ACIP Smallpox Vaccine Work Group

Use of ACAM2000 Smallpox Vaccine in Laboratory and Healthcare Personnel

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Background

- **Orthopoxviruses are a group of large double-stranded DNA viruses within the family *Poxviridae***
  - Four species are known to infect humans: Variola (Smallpox), Vaccinia (Smallpox Vaccine), Monkeypox, and Cowpox
- **Orthopoxvirus infection provides cross protection across species**
  - Development of vaccinia as a vaccine for smallpox
- **Orthopoxviruses remain an active subject of research**

Vaccinia Virus

- **Many historic vaccine seed stocks and derivatives**
  - New York City Board of Health (NYCBH), Lister, Modified Vaccinia Ankara (MVA), Western Reserve, LC16M8, Copenhagen, among others
  - Varying degrees of attenuation and safety profiles
- **Recombinant vaccinia viruses:**
  - Viral vector for expression of foreign genes (gene therapy or genetic engineering)
  - Recombinant vaccines
  - Oncolytic or immunotherapy for cancer

2001 ACIP Recommendations
Vaccinia (Smallpox) Vaccine

- **Vaccinia vaccine is recommended for laboratory workers who directly handle:**
  - Cultures or animals contaminated or infected with nonhighly attenuated vaccinia virus, recombinant vaccinia viruses derived from nonhighly attenuated vaccinia strains, or other orthopoxviruses that infect humans (e.g. monkeypox, cowpox, vaccinia, and variola)
- **Vaccination can be offered to healthcare workers with direct contact with dressings or other infectious material from volunteers in clinical studies where nonhighly attenuated vaccinia viruses or recombinant viruses derived from these strains are used**

2001 ACIP Recommendations
Vaccinia (Smallpox) Vaccine

- Persons working with vaccinia virus, recombinant vaccinia viruses, or other nonvariola Orthopoxviruses should be revaccinated at least every 10 years
- Revaccination every 3 years can be considered for persons working with more virulent nonvariola Orthopoxviruses (e.g., monkeypox)

2001 ACIP Recommendations Vaccinia (Smallpox) Vaccine

- Laboratory and healthcare personnel working with highly attenuated poxvirus strains do not require routine vaccinia vaccination
- Highly attenuated poxvirus strains:
  - MVA – Derived from vaccinia virus Ankara
  - NYVAC – Derived from vaccinia virus Copenhagen
  - TROVAC – Derived from fowlpox virus
  - ALVAC – Derived from canarypox virus

Population at Risk

- **Difficult to estimate - no registry of persons who work with orthopoxviruses**
- **Indirect measures:**
  - 431 orthopoxvirus-related publications in 2013 on PubMed (361 with "vaccinia" in title or abstract, 34 "monkeypox", 36 "cowpox")
  - 185 active projects listed on NIH Research Portfolio Online Reporting Tools (http://projectreporter.nih.gov/)
  - 25 open clinical trials involving vaccinia virus listed on NIH's clinicaltrials.gov
  - 31 different sites received 80 shipments of smallpox vaccine from CDC in 2013 (96 different sites received 523 shipments during 2009–2013)

Risk of Orthopoxviral Disease

- **Difficult to estimate**
  - Vaccinia and cowpox infections are not reportable conditions
  - Orthopoxvirus exposures not always reported
  - Pathogenicity and virulence of the virus may not be well characterized (particularly with recombinant viruses)

Laboratory-related Orthopoxvirus Exposures and Infections Reported to CDC

Year	State	Virus (Strain, if known)	Met ACIP Vaccination Recommendations?	Exposure	Infection?
2004	PA	Vaccinia (Recombinant Western Reserve)	No	Eye Splash	Yes
2005	CA	Vaccinia	No	Eye Splash	No
2005	FL	Vaccinia (Rabbitpox)	Yes	Eye Splash	No
2005	CT	Vaccinia (Recombinant Western Reserve)	No	Needlestick	Yes (Hospitalized)
2006	PA	Vaccinia (Recombinant Western Reserve)	No	Needlestick	Yes
2006	CT	Vaccinia	Unknown	Eye Splash	No
2006	PA	Vaccinia (Recombinant Western Reserve)	No	Needlestick	Yes
2007	IA	Vaccinia (Recombinant Western Reserve)	No	Needlestick	Yes
2007	NM	Vaccinia	Unknown	Animal Care	No
2007	MD	Vaccinia (Recombinant Western Reserve)	No	Needlestick	No
2007	NH	Vaccinia (Recombinant Western Reserve)	No	Needlestick	Yes (Hospitalized)
2007	MA	Vaccinia (Recombinant NYCBH)	No	Needlestick	Yes (Hospitalized)
2007	MO	Monkeypox	Yes	Needlestick	No

