



Background information to interpret GRADE tables and Evidence to Recommendations framework about JYNNEOS[®]

Agam Rao, MD

CAPT, US Public Health Service

ACIP Meeting
September 29, 2021

Populations in the United States at risk of orthopoxvirus infections

- By 1972, routine smallpox vaccinations for children ended in the U.S.
- Vaccinations to prevent smallpox have continued for some populations
 - Members of the military*
 - Designated healthcare workers and response personnel
 - Laboratorians with occupational risk
- Risk for orthopoxvirus infections other than smallpox exists
 - Monkeypox infections re-emerging in parts of Africa
 - Vaccinia virus increasingly used in research laboratories to study orthopoxviruses but also, as functional vector for development of vaccines against unrelated agents
- Difficult to specify the number of persons at risk[#]

*The U.S. military (not ACIP) develops vaccine recommendations for military personnel

[#]There is no systematic surveillance to discern the number of persons at occupational risk for orthopoxviruses; CDC sends ~80 shipments / year but the number of persons treated by each shipment is unclear and some “at risk” are not getting vaccinated

Recognized morbidity after exposures to orthopoxviruses

- Inadvertent exposures to vaccinia virus and cowpox virus have occurred
 - Needlesticks and eye splashes
 - Several persons hospitalized
 - Nearly all were not vaccinated
- Multiple CDC guidelines about vaccination for persons at occupational risk for orthopoxvirus infections (e.g., 2003, 2008, 2015)



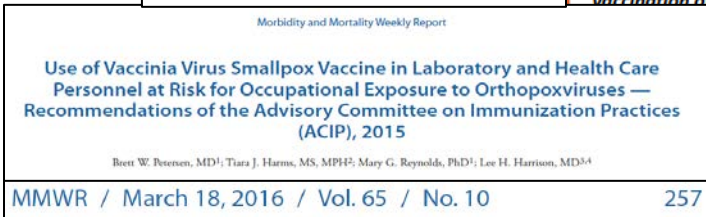
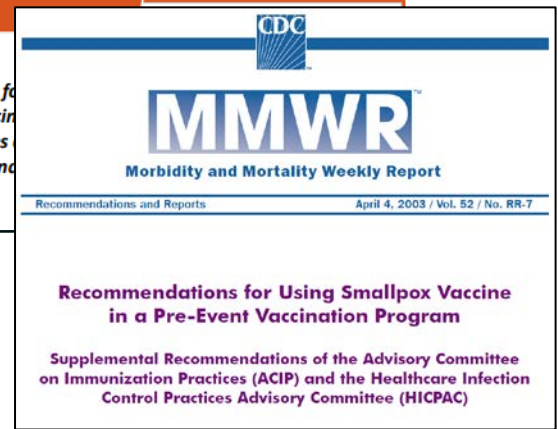
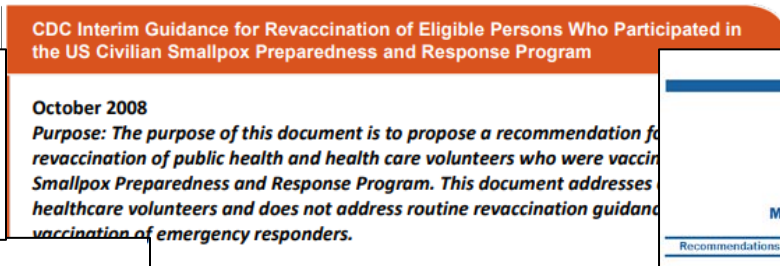
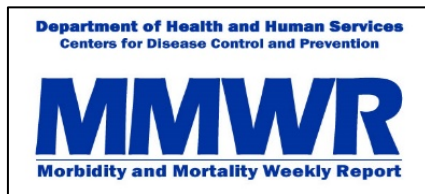
Left eye and right ear of man with laboratory-acquired vaccinia virus infection—Virginia, 2008 (<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5829a1.htm>)



Moussatché Net al. Accidental infection of laboratory worker with vaccinia virus. *Emerg Infect Dis.* 2003 Jun;9(6):724-6.

