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

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Proposed policy question #1

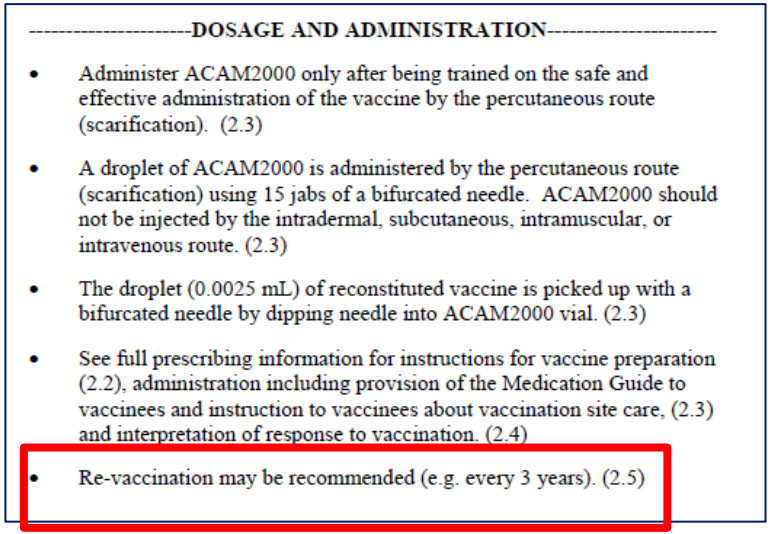
Should persons who are at occupational risk for orthopoxviruses be offered JYNNEOS® as a vaccination option

Policy question #1

	Policy question: Should JYNNEOS® be recommended for persons who are at risk for occupational exposure to orthopoxviruses?
Population	Persons who are at risk for occupational exposure to orthopoxviruses
Intervention	Vaccination with JYNNEOS®
Comparison	Vaccination with ACAM2000
Outcome	1) Prevention of disease 2) Severity of disease 3) Severe adverse events 4) Myo-/ peri- carditis

Booster doses

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

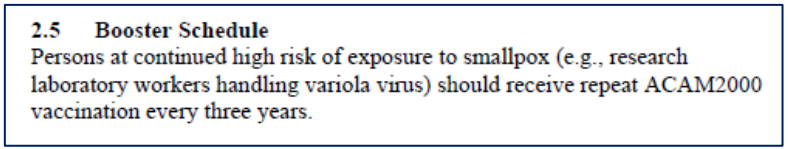


----------DOSAGE AND ADMINISTRATION----------

- Administer ACAM2000 only after being trained on the safe and effective administration of the vaccine by the percutaneous route (scarification). (2.3)
- A droplet of ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a bifurcated needle. ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route. (2.3)
- The droplet (0.0025 mL) of reconstituted vaccine is picked up with a bifurcated needle by dipping needle into ACAM2000 vial. (2.3)
- See full prescribing information for instructions for vaccine preparation (2.2), administration including provision of the Medication Guide to vaccinees and instruction to vaccinees about vaccination site care, (2.3) and interpretation of response to vaccination. (2.4)
- Re-vaccination may be recommended (e.g. every 3 years). (2.5)

Figures: Screenshots from ACAM2000 package inserts (accessed 2/20/2021)

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



2.5 Booster Schedule

Persons at continued high risk of exposure to smallpox (e.g., research laboratory workers handling variola virus) should receive repeat ACAM2000 vaccination every three years.

Policy questions developed since October ACIP meeting

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

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

Return

Orthopoxvirus	Revaccination schedule
Replication-competent vaccinia viruses and recombinant viruses developed from replication-competent vaccinia viruse	At least every 10 years
More virulent orthopoxviruses (e.g., variola, monkeypox)	Every 3 years
Replication-deficient vaccinia viruses and recombinant viruses developed from replication-deficient vaccinia viruses*	Not recommended

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

Table from Petersen et al, Use of Vaccinia Virus Smallpox Vaccine in Laboratory and Health Care Personnel at Risk for Occupational Exposure to Orthopoxviruses– Recommendations of the ACIP, 2015

