---|---|---|---|---|---|
| Benefits: How substantial are the desired anticipated effects | Small | Values: Does the target population feel desirable effects are large | Probably yes | Impact on health equity | Increased |
| Harms: How substantial are undesirable anticipated effects? | Minimal | Is there important uncertainty about or variability in values? | Probably important uncertainty or variability | Feasible to impleme nt? | Yes |
| Benefit / Harm: | Favors intervention | Acceptable to stakeholders? | Yes | Balance of consequences: Desirable consequences probably outweigh undesirable consequences in most settings | |
| Overall certainty of the evidence for the critical outcomes | Effectiveness: moderate<br><br>Safety: low | Reasonable and efficient allocation of resources? | Yes | | |

# Proposed recommendation #2

**The ACIP recommends JYNNEOS®, based on shared clinical decision-making, as an alternative to ACAM2000 for healthcare personnel who administer ACAM2000 or care for patients infected with replication competent orthopoxviruses***

* For example, those caring for patients enrolled in clinical trials for replication-competent orthopoxvirus vaccines and those caring for persons with suspected or confirmed orthopoxvirus infections (e.g., clinicians and environmental services personnel)

# EtRs 3 and 4:  Booster with JYNNEOS® after JYNNEOS® primary series

# Problem: Booster

- Virulent orthopoxviruses (e.g., variola virus and monkeypox virus)
  - Increasing number of laboratories are working with monkeypox virus (e.g., primate laboratories
  - Work with these typically require personal protective equipment and other safeguards; but ensuring long-term immunogenicity through a booster, provides an additional level of protection if unintentional breaches occur
- Less virulent orthopoxviruses (e.g., vaccinia virus, cowpox virus, and Alaskapox virus)
  - Morbidity may be prevented, e.g., A mild case of vaccinia infection occurred in a laboratorian in the United States who had not received a booster >10 years after his primary ACAM2000 vaccination; these could potentially be prevented with the recommended booster
- Stakes higher to individual and public health, if virulent orthopoxvirus infection is acquired; for this reason, boosters historically given more frequently for those working with virulent orthopoxviruses

# Proposed recommendations for JYNNEOS® compared to those for ACAM

| | ACAM2000 | JYNNEOS® |
|---|---|---|
| **Population recommended** | Persons at occupational risk for orthopoxviruses (i.e., diagnostic laboratorians, healthcare response teams) | |
| **Populations offered** | Persons who administer ACAM2000 or care for patients with infection or after vaccination with replication competent virus | |
| **Populations for whom booster is recommended at specific intervals** | Persons who are at continued or sustained risk for orthopoxviruses [Note: Response teams are not at continued risk and will receive boosters only at the time of a smallpox/monkeypox event] | |
| **Frequency of boosters:** Those working with smallpox and monkeypox | Every 3 years (had previously been every year) | Every 2 years |
| **Frequency of boosters:** Those working with less virulent orthopoxviruses | At least every 10 years | |

# PICO #3

| | Policy question: Should persons who are at continued risk* for occupational exposure to more virulent orthopoxviruses such as variola virus or monkeypox virus receive a booster dose of JYNNEOS® every two years after the primary JYNNEOS series? |
|---|---|
| **Population** | Persons who are at risk for occupational exposure to variola virus or monkeypox virus |
| **Intervention** | Booster with JYNNEOS® every 2 years after primary series |
| **Comparison** | No vaccine booster after JYNNEOS primary series |
| **Outcome** | a) Prevention of disease ← Assesses efficacy<br>b) Severity of disease<br>c) Serious adverse events ← Assesses safety<br>d) Myo-/ peri- carditis ← Assesses safety |

* Continued risk refers to persistent risk due to occupational work performed. Designated public health and healthcare worker response teams approved by public health authorities are not at "continued risk" because they are vaccinated for the purposes of preparedness

# PICO #4

| | |
|---|---|
| | **Policy question: Should persons who are at continued risk for occupational exposure to less virulent replication-competent orthopoxviruses like vaccinia virus or cowpox virus receive a booster dose of JYNNEOS® at least every 10 years after the primary JYNNEOS series?** |
| **Population** | Persons who are at risk for occupational exposure to less virulent replication competent orthopoxviruses like vaccinia virus or cowpox virus |
| **Intervention** | Booster with JYNNEOS® at least every 10 years |
| **Comparison** | No vaccine booster after JYNNEOS primary series |
| **Outcome** | a) Prevention of disease<br>b) Severity of disease<br>c) Severe adverse events<br>d) Myo-/ peri- carditis |

# Summary of Benefits and Harms Domain for PICOs 3 & 4

| Benefits and harms domains | |
|---|---|
| Benefits: How substantial are the desired anticipated effects | Small: The evidence tables show a small increase in disease prevention after JYNNEOS booster to the JYNNEOS primary series; boosters may provide reassurance of continued protection from inadvertent exposures |
| Harms: How substantial are undesirable anticipated effects? | Minimal: No serious adverse events or myopericarditis observed among those who received JYNNEOS booster dose 2 years after the primary series |
| Benefit / Harm: | Favors intervention |
| Overall certainty of the evidence for the critical outcomes | Effectiveness: very low<br><br>Safety: very low |

