Evidence to Recommendations Frameworks for Use of JYNNEOS®

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Reminder

- PICOs 1 and 2: Primary vaccination with JYNNEOS® in at-risk populations
- PICOs 3 and 4: Booster after primary JYNNEOS® series in person with continued risk
- PICO 5: Change from booster with ACAM2000 to booster with JYNNEOS®

Evidence to Recommendation Frameworks (EtRs) 1 and 2: Primary vaccination with JYNNEOS®

Problem: Primary vaccination

- Orthopoxvirus infections cause morbidity and mortality
- Several populations are at occupational risk
  - Research and clinical laboratory personnel performing diagnostic testing for orthopoxviruses
  - Designated response teams approved by public health authorities
  - Select healthcare personnel who administer ACAM2000 or care for patients after vaccination with replication competent orthopoxviruses (e.g., patients enrolled in clinical trials)
- ACAM2000 is currently recommended by the ACIP
  - There are benefits to having more than one recommended vaccine
  - Vaccination is effective; breakthrough infection despite adherence to ACIP recommendations has been reported only once*

*Hsu CH et al. Laboratory-acquired vaccinia virus infection in a recently immunized person--Massachusetts, 2013. MMWR Morb Mortal Wkly Rep. 2015 May 1;64(16):435-8.

PICO #1

	Policy question: Should JYNNEOS® be recommended for research and clinical laboratory personnel performing diagnostic testing for orthopoxviruses* and for designated response teams# 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 b) Severity of disease c) Serious adverse events d) Myo-/ peri- carditis

*Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect 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 (i.e., in the event of a smallpox or monkeypox outbreak)

PICO #1

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Intervention	Vaccination with JYNNEOS®
Comparison	Vaccination with ACAM2000
Outcome	a) Prevention of disease b) Severity of disease ← This outcome deemed "important" by WG; all other outcomes deemed "critical" c) Serious adverse events d) Myo-/ peri- carditis

*Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect 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 (i.e., in the event of a smallpox or monkeypox outbreak)

Policy question #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 b) Severity of disease ← This outcome deemed "important" by WG; all other listed here deemed "critical" c) Serious adverse events d) Myo-/ peri- carditis

*Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect 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 (i.e., in the event of a smallpox or monkeypox outbreak)

Benefits

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

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

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 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 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

- No expected harms because JYNNEOS® is a non-replicating virus; serious adverse events reported from ACAM2000 have been attributed to uncontrolled replication
- There are fewer relative contraindications to JYNNEOS ® compared to ACAM2000
- Evidence tables
  - RCTs: Suggested serious adverse events less likely with JYNNEOS® but too few subjects enrolled to assess for this rare event
  - Pooled observational data was reassuring and showed fewer serious adverse events and myo-/ pericarditis

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 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 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

Certainty of the evidence for the outcomes

Outcome	Importance	Included in profile	Certainty
Prevention of disease	Critical	Yes	Moderate
Severity of disease	Important	Yes	Very low
Serious adverse events	Critical	Yes	Low
Myo-/pericarditis	Critical	Yes	Low

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

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)

- Based on the assessments of the evidence, we estimate there are fewer serious adverse events and cases of myocarditis after JYNNEOS® primary series vs. ACAM2000 primary series
- However, we have low certainty in this estimate
  - RCT data was downgraded due to sample size being small and therefore not meeting the optimal size to assess these outcomes suggesting fragility of the estimate. Also, the 95% CI includes the potential for meaningful harm
  - Observational data contributed data about a larger sample size but was downgraded (from Level 3 to Level 4) because of concerns for selection bias and data was Indirect comparison of naively pooled single-arm studies compared to a historical control

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 workers 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
- 2-doses of JYNNEOS® administered over 28 days but only one vaccination for ACAM2000; it will therefore take longer (from first vaccination) before a person given JYNNEOS® will be considered fully vaccinated

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

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 to the patient
- 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

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

Feasibility

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

- No research identified but 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 12 hours; Thawed ACAM2000 is good for 18 months. CDC is evaluating distributing JYNNEOS at -20C and the product sponsor is assessing more lenient cold chain requirements

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:	
Overall certainty of the evidence for the critical outcomes	Effectiveness: moderate Safety: low	Reasonable and efficient allocation of resources?	Yes		

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 Safety: low	Reasonable and efficient allocation of resources?	Yes		

Proposed recommendation 1

The ACIP recommends JYNNEOS as an alternative to ACAM2000 for research and clinical laboratory personnel performing diagnostic testing for Orthopoxviruses* and for designated response teams# at risk for occupational exposure to Orthopoxviruses

*Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect 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 (i.e., in the event of a smallpox or monkeypox outbreak)