Proposed policy question #2

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

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

Policy question #2

	Policy question: Should persons who are at continued risk for occupational exposure to more virulent orthopoxviruses such as smallpox or monkeypox receive a booster dose of JYNNEOS® two years after the primary JYNNEOS series?
Population	Persons who are at risk for occupational exposure to smallpox or monkeypox
Intervention	Booster with JYNNEOS® 2 years after primary series
Comparison	No vaccine booster after JYNNEOS primary series
Outcome	1) Prevention of disease 2) Severity of disease 3) Severe adverse events 4) Myo-/ peri- carditis

Proposed policy question #3

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

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

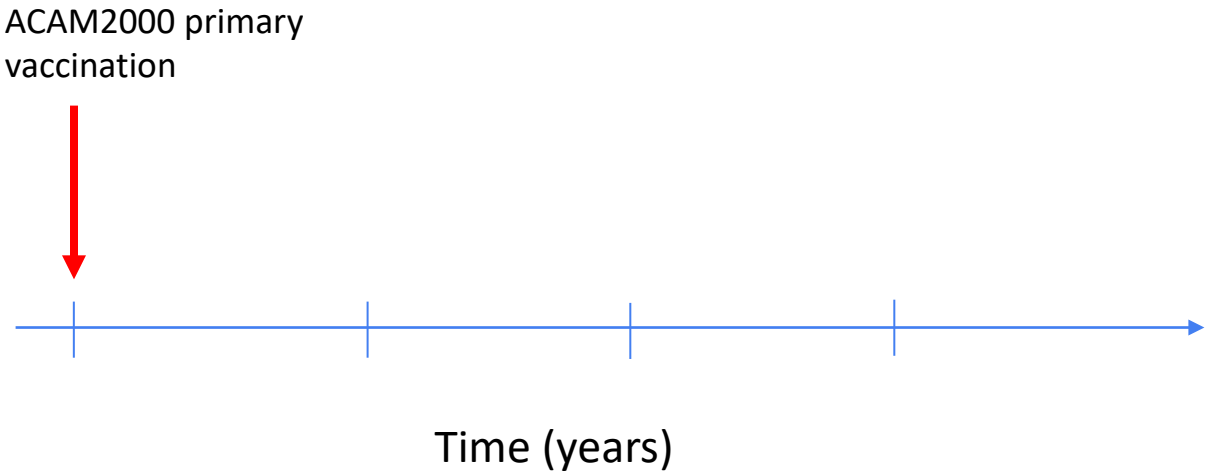
Policy question #3

	Policy question: Should persons who are at continued risk for occupational exposure to replication competent orthopoxviruses like vaccinia or cowpox receive a booster dose of JYNNEOS® after the primary JYNNEOS series?
Population	Persons who are at risk for occupational exposure to replication competent orthopoxviruses like vaccinia or cowpox
Intervention	Booster with JYNNEOS®
Comparison	No booster
Outcome	1) Prevention of disease 2) Severity of disease 3) Severe adverse events 4) Myo-/ peri- carditis