# Policy Questions #3 and #4: Outcome A: Prevention

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS® OPXV vaccine primary series followed by a JYNNEOS® booster every 2 years | JYNNEOS® OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | | |
| **A. Prevention of disease (assessed with: Geometric mean titer)** | | | | | | | | | | | | |
| **1** [1,2] | randomized trials | serious [a] | not serious | serious [b,c] | very serious [d] | none | 26 | 20 | - | mean 3.56 titer units more (1.84 more to 6.89 more) | Level 4 VERY LOW | CRITICAL |
| **A. Prevention of disease (assessed with: seroconversion rate)** | | | | | | | | | | | | |
| **1** [1,2] | randomized trials | serious [a] | not serious | serious [b,c] | very serious [d,e] | none | 26/26 (100.0%) | 20/20 (100.0%) | RR 1.00 (0.94 to 1.06) | 0 fewer per 1,000 (from 60 fewer to 60 more) | Level 4 VERY LOW | CRITICAL |
| **A. Prevention (assessed with: seroconversion rate)** | | | | | | | | | | | | |
| **13** [3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,39] | observational studies | serious [f] | serious [g] | #3: serious [h] #4: very serious | serious [i] | none | 74/75 (98.7%) | 3326/3539 (94.0%) | RR 1.05 (1.02 to 1.08) | 47 more per 1,000 (from 19 more to 75 more) | Level 4 VERY LOW | CRITICAL |

# Policy Questions #3 and #4
# Outcome C: Serious adverse events

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS® OPXV vaccine primary series followed by a JYNNEOS® booster every 2 years | JYNNEOS® OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | | |
| **C. Serious adverse events (assessed with: vaccine related SAE rate)** | | | | | | | | | | | | |
| **1** [1,2] | randomized trials | not serious | not serious | serious [c] | very serious [j] | none | 0/31 (0.0%) | 0/27 (0.0%) | not estimable | | Level 4 VERY LOW | CRITICAL |
| **C. Serious adverse events (assessed with: vaccine related SAE rate)** | | | | | | | | | | | | |
| **17** [3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39] | observational studies | serious [f] | not serious | serious [h] | serious [k] | none | 0/75 (0.0%) | 3/5265 (0.1%) | not estimable | | Level 4 VERY LOW | CRITICAL |

See slide 47 for footnotes

# Policy Questions #3 and #4
# Outcome D: Myopericarditis

| Certainty assessment | | | | | | | № of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | JYNNEOS® OPXV vaccine primary series followed by a JYNNEOS® booster every 2 years | JYNNEOS® OPXV vaccine primary series | Relative (95% CI) | Absolute (95% CI) | **Certainty** | **Importance** |
| **D. Myo-/pericarditis (assessed with: myo-/pericarditis event rate)** | | | | | | | | | | | | |
| **1** [1,2] | randomized trials | serious [l] | not serious | serious [c] | very serious [j] | none | 0/31 (0.0%) | 0/27 (0.0%) | not estimable | | Level 4<br>VERY LOW | CRITICAL |

c. Available intervention data gives a booster at day 84. Indirect evidence for 2-year booster.

j. Study population is very small and would be poor at estimating the rate of rare outcomes.

l. High attrition rate and unclear information about randomization procedure.

# Summary of remaining domains

| Domains | | Explanation | Domains | | |
|---|---|---|---|---|---|
| Values: Does the target population feel desirable effects are large | Probably yes | Booster may be desirable to those who want to ensure long-term immunogenicity | Impact on health equity | Probably no impact | For many, employers absorb the cost |
| Is there important uncertainty about or variability in values? | Probably not | Stakeholders expected to value persistent immunity | Feasible to implement? | Probably yes | Need to get a booster dose. But many clinicians can provide subQ injection |
| Acceptable to stakeholders? | Yes | Easy to find caregiver to administer vaccine | Balance of consequences: Desirable consequences probably outweigh undesirable consequences in most settings | | |
| Reasonable and efficient allocation of resources? | Yes for #3 and Probably yes for #4 | For persons working with less virulent orthopoxviruses, costs of clinic visit likely still acceptable | | | |

# Proposed recommendation 3

**The ACIP recommends persons who are at continued risk* for occupational exposure to more virulent orthopoxviruses like variola virus or monkeypox virus receive booster doses of JYNNEOS every 2 years after the primary JYNNEOS series**

* Continued risk refers to persistent risk due to occupational work performed. Designated public health and healthcare worker response teams approved by public health authorities are not at “continued risk” because they are vaccinated for the purposes of preparedness