2019, JYNNEOS® joined ACAM2000 as FDA-approved vaccine to prevent orthopoxvirus infections

- Work group goals:
 - Develop recommendations for the newly licensed live, replication-deficient modified vaccinia virus vaccine, JYNNEOS®
 - Merge all previous CDC recommendations about pre-exposure use of Dryvax/ACAM2000 so that these recommendations are consolidated with those for JYNNEOS®



Dryvax/ACAM2000 considerations

- **Recommended populations**

- Select laboratorians, healthcare personnel (HCP) and response team members
- Some persons in populations not uniformly at risk for orthopoxvirus infections who choose to be vaccinated; e.g., HCP who change dressings after ACAM2000 vaccination

- **Recommendations for booster doses**

- There would be serious implications (both to the affected individual and to public health) if infections from more virulent orthopoxviruses (e.g., smallpox and monkeypox) occurred
- Booster doses recommended more frequently for persons working with more virulent orthopoxviruses than those working with less virulent ones
- Only those with continuous risk receive booster doses at specific intervals

ACIP recommendations for ACAM2000

	ACAM2000
Populations recommended	Persons at occupational risk for orthopoxviruses (i.e., diagnostic laboratorians, healthcare response teams)
Populations offered	Persons who administer ACAM2000 or care for patients after vaccination with replication competent virus (e.g., dressing changes)
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 booster 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)
Frequency of boosters: Those working with less virulent orthopoxviruses	At least every 10 years

ACIP recommendations for ACAM2000

	ACAM2000
Populations recommended	Persons at occupational risk for orthopoxviruses (i.e., diagnostic laboratorians, healthcare response teams)
Populations offered	Persons who administer ACAM2000 or care for patients after vaccination with replication competent virus (e.g., dressing changes)
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 booster 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)
Frequency of boosters: Those working with less virulent orthopoxviruses	At least every 10 years

ACIP recommendations for ACAM2000

	ACAM2000
Populations recommended	Persons at occupational risk for orthopoxviruses (i.e., diagnostic laboratorians, healthcare response teams)
Populations offered	Persons who administer ACAM2000 or care for patients after vaccination with replication competent virus (e.g., dressing changes)
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 booster 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)
Frequency of boosters: Those working with less virulent orthopoxviruses	At least every 10 years

WG considerations for JYNNEOS[®] recommendations

- ACAM2000 is a clonal derivative of Dryvax
- Extensive data about Dryvax helped inform recommendations for ACAM2000

- JYNNEOS[®] is different from ACAM2000
- Recommendations for JYNNEOS[®] will need to rely on data specifically about JYNNEOS[®]

Proposed recommendations for JYNNEOS® compared to those for ACAM

	ACAM2000	JYNNEOS®
Populations 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 questions 1 & 2

- 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?
- Should JYNNEOS[®] be recommended, for healthcare personnel who administer ACAM2000 or care for patients vaccinated with replicating orthopoxviruses*

*Example, in clinical trials

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	

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 questions 3 & 4

- 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?
- Should persons who are at continued risk for occupational exposure to 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?

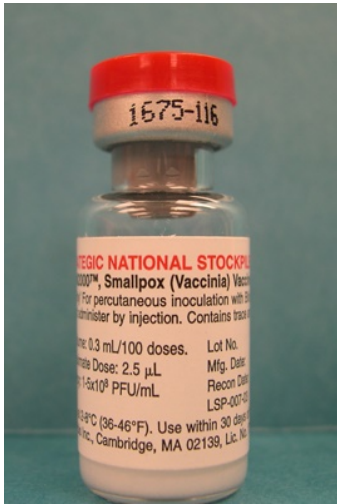
**Important distinctions between JYNNEOS®
and ACAM2000**