PICO #2

	Policy question: Should JYNNEOS® be recommended, for healthcare personnel who administer ACAM2000 or care for patients after vaccination 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 b) Severity of disease c) Serious adverse events d) Myo-/ peri- carditis

*For example, patients enrolled in clinical trials

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 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, 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 • 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 • 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 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 vaccinated with replication competent orthopoxviruses*

* For example, patients enrolled in clinical trials

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® **2 years** after primary series
Comparison	No vaccine booster after JYNNEOS primary series
Outcome	a) Prevention of disease b) Severity of disease c) Serious adverse events d) Myo-/ peri- carditis

Benefits

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

- We estimate, from the Evidence Tables, that there is a small increase in disease prevention after JYNNEOS® booster to the JYNNEOS® primary series
- Boosters at recommended time intervals may provide reassurance of continued protection from inadvertent exposures because smallpox and monkeypox are highly virulent

Summary of 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]	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

Harms

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

- There were no serious adverse events or myocarditis cases observed among those persons who received JYNNEOS® booster dose 2 years after JYNNEOS primary series
- The adverse events are expected to be minimal because no harmful events were observed

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 next slide for footnotes

Outcome D: Myopericarditis

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)		
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 VERY LOW	IMPORTANT

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.

Benefit/Harm ratio

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

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

Certainty of the evidence for the outcomes

Outcome	Importance	Included in profile	Certainty
Prevention of disease	Critical	Yes	Very low
Severity of disease	Important	Yes	Data not available
Serious adverse events	Critical	Yes	Very low
Myo-/pericarditis	Critical	Yes	Very low

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)

- RCT data was downgraded to very low certainty due to concerns for risk of bias, indirectness and imprecision
- Observational data was downgraded to very low, for risk of bias because it was observational data, for inconsistency because there was only one study with intervention data, and imprecision due to the small sample size for the intervention.

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)

- RCT data for serious adverse events and myo-/pericarditis were downgraded to very low for multiple reasons including indirectness for the 2-year time point and imprecision because the study population was too small to identify rare events like these
- Observational data for the 2-year time point existed to assess serious adverse events but the certainty level was downgraded from low certainty to very low certainty because of risk of bias, and indirectness, and imprecision

Target Population Sentiments

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.
- However, a booster dose is expected to be interpreted as having large desirable effects relative to undesirable effects.
- The desirable effect is “protection” from inadvertently acquiring virulent pathogens and are no undesirable effects

Target Population Sentiments

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

- Stakeholders (vaccinee and employers) are expected to value persistent immunity
- Employers of persons who work with smallpox currently mandate booster doses and diligently enforce compliance

Acceptability

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

- There is data (albeit limited) to indicate boostability 2 years after the primary series
- This is 1 year sooner than the booster frequency for ACAM2000 but is expected to be acceptable to stakeholders; ACAM2000 booster doses were initially annually and as more data became available, changed
- Clinicians are more willing to administer subcutaneous injection; identifying a provider will not be difficult

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' SNS free of cost
- For many recipients, employers absorb the clinic costs (e.g., occupational health). For some, there may be costs associated with clinic appointments for booster doses; these are expected to be reasonable
- Stakeholders are accustomed to booster doses being needed for ACAM2000 and particularly because many more clinicians will be willing to administer the JYNNEOS ® subcutaneous injection, finding clinic time will not be a burden

Equity

What would be the impact on health equity?			
☐ Reduced	☐ Probably Reduced	☒ Probably no impact	☐ Probably increased
☐ Increased	☐ Varies	☐ Don't know	

- Many employers will pay the cost of the clinic appointment
- Some may not but because JYNNEOS® is more accessible, costs would not involve hotel and travel costs
- No other costs are expected for the vaccine because it is provided by the SNS at no cost

Feasibility

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

- No research identified
- It may take some effort to plan for booster doses but since nearly every provider will be willing to administer a subcutaneous vaccine, scheduling can be with a wide variety of providers which likely makes it feasible
- JYNNEOS®, once thawed/refrigerated, is good for 12 hours; Thawed ACAM2000 is good for 18 months. CDC is evaluating distributing JYNNEOS at -20C and the product sponsor is assessing more lenient cold chain requirements

Summary

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	Probably no impact
Harms: How substantial are undesirable anticipated effects?	Minimal	Is there important uncertainty about or variability in values?	Probably not	Feasible to implement?	Probably yes
Benefit / Harm:	Favors intervention	Acceptable to stakeholders?	Yes	Balance of consequences:	
Overall certainty of the evidence for the critical outcomes	Effectiveness: very low Safety: very low	Reasonable and efficient allocation of resources?	Probably yes		