# Proposed recommendation #4

**The ACIP recommends persons who are at continued risk* for occupational exposure to replication competent orthopoxviruses like vaccinia or cowpox receive booster doses of JYNNEOS® after the primary JYNNEOS® series**

*Continued risk refers to persistent risk due to occupational work performed

# EtR #5: Change from ACAM2000 boosters to JYNNEOS® boosters for those who received the ACAM2000 primary series

# Problem

- Health authorities and JYNNEOS® sponsor are routinely being asked when this vaccine will be available
- Some laboratory directors have indicated that many of those who receive ACAM2000 boosters would like to change to JYNNEOS® if the ACIP recommendations explicitly allow for this
  - Ease of identifying a clinician who can administer it
  - No risk for infection spread to others
  - No dressings to manage
  - Fewer relative contraindications
- Unpublished data from the Democratic Republic of Congo indicates that JYNNEOS® is preferred to ACAM2000

# PICO #5

| | |
|---|---|
| | **Policy question:** 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? |
| **Population** | Persons who are at risk for occupational exposure to orthopoxviruses |
| **Intervention** | Booster with JYNNEOS® |
| **Comparison** | Booster with ACAM2000 |
| **Outcome** | a) Prevention of disease ← Assesses efficacy<br>b) Severity of disease<br>c) Severe adverse events ← Assesses safety<br>d) Myo-/ peri- carditis ← Assesses safety |

* Continued risk refers to persistent risk due to occupational work performed. Designated public health and healthcare worker response teams approved by public health authorities are not at "continued risk" because they are vaccinated for the purposes of preparedness

# Benefits and harms summary:

| Domains | | Explanation |
|---|---|---|
| Benefits: How substantial are the desired anticipated effects | Don't know | Only observational data was available for this outcome There was no available comparison data so it is unknown, from the Evidence table, how substantial the desirable anticipated effects are |
| Harms: How substantial are undesirable anticipated effects? | Minimal | No serious adverse events or myo- / pericarditis cases were identified |
| Benefit / Harm: | Unclear | We don't know if there are benefits to administering JYNNEOS® boosters compared to ACAM2000 boosters |
| Overall certainty of the evidence for the critical outcomes | Effectiveness: Very low<br><br>Safety: very low | Outcome A RCTs: Serious concerns about risk of bias, indirectness, and imprecision<br>Outcome C and D RCTs: Serious or very serious concerns about risk of bias and very serious concerns about imprecision |

# Policy Question #5
# Outcome A: Prevention

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | a booster dose of JYNNEOS | a booster dose of ACAM2000 | Relative (95% CI) | Absolute (95% CI) | | |
| **A. Prevention of disease (assessed with: seroconversion rate)** | | | | | | | | | | | | |
| **3** [1,2,3,4,5,6,7] | observational studies | serious [a] | not serious | serious [b] | serious [c] | none | No comparison data available. Intervention data from the systematic review: 272/333 (81.68 %) participants from 3 studies seroconverted 14 days after booster with MVA. | | | | Level 4<br>VERY LOW | CRITICAL |

a. Risk of bias due to lack of comparison data.

b. SCR is an indirect measure of prevention.

c. Small sample size, no comparison.

# Summary: Policy Question #5
# Outcome C: Serious Adverse Events

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | a booster dose of JYNNEOS | a booster dose of ACAM2000 | Relative (95% CI) | Absolute (95% CI) | | |
| **C. Serious adverse events (assessed with: vaccine related SAE event rate)** | | | | | | | | | | | | |
| **1** [8] | randomized trials | serious [f] | not serious | not serious | very serious [g] | none | 0/22 (0.0%) | 0/28 (0.0%) | not estimable | | Level 4 VERY LOW | CRITICAL |
| **C. Serious adverse events (assessed with: vaccine related SAE event rate)** | | | | | | | | | | | | |
| **3** [1,2,3,4,5,6,7] | observational studies [h] | not serious | not serious | serious [i] | very serious [g] | none | 0/349 (0.0%) [j] | 3/1371 (0.2%) [k] | RR 0.56 (0.03 to 10.85) | 1 fewer per 1,000 (from 2 fewer to 22 more) | Level 4 VERY LOW | CRITICAL |

f. In the protocol it is unclear how serious adverse events were assessed.

g. Sample size is small, too small to detect rare adverse events.

h. Observational data was included in the evidence profile for this outcome because the effect estimate for the randomized trials was not estimable.

i. Single-arm studies contribute data to the intervention, but no available data for the comparison from the systematic review. Downgraded for indirectness because historical data was used for comparison.

j. Intervention data was drawn from 3 observational studies included in the systematic review. 0/349 (0.00 %) participants from 3 studies developed vaccine related serious adverse events.

k. Comparison data was drawn from historical data. In a phase III clinical trial for ACAM2000 enrolling participants with previous smallpox vaccination 3/1371 (0.22%) developed vaccine related serious adverse events after ACAM2000 administration. No smallpox vaccine-specific serious adverse event was recorded.