ACAM2000 and JYNNEOS®

	ACAM2000	JYNNEOS®
Vaccine virus	Replication-competent vaccinia virus	Replication-deficient Modified vaccinia Ankara
Inadvertent inoculation and autoinoculation	Risk exists	No risk
Serious adverse event	Risk exists	Fewer expected
Cardiac adverse events	Myopericarditis in 5.7 per 1,000 primary vaccinees	Risk believed to be lower than that for ACAM2000
Effectiveness	FDA assessed by comparing immunologic response and “take” rates to Dryvax*	FDA assessed by comparing immunologic response to ACAM2000 & animal studies
Administration	Percutaneously by multiple puncture technique in single dose	Subcutaneously in 2 doses, 28 days apart
“Take”	“Take” occurs	No “take” after vaccination

*Both ACAM2000 and Dryvax are derived from the NYC Board of Health strain of vaccinia; ACAM2000 is a “second generation” smallpox vaccine derived from a clone of Dryvax, purified, and produced using modern cell culture technology.

ACAM2000: Bifurcated needle to administer vaccine and evolution of resulting “Take”



Day 5



Day 8



Day 10



Day 14

Adverse events that can occur after live, replication competent orthopoxvirus vaccines

- Auto-inoculation from “take” to other part(s) of the body (e.g., eye)
- Inadvertent inoculation to others (e.g., family members)
- Progressive vaccinia (vaccinia necrosum)
- Postvaccinal encephalitis and encephalomyelitis
- Eczema vaccinatum
- Generalized vaccinia
- Erythema multiforme major (Stevens-Johnson Syndrome)
- Fetal vaccinia and fetal death

ACAM2000 package insert: Warnings and precautions

- Contraindicated for individuals with severe immunodeficiency who are not expected to benefit from the vaccine
- Some individuals experience serious adverse events
 - Risk for serious adverse events is increased in the following populations: Pregnant persons, infants <12 months of age, persons treated with topical steroids for eye disease, and those with a history of cardiac disease or presence of eczema and other skin conditions
 - Serious adverse events may result in severe disability, permanent neurological sequelae and/or death
- Contact spread can lead to inadvertent inoculation and infection to household members and close contacts

<https://www.fda.gov/media/75792/download>

JYNNEOS[®] package insert: Warnings and precautions

- Immunocompromised persons may have a diminished immune response to the vaccine
- Insufficient data to inform JYNNEOS vaccine-associated risks in pregnancy and during lactation

<https://www.fda.gov/media/131078/download>

Relative contraindications to vaccination with ACAM2000 and JYNNEOS

Conditions	Presence in ACAM2000 vaccinee	Presence in household contact of ACAM2000 vaccinee	Presence in JYNNEOS® vaccinee
History or presence of atopic dermatitis	X	X	
Other active exfoliative skin conditions	X	X	
Conditions associated with immunosuppression	X	X	X
Pregnancy	X	X	X
Aged <1 year	X	X	
Breastfeeding	X		X
Serious vaccine component allergy	X		X
Known underlying heart disease or ≥ 3 cardiac risk factors	X		

Requests for JYNNEOS®

- JYNNEOS®, like ACAM2000, would be available from US Government stockpiles
- No vaccine cost to recipients
- Familiar administration technique (i.e., subcutaneous rather than multiple punctures with bifurcated needle)
- Involves non-replicating virus
 - Lower risk for serious adverse events
 - No concern for inadvertent infection to household members and self
 - Fewer relative contraindications
- Many requests for JYNNEOS®

PICO question #5

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?

Acknowledgements

- Orthopoxvirus WG
- Brett Petersen
- Florence Whitehill
- Andres Velasco-Villa
- Sathesh Panayampalli
- Andrea McCollum
- Whitney Davidson
- Michael Townsend
- Christy Hutson
- Christy Hughes

Questions?

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

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.