Summary

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	Probably no impact
Harms: How substantial are undesirable anticipated effects?	Minimal	Is there important uncertainty about or variability in values?	Probably not	Feasible to implement?	Probably 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: very low Safety: very low	Reasonable and efficient allocation of resources?	Yes		

Proposed recommendation 3

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

*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 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 #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 b) Severity of disease c) Severe adverse events d) Myo-/ peri- carditis

Benefits and harms:

Domains		Explanation
Benefits: How substantial are the desired anticipated effects	Small	Same Evidence table as for EtR#3
Harms: How substantial are undesirable anticipated effects?	Minimal	Same Evidence table as for EtR#3
Benefit / Harm:	Favors the intervention	Benefits are small but harms are minimal
Overall certainty of the evidence for the critical outcomes	Effectiveness: Very low Safety: very low	The Certainty levels are the same as for EtR#3; except that for observational data, indirectness was deemed “very serious” (instead of “serious”) because there was no data about booster at 10 years

Summary of 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]	#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

Summary

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			
Reasonable and efficient allocation of resources?	Probably yes	Costs of clinic visit likely acceptable even though this population works with less virulent pathogens			

Summary

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?	Probably yes	Costs of clinic visit likely acceptable even though this population works with less virulent pathogens			

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

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 b) Severity of disease c) Severe adverse events d) Myo-/ peri- carditis

Benefits

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

- 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

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 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.

Harms

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

- No serious adverse events or myo- / pericarditis cases were identified
- We estimate that there are fewer serious adverse events after JYNNEOS booster vs. ACAM2000 booster in people previously vaccinated with ACAM2000
- The effect was not estimable for myo-/ pericarditis but no cases were identified in either of the arms

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.

Benefit/Harm ratio

Do the desirable effects outweigh the undesirable effects?
Favors intervention ☐ Favors comparison ☐ Favors both ☐ Favors neither ☒ Unclear

- We don’t know if there are benefits to administering JYNNEOS® boosters compared to ACAM2000 boosters
- However, there are no identified harms and there is no reason to suspect that there would be no benefit from a JYNNEOS® booster

Certainty of the evidence for the outcomes

Outcome	Importance	Included in profile	Certainty
Prevention of disease	Critical	Yes	Very low
Severity of disease	Important	Yes	Data not available
Serious adverse events	Critical	Yes	Very low
Myo-/pericarditis	Critical	Yes	Very low

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)

- Only observational data was available to assess this outcome
- This data was downgraded from “low” to “very low”
  - Risk of bias due to lack of comparison data,
  - Indirectness because seroconversion rate is an indirect measure of prevention
  - Imprecision because sample size was small and without a comparison

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)

We have very low certainty in the estimate because of risk of bias, imprecision, and indirectness

Target Population Sentiments

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

- Target populations have made multiple requests for this vaccine
- Unpublished data from the DRC indicates strong interest in JYNNEOS®

Target Population Sentiments

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
- However, 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

Acceptability

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

- Ease of finding provider to administer the vaccine
- No risk of transmission to others
- No absences from work or self-costs associated with getting the booster
- Fewer relative contraindications

Resource Use

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

- Provided by SNS free of cost to patient
- If employer does not absorb clinic costs, these may be absorbed by the vaccinee; however, about the same number of visits may be needed after ACAM2000 booster doses

Equity

What would be the impact on health equity?

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

- For those whose employers do not absorb clinic visits, equity will probably still be increased
  - No costs associated with traveling to a provider who is willing to administer ACAM2000 using a bifurcated needle
  - Increased access to the vaccine because more providers can provide it

Feasibility

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

- We estimate that the same number of clinic visits would be needed and that more providers would be able to provide the JYNNEOS® vaccine booster than ACAM2000
- JYNNEOS®, once thawed/refrigerated, is good for 12 hours; Thawed ACAM2000 is good for 18 months. CDC is evaluating distributing JYNNEOS at -20C and the product sponsor is assessing more lenient cold chain requirements

Summary

Domains		Domains		Domains	
Benefits: How substantial are the desired anticipated effects	Don't know	Values: Does the target population feel desirable effects are large	Yes	Impact on health equity	Probably 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:	Unclear	Acceptable to stakeholders?	Yes	Balance of consequences:	
Overall certainty of the evidence for the critical outcomes	Effectiveness: very low Safety: low	Reasonable and efficient allocation of resources?	Yes		

Summary

Domains		Domains		Domains	
Benefits: How substantial are the desired anticipated effects	Don't know	Values: Does the target population feel desirable effects are large	Yes	Impact on health equity	Probably 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:	Unclear	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: very low Safety: low	Reasonable and efficient allocation of resources?	Yes		

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?

*Public health and healthcare worker response teams approved by public health authorities for the purposes of preparedness are not considered to be at “continued risk”

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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

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

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 38

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 40

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 58

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.