# Policy Question #5
# Outcome D: Myo-/pericarditis

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | a booster dose of JYNNEOS | a booster dose of ACAM2000 | Relative (95% CI) | Absolute (95% CI) | | |
| **D. Myo-/pericarditis (assessed with: myo-/pericarditis event rate)** | | | | | | | | | | | | |
| **1** [8] | randomized trials | very serious [l] | not serious | not serious | very serious [m] | none | 0/22 (0.0%) | 0/28 (0.0%) | not estimable | | Level 4 VERY LOW | IMPORTANT |
| **D. Myo-/pericarditis (assessed with: myo-/pericarditis event rate)** | | | | | | | | | | | | |
| **3** [1,2,3,4,5,6,7] | observational studies | not serious | not serious | serious [i] | very serious [m] | none | 0/349 (0.0%) [n] | 0/1371 (0.0%) [o] | not estimable | | Level 4 VERY LOW | IMPORTANT |

i. Single-arm studies contribute data to the intervention, but no available data for the comparison from the systematic review. Downgraded for indirectness because historical data was used for comparison.

l. Assessment of myo-/pericarditis was initiated late in the study at the request of FDA. Very few subjects could be evaluated at that point. It was unclear how many subjects were evaluated.

m. Sample size is small, too small to detect rare events of myopericarditis after JYNNEOS,

n. Intervention data was drawn from 3 observational studies included in the systematic review. 0/349 (0.00 %) participants developed myo-/pericarditis.

o. Comparison data was drawn from historical data. In a phase III clinical trial for ACAM2000 enrolling participants with previous smallpox vaccination, 0/1371 (0.00%) developed myo-/pericarditis after ACAM2000 administration.

# Summary of remaining domains

| Domains | | Domains | |
|---|---|---|---|
| Values: Does the target population feel desirable effects are large | Yes: Target populations have made multiple requests for this vaccine Unpublished data from the DRC indicates strong interest in JYNNEOS® | Impact on health equity | Probably increased: No costs with travel to find provider |
| Is there important uncertainty about or variability in values? | Probably not: Anecdotally, we know that some laboratory directors anticipate many of their staff to change to JYNNEOS® boosters if the ACIP explicitly indicates it is acceptable | Feasible to implement? | Yes: Feasible for CDC Drug Services to ship and for product to be used within the 6 month time interval after that |
| Acceptable to stakeholders? | Yes: Ease of finding provider, no risk of transmission to others, no work absences due to travel to get vaccine, fewer contraindications | Balance of consequences: Desirable consequences probably outweigh undesirable consequences in most settings | |
| Reasonable and efficient allocation of resources? | Yes: Would be same as for ACAM2000 booster | | |

# Proposed recommendation #5

The ACIP recommends 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

* Continued risk refers to persistent risk due to occupational work performed. Designated public health and healthcare worker response teams approved by public health authorities are not at “continued risk” because they are vaccinated for the purposes of preparedness

# Proposed clinical guidance

- If recipients change from ACAM2000 to JYNNEOS®, recipients should
  - Receive subsequent boosters with JYNNEOS®
  - Adhere to the booster schedule for JYNNEOS®

- Changes from JYNNEOS® to ACAM2000 are expected to occur less frequently

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# Questions?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

# Footnotes for slide 11 and 17

j. The sample size is small and does not meet the optimal size to assess this outcome and suggest fragility of the estimate. Also, the 95% CI includes the potential for meaningful harm.

k. One vaccine-related SAE was experienced after Dryvax administration in the comparison group. The SAE was characterized by severe elevated liver enzymes 84 days after the first Dryvax vaccine. This was reported in the Parrino et al. 2007 study. This SAE was deemed "possibly related to vaccination." No other information is available.

l. There are some concerns with selection bias.

m. Indirect comparison of naively pooled single-arm studies compared to a historical control.

n. Fragility suspected based on few events.

o. Serious adverse events were defined according to the standard FDA definition including: death, life-threatening illness, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage, and other serious medical events. In addition, data was collected about any smallpox vaccine-specific adverse event: postvaccinial encephalitits, eczema vaccinatum, progressive vaccinia, and generalized vaccinia.

p. Vaccine related serious adverse events in the intervention group: 1) **Extra ocular muscle paresis** event in one person 8 days after second MVA-BN vaccination; deemed probably related by investigators. 2) **Sarcoidosis** event in one person during the 6 month follow up period; deemed related because causal relationship with vaccine could not be ruled out. 3) **Acute myocardial infarction** event in one person 117 days after the first MVA-BN dose. Deemed related to vaccination because no other reasonable etiology was found. 4) **Pneumonia and pleurisy** event in one person 1 day after second MVA-BN dose. Deemed "possibly but unlikely" to be associated with vaccination.

q. Vaccine related serious adverse events from historical data for the comparison. 1) One participant developed **severe somatization disorder** that was deemed definitely related to vaccination with ACAM2000. 2) One participant developed **abnormal ECG changes** that was deemed possibly related to vaccination. 3) One participant developed **increased cardiac enzymes** that was deemed probably related to vaccination. Reference: Rosenthal, S., Merchlinsky, M., & Chowdhury, M. (2007). VRBPAC Background Document: ACAM200 (Live vaccinia Virus Smallpox Vaccine). Trial number H-400-009.

r. Comparison data was drawn from historical data. In a phase III clinical trial for ACAM2000, 3/873 (0.34%) developed vaccine related serious adverse events after ACAM2000 administration.