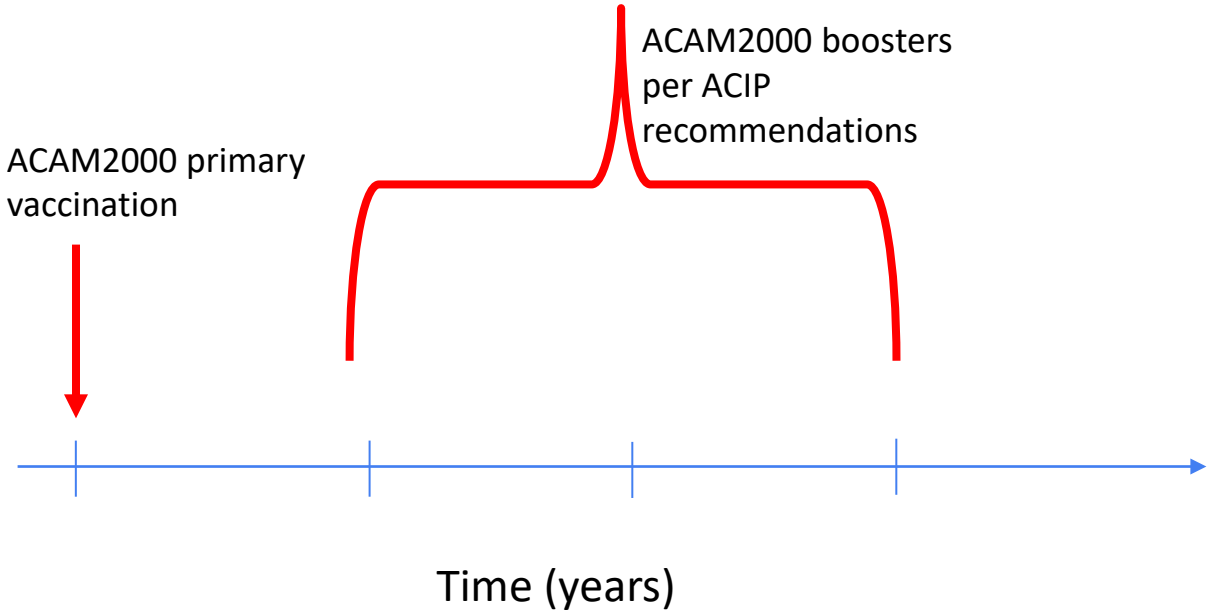
Proposed policy question #4

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

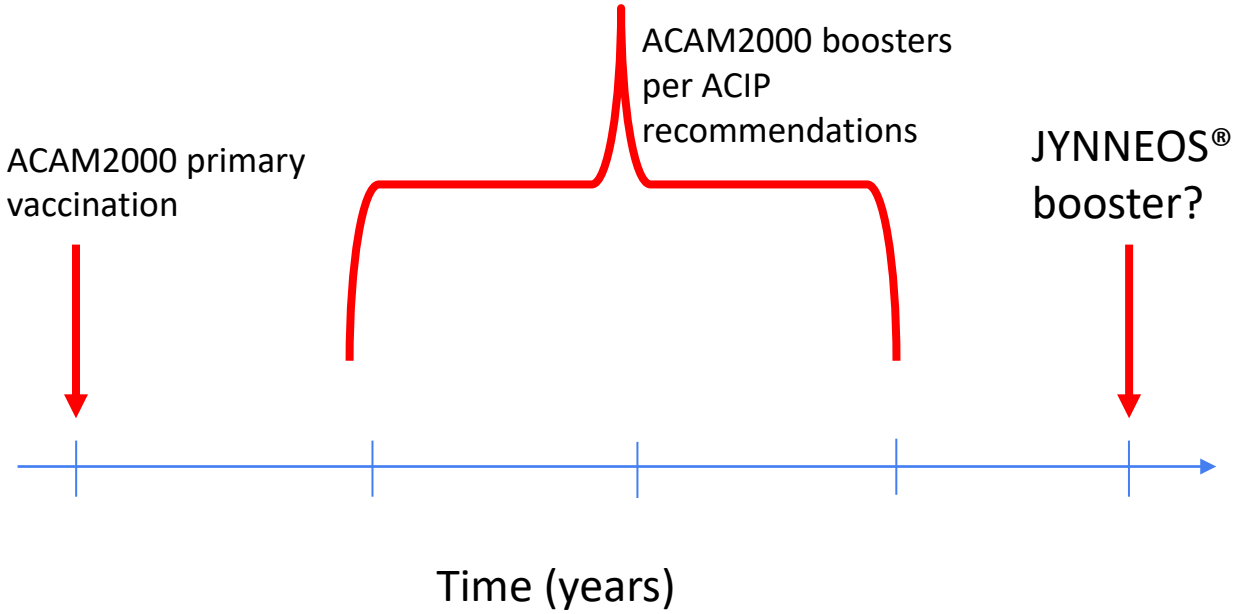
JYNNEOS® after ACAM2000



JYNNEOS® after ACAM2000



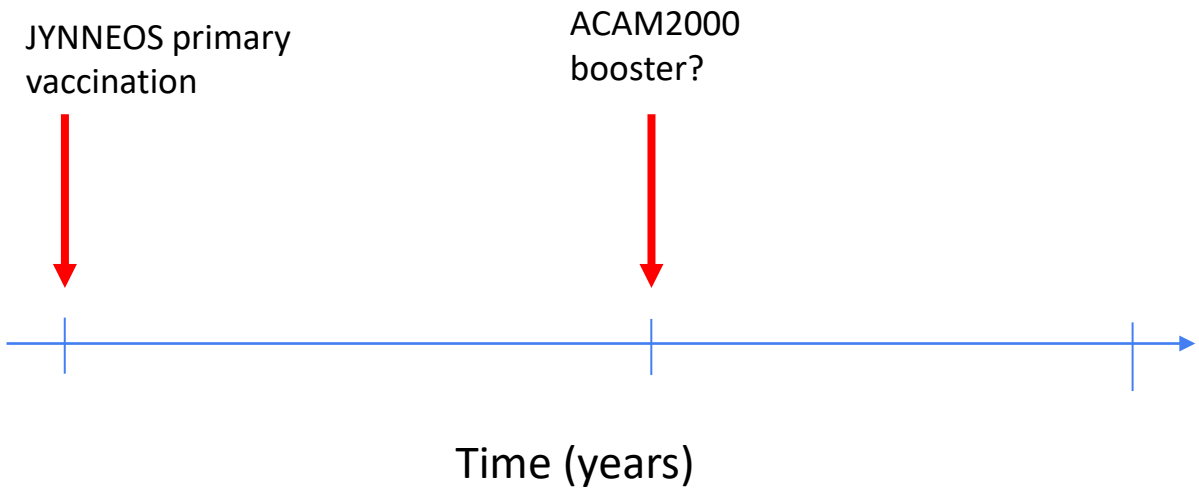
JYNNEOS® after ACAM2000



Policy question #4

	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	1) Prevention of disease 2) Severity of disease 3) Severe adverse events 4) Myo-/ peri- carditis 5) Adverse events due to interaction between JYNNEOS and ACAM2000