# Footnotes for slide 12 and 18

l. There are some concerns for selection bias.

m. Indirect comparison of naively pooled single-arm studies compared to a historical control.

s. Number of participants is not large enough to capture myopericarditis events.

t. "One individual in Group 3 experienced symptoms indicating possible acute pericarditis according to protocol criteria (chest pain worsening when lying down). A thorough cardiac examination, including auscultation, ECG, Troponin I testing and echocardiography did not confirm the diagnosis. The echocardiography did not reveal any signs of pericardial effusion, pericardial rub, ECG changes suggestive of pericarditis, Troponin I increase or decreased exercise capacity. A detailed laboratory examination revealed a positive serology for Coxsackie B virus in temporal relation to the reported chest pain, suggesting a possible acute viral infection as the potential cause of the symptoms."

Overton ET, Lawrence SJ, Wagner E, et al. Immunogenicity and safety of three consecutive production lots of the non replicating smallpox vaccine MVA: A randomized, double blind, placebo controlled phase III trial. *PLoS ONE [Electronic Resource]. 2018;13(4):e0195897.*

u. No comparison data was available from the systematic review. Comparison is drawn from historical data, a study reporting myopericarditis rate after ACAM2000 administration. Source: ACAM2000 package insert, FDA.

v. Number of decimal places increased to more accurately present lower limit of confidence interval.

# Footnotes for slide 40

a. High attrition rate in per protocol population.

b. Immunogenicity as assessed with GMT is an indirect measure of efficacy.

c. Available intervention data gives a booster at day 84. Indirect evidence for 2-year booster.

d. There is one study with a small sample size.

e. 95% CI suggests there may be the potential for benefit or harm.

f. Many studies have serious concerns for risk of bias. Observational data has a higher risk for bias there were some concerns in a few studies for attrition and timing of outcome ascertainment.

g. Only one study contributes data to the intervention. Others contribute data to the comparison. Can't assess inconsistency for intervention.

h. This is the only place where the evidence profiles for policy questions #3 and #4 differ. For both #3 and #4: Downgrade for indirectness because the comparisons are between studies. PQ #4: Further downgrade for indirectness because 2-year booster data is indirect data for 10-year booster data.

i. Though the confidence interval is small, the number of participants in the intervention group is small and therefore may not provide a precise estimate.

# Footnotes for slide 42

c. Available intervention data gives a booster at day 84. Indirect evidence for 2-year booster.

f. Many studies have very serious concerns for risk of bias. Edit: Explain a bit more. More an issue with the fact they are obs. some concerns in a few studies for attrition and timing.

h. Downgrade for indirectness because the comparisons are between studies.

j. Study population is very small and would be poor at estimating the rate of rare outcomes.

k. Few people in the intervention group. Wide confidence interval.

# Footnotes for slide 61

a. High attrition rate in per protocol population.

b. Immunogenicity as assessed with GMT is an indirect measure of efficacy.

c. Available intervention data gives a booster at day 84. Indirect evidence for 2-year booster.

d. There is one study with a small sample size.

e. 95% CI suggests there may be the potential for benefit or harm.

f. Many studies have serious concerns for risk of bias. Observational data has a higher risk for bias there were some concerns in a few studies for attrition and timing of outcome ascertainment.

g. Only one study contributes data to the intervention. Others contribute data to the comparison. Can't assess inconsistency for intervention.

h. This is the only place where the evidence profiles for policy questions #3 and #4 differ. For both #3 and #4: Downgrade for indirectness because the comparisons are between studies. PQ #4: Further downgrade for indirectness because 2-year booster data is indirect data for 10-year booster data.

i. Though the confidence interval is small, the number of participants in the intervention group is small and therefore may not provide a precise estimate.

# Back-up slides: EtR1 and 2

# Policy Questions #1 and #2

## Summary of studies contributing data to PQ #1 and #2

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Randomized data** | | | | | | | | | |
| **NCT01913353 Pittman**<br><br>**Pittman 2019** | Phase 3, open-label, randomized clinical trial | U.S. military, stationed in Korea | Mean 23.5<br>SD 4.67 | 433 | 220 | 213 | MVA-BN ACAM2000 | Immunogenicity, Surrogate efficacy (ACAM2000 challenge), Adverse events | Bavarian Nordic, US Army Medical Research Institute of Infectious Diseases |
| **NCT00082446 Frey1**<br><br>**Frey 2007**<br>**Sano 2009** | Phase I, randomized, partially blinded, placebo controlled clinical trial | U.S. | Mean 24.8<br>SD 3.8 | 90 | 30 | 15 | MVA-BN Dryvax | Immunogenicity, Cell-mediated immunity, Surrogate efficacy (Dryvax challenge), Adverse events | NIAID |
| **VRC 201 Parrino1**<br><br>**Parrino 2007** | Phase I/Ib randomized, placebo controlled, double-blinded trial | U.S. | Mean and SD NR adults | 77 | 18 | 31 | MVA-BN Dryvax | Immunogenicity, safety, Dryvax challenge, cell mediated/humoral immune responses | NIAID |

# Policy Questions #1 and #2

## Summary of studies contributing data to PQ #1 and #2

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational data** | | | | | | | | | |
| **NCT00437021 Frey 2**<br><br>**Frey et al. 2013**<br>**Troy et al. 2015** | Phase II, Double-blind, Randomized, Dose-finding Study | USA | Mean 24.7<br>SD 4.2 | 208 | 67 | NA | MVA-BN | Safety and immunogenicity | NIAID |
| **NCT01668537 Greenburg4**<br><br>**2014** | Phase II, Randomized, Double-blind, Multicenter | USA | Mean 27.7<br>SD 6.28 | 651 | 327 | NA | MVA-BN | Safety and immunogenicity | Bavarian Nordic |
| **NCT00879762 Frey3**<br><br>**Troy et al. 2015**<br>**Frey et al. 2014** | Phase II, randomized, double blinded | USA | Mean 26.5<br>SD NR | 91 | 45 | NA | MVA-BN | Safety and immunogenicity | NIAID |
| **NCT00316602 Greenburg2**<br><br>**Greenberg 2015** | Phase II, non-randomized, open-label | USA and Mexico | Mean 27.7<br>SD 6.11 | 632 | 623 | NA | MVA-BN | Safety and immunogenicity in people with atopic dermatitis | NIAID and Bavarian Nordic |

# Policy Questions #1 and #2

## Summary of studies contributing data to PQ #1 and #2

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational data** | | | | | | | | | |
| **NCT00914732 Frey4**<br><br>**Troy et al. 2015 Frey et al. 2015** | Phase II, randomized, triple blinded | USA | Mean 27.2<br>SD 4.6 | 523 | 167 | NA | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |
| **NCT00316524 von Sonnenburg1**<br><br>**Zitzman-Roth et al. 2015** | Partially Randomized, Partially Double-blind, Placebo-controlled Phase II Non-inferiority Study | Germany | Mean 29.8<br>SD 9.07 | 745 | 183 | NA | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |
| **NCT00189904 Greenburg1**<br><br>**Greenberg et al. 2013** | Phase I/II, non-randomized, open-label | USA | Mean 37.9<br>SD NR | 151 | 60 | NA | MVA-BN | Safety and immunogenicity in HIV positive patients | NIAID |
| **NCT01144637 Overton2**<br><br>**Overton et al. 2018** | Randomized, Double-Blind, Placebo-Controlled Phase III Trial | USA | Mean 27.7<br>SD 6.3 | 4005 | 3003 | NA | MVA-BN | immunogenicity, safety, and tolerability | Bavarian Nordic and BARDA |

# Policy Questions #1 and #2

## Summary of studies contributing data to PQ #1 and #2

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational data** | | | | | | | | | |
| **NCT00189917 von Sonnenburg2**<br><br>**Darsow et al. 2016 Von Sonnenburg et al. 2014** | Open-label, Controlled Phase I Pilot Study | Germany | Mean NR<br>SD NR | 60 | 60 | NA | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |
| **NCT00133575 Seaman/Wilck**<br><br>**Seaman et al. 2010 Wilck et al. 2010** | Phase I/II, randomized, double blinded, placebo-controlled | USA | Mean 25.2, SD=3.7 | 72 | 10 | NA | ACAM3000* | Safety and immunogenicity and surrogate efficacy (Dryvax challenge) | NIAID |
| **NCT01827371 Frey5**<br><br>**Anderson et al. 2020 Jackson et al. 2017** | Phase II, Randomized, Open-Label | USA | Mean 27.4<br>SD 5.3 | 435 | 115 | NA | MVA-BN | Safety and immunogenicity | NIAID |

*ACAM3000, or Acambis MVA, is a modified vaccinia Ankara (MVA) vaccine.