ACAM2000 After JYNNEOS®

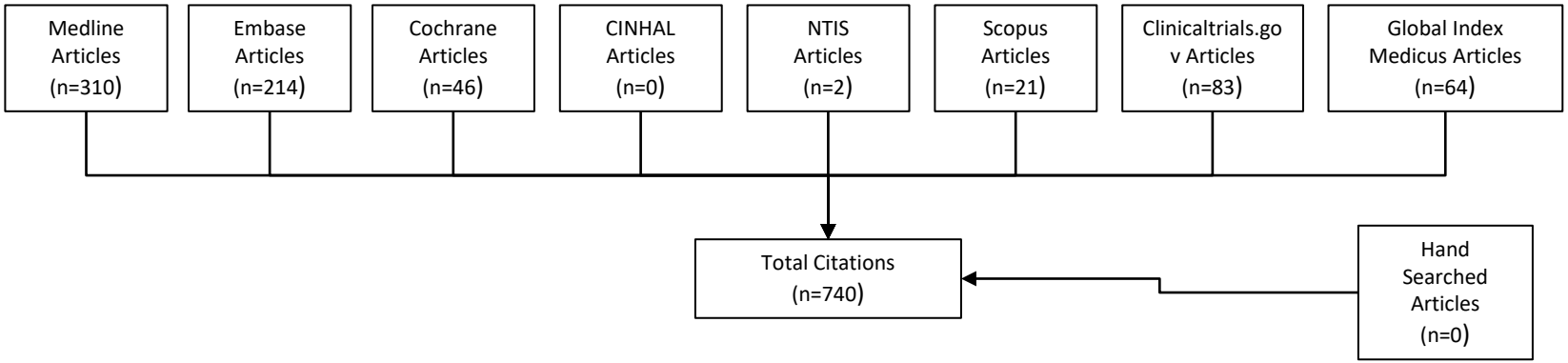


Progress on systematic review

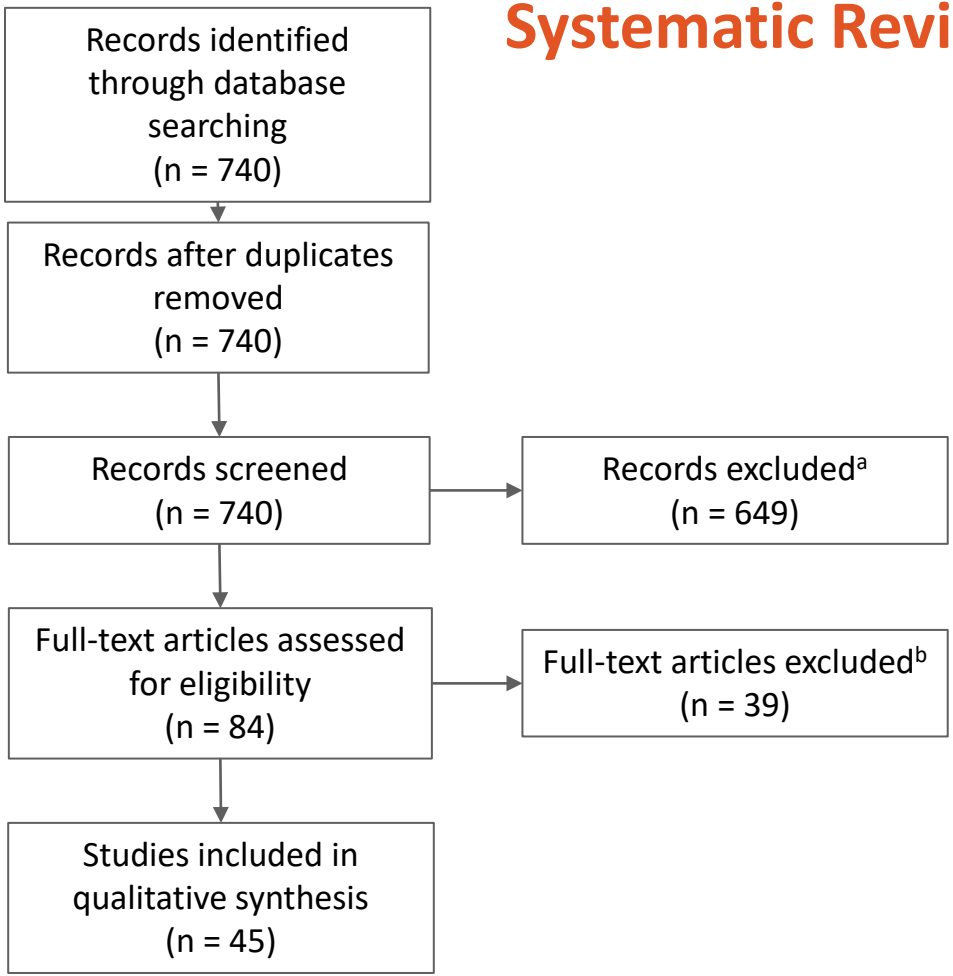
Anticipated Timeline

Systematic Review: Search Terms

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



Systematic Review– Progress



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

[b]Reasonsfor exclusion:
15 No results posted (no data available)
6 MVA recombinant
6 No clinical data available (review article)
4 Erratum no data available
3 Animal model data
2 Wrong setting
2 Wrong study design
1 Opinion article (no clinical data available)

Systematic review challenges

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

WG Considerations for EtR and Clinical Guidance

Differences between ACIP and JYNNEOS®

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

Some Considerations for Evidence to Recommend Framework

- Access to providers with training to administer ACAM2000
- No visual evidence of immunogenicity, e.g., “take”
- Two clinic appointments for JYNNEOS®
- Both vaccines would be available from Strategic National Stockpile (free of cost)

Acknowledgements

- Orthopoxvirus WG
- Florence Whitehill, CDC Poxvirus and Rabies Branch
- Doug Campos-Outcalt, GRADE consultant
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- Jessica MacNeil, ACIP

Thank you!

Questions

For more information, contact CDC
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TTY: 1-888-232-6348 www.cdc.gov