# Policy Questions #1 and #2

## Summary of studies contributing data to PQ #1 and #2

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational data** | | | | | | | | | |
| **NCT02038881 Overton3**<br><br>**Overton et al. 2020** | Phase II, Randomized, Open-label | USA | Mean 35<br>SD 6.7 | 87 | 58 | NA | MVA-BN | Safety and immunogenicity in HIV+ patients | Bavarian Nordic |
| **NCT00316589 Overton1**<br><br>**Overton et al. 2015** | Phase II, Multicenter, Open-label, Controlled | USA | Mean 37.5<br>SD 8.0 | 479 | 439 | NA | MVA-BN | Safety and immunogenicity | HHS and NIAID |
| **NCT00189959 Pokorny**<br><br>**Von Kremplehuber et al. 2010** | Phase II, Double-blind, randomized, Dose-finding Study | Switzerland | Mean 23.3<br>SD 3.0 | 165 | 55 | NA | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |

# Policy Questions #1 and #2
# Outcome D: Myo-/pericarditis

"One [MVA vaccinated] individual…experienced **symptoms indicating possible acute pericarditis according to protocol criteria (chest pain worsening when lying down)**…A thorough cardiac examination, including auscultation, ECG, Troponin I testing and echocardiography did not confirm the diagnosis. The echocardiography did not reveal any signs of pericardial effusion, pericardial rub, ECG changes suggestive of pericarditis, Troponin I increase or decreased exercise capacity. A detailed laboratory examination revealed a positive serology for Coxsackie B virus in temporal relation to the reported chest pain, suggesting a possible acute viral infection as the potential cause of the symptoms."(Overton et al. 2018)

This event does not meet the CDC case definition for myopericarditis (see Casey et al. 2006), however Overton et al. describe this event as "possible acute pericarditis" according to the case definition outlined in the study protocol. We chose to include this event in the effect estimate calculation in order to provide a conservative estimate.

Casey C, Vellozzi C, Mootrey GT, et al. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. MMWR Recomm Rep. Feb 3 2006;55(Rr-1):1-16.

Overton ET, Lawrence SJ, Wagner E, et al. Immunogenicity and safety of three consecutive production lots of the non replicating smallpox vaccine MVA: A randomized, double blind, placebo controlled phase III trial. *PLoS ONE [Electronic Resource]. 2018;13(4):e0195897.*

# Back-up slides: EtR 3 and 4

# Policy Questions #3 and #4

## Summary of studies contributing data to PQ #3 and #4

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Randomized data** | | | | | | | | | |
| **NCT02038881 Overton3**<br><br>**Overton et al. 2020** | Phase II, Randomized, Open-label | United States | Mean 35<br>SD 6.7 | 87 | 31 | 27 | MVA-BN | Safety including cardiac outcomes, immunogenicity, CD4+ T cell counts in HIV+ patients | Bavarian Nordic |

# Policy Questions #3 and #4

## Summary of studies contributing data to PQ #3 and #4

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational Intervention data** | | | | | | | | | |
| **NCT00686582 Von Sonnenburg 3**<br><br>**Bavarian Nordic 2008** | Phase II, non-randomized, open-label | Germany | Mean 34.6<br>SD 10.2 | 304 | 92 | NA | MVA-BN | Safety and immunogenicity | Bavarian Nordic |

# Policy Questions #3 and #4

## Summary of studies contributing data to PQ #3 and #4

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational comparison data** | | | | | | | | | |
| **VRC 201 Parrino1**<br><br>**Parrino 2007** | Phase I/Ib randomized, placebo controlled, double-blinded trial | USA | Mean and SD NR, adults | 77 | NA | 19 | TBC-MVA | Immunogenicity, safety, Dryvax challenge, cell mediated/humoral immune responses | NIAID |
| **NCT00437021 Frey 2**<br><br>**Frey et al. 2013**<br>**Troy et al. 2015** | Phase II, Double-blind, Randomized, Dose-finding Study | USA | Mean 24.7 SD 4.2 | 208 | NA | 67 | MVA-BN | Safety and immunogenicity | NIAID |
| **NCT01668537 Greenburg4**<br><br>**2014** | Phase II, Randomized, Double-blind, Multicenter | USA | Mean 27.7 SD 6.28 | 651 | NA | 327 | MVA-BN | Safety and immunogenicity | Bavarian Nordic |
| **NCT00879762 Frey3**<br><br>**Troy et al. 2015**<br>**Frey et al. 2014** | Phase II, randomized, double blinded | USA | Mean 26.5 SD NR | 91 | NA | 45 | MVA-BN | Safety and immunogenicity | NIAID |

# Policy Questions #3 and #4

## Summary of studies contributing data to PQ #3 and #4

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational comparison data** | | | | | | | | | |
| **NCT00316602 Greenburg2**<br><br>**Greenberg 2015** | Phase II, non-randomized, open-label | USA and Mexico | Mean 27.7<br>SD 6.11 | 632 | NA | 632 | MVA-BN | Safety and immunogenicity in people with atopic dermatitis | NIAID and Bavarian Nordic |
| **NCT00914732 Frey4**<br><br>**Troy et al. 2015**<br>**Frey et al. 2015** | Phase II, randomized, triple blinded | USA | Mean 27.2<br>SD 4.6 | 523 | NA | 167 | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |
| **NCT00189904 Greenburg1**<br><br>**Greenberg et al. 2013** | Phase I/II, non-randomized, open-label | USA | Mean 37.9<br>SD NR | 151 | NA | 60 | MVA-BN | Safety and immunogenicity in HIV positive patients | NIAID |
| **NCT01144637 Overton2**<br><br>**Overton et al. 2018** | Randomized, Double-Blind, Placebo-Controlled Phase III Trial | USA | Mean 27.7<br>SD 6.3 | 4005 | NA | 4005 | MVA-BN | immunogenicity, safety, and tolerability | Bavarian Nordic and BARDA |

# Policy Questions #3 and #4

## Summary of studies contributing data to PQ #3 and #4

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational comparison data** | | | | | | | | | |
| **NCT00189917 von Sonnenburg2**<br><br>**Darsow et al. 2016 Von Sonnenburg et al. 2014** | Open-label, Controlled Phase I Pilot Study | Germany | Mean NR<br>SD NR | 60 | NA | 60 | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |
| **NCT00133575 Seaman/Wilck**<br><br>**Seaman et al. 2010 Wilck et al. 2010** | Phase I/II, randomized, double blinded, placebo-controlled | USA | Mean 25.2, SD=3.7 | 72 | NA | 10 | ACAM3000* | Safety and immunogenicity and surrogate efficacy (Dryvax challenge) | NIAID |
| **NCT01913353 Pittman**<br><br>**Pittman 2019** | Phase 3, open-label, randomized clinical trial | U.S. military, stationed in Korea | Mean 23.5<br>SD 4.67 | 433 | NA | 220 | MVA-BN | Immunogenicity,<br>Surrogate efficacy (ACAM2000 challenge),<br>Adverse events | Bavarian Nordic, US Army Medical Research Institute of Infectious Diseases |

*ACAM3000, or Acambis MVA, is a modified vaccinia Ankara (MVA) vaccine.

# Policy Question #3 and #4

## Summary of studies contributing data to PQ #3

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Observational comparison data** | | | | | | | | | |
| **NCT01827371 Frey5**<br><br>**Anderson et al. 2020**<br>**Jackson et al. 2017** | Phase II, Randomized, Open-Label | USA | Mean 27.4<br>SD 5.3 | 435 | NA | 115 | MVA-BN | Safety and immunogenicity | NIAID |
| **NCT00082446 Frey1**<br><br>**Frey 2007**<br>**Sano 2009** | Phase I, randomized, partially blinded, placebo controlled | USA | Mean 24.8<br>SD 3.8 | 90 | NA | 30 | MVA-BN | Immunogenicity, Cell-mediated immunity, Surrogate efficacy (Dryvax challenge),<br>Adverse events | NIAID |
| **NCT00316589 Overton1**<br><br>**Overton et al. 2015** | Phase II, Multicenter, Open-label, Controlled | USA | Mean 37.5<br>SD 8.0 | 579 | NA | 439 | MVA-BN | Safety and immunogenicity | HHS and NIAID |
| **NCT00189959 Pokorny**<br><br>**Von Kremplehuber et al. 2010** | Phase II, Double-blind, randomized, Dose-finding Study | Switzerland | Mean 23.3<br>SD 3.0 | 165 | NA | 55 | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |

# Back-up slides: EtR 5

# Policy Question #3 and #4

## Summary of studies contributing data to PQ #3

| Last name first author, Publication year | Study design | Country (or more detail, if needed) | Age (measure central tendency – mean/SD; median/IQR; range) | Total population | N Intervention | N comparison | Vaccines | Outcomes | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| **Randomized data** | | | | | | | | | |
| **VRC-203 Parrino 2**<br><br>**Parrino et al. 2007** | Phase I/Ib randomized, placebo controlled, double-blinded trial | USA | Mean 47.2<br>SD 8.6 | 75 | 22 | 30 | TBC-MVA Dryvax | Immunogenicity of TBC-MVA, safety, Dryvax challenge, cell mediated/humoral immune responses | NIAID |
| **Observational data for the intervention** | | | | | | | | | |
| **NCT00316524 von Sonnenburg1**<br><br>**Zitzman-Roth et al. 2015** | Partially Randomized, Partially Double-blind, Placebo-controlled Phase II Non-inferiority | Germany | Mean 29.8<br>SD 9.07 | 745 | 200 | NA | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |
| **NCT00189904 Greenburg1**<br><br>**Greenberg et al. 2013** | Phase I/II, non-randomized, open-label | USA | Mean 37.9<br>SD NR | 151 | 91 | NA | MVA-BN | Safety and immunogenicity | NIAID |
| **NCT00857493 Greenburg 3**<br><br>**Greenburg et al. 2016** | Randomized, Double-Blind, Placebo Controlled Phase II Trial | USA | Mean 35.8<br>SD NR | 120 | 58 | NA | MVA-BN | Safety and immunogenicity | NIAID and Bavarian Nordic |