Adapted from MacNeil A, Reynolds MG, Damon IK. Risks associated with vaccinia virus in the laboratory. Virology. 2009 Mar 1;385(1):1-4 and CDC records.

Laboratory-related Orthopoxvirus Exposures and Infections Reported to CDC

Year	State	Virus (Strain, if known)	Met ACIP Vaccination Recommendations?	Exposure	Infection?
2008	GA	Vaccinia	Yes	Animal Care	No
2008	CA	Vaccinia (Recombinant Western Reserve)	No	Eye Splash	No
2008	NH	Vaccinia (Recombinant Western Reserve)	No	Eye Splash	No
2008	VA	Vaccinia (Recombinant Western Reserve)	No	Undetermined	Yes (Hospitalized)
2008	FL	Vaccinia	Yes	Tube leakage	No
2010	GA	Vaccinia (Recombinant Western Reserve)	Yes	Undetermined	Yes
2010	IL	Cowpox (Recombinant)	No	Needlestick?	Yes
2010	CA	Cowpox (Recombinant)	No	Needlestick	Yes
2012	NM	Monkeypox (Recombinant)	Yes	PAPR Failure	No
2012	GA	Monkeypox	Yes	Needlestick	No
2013	MA	Vaccinia (Wildtype Western Reserve)	Yes	Needlestick	Yes
2013	MD	Vaccinia (Recombinant Western Reserve)	No	Needlestick	Yes
2014	MD	Vaccinia (Wildtype Western Reserve)	No	Needlestick	Yes

Adapted from MacNeil A, Reynolds MG, Damon IK. Risks associated with vaccinia virus in the laboratory. Virology. 2009 Mar 1;385(1):1-4 and CDC records.

Summary of Laboratory-related Orthopoxvirus Exposures Reported to CDC

- **26 exposure incidents**
  - 18/26 (69%) involved recombinant viruses
- **14/26 (54%) resulted in infections**
  - 12/14 (86%) involved recombinant viruses
  - 12/14 (86%) vaccinia infections, 2/14 (14%) cowpox infections
  - 4/14 (29%) required hospitalization
  - 4/14 (29%) infected with a strain other than that with which they were working (or thought they were working)
- **7/26 (27%) met ACIP vaccination recommendations**
  - 1/7 (14%) resulted in infection
    (one other infection occurred in an individual vaccinated >10 years prior)

Smallpox Vaccine Overview

- ACAM2000 is the only smallpox vaccine licensed and available in the U.S.
- Licensed in 2007 and replaced previously used smallpox vaccine Dryvax (no longer available)
- Used in laboratory/healthcare workers and select DOD personnel

ACAM2000

- Live vaccinia virus vaccine produced in vero cells
- Derived from a clonal isolate of Dryvax, a New York City Board of Health strain used during the smallpox eradication campaign
- Administered percutaneously via multiple puncture with a bifurcated needle

Smallpox Vaccine (Dryvax) Adverse Events Primary Vaccination

Rates of reported complications from primary vaccination (cases per 1,000,000 vaccinations)					
Age (yrs)	<1	1-4	5-19	≥20	Overall Rates
Inadvertent Inoculation	507.0	577.3	371.2	606.1	**529.2**
Generalized Vaccinia	394.4	233.4	139.7	212.1	**241.5**
Eczema Vaccinatum	14.1	44.2	34.9	30.3	**38.5**
Progressive Vaccinia	0.0	3.2	0.0	0.0	**1.5**
Postvaccinial Encephalitis	42.3	9.5	8.7	0.0	**12.3**
Death	14.1	0.0	0.0	0.0	**1.5**
Total	**1549.3**	**1261.8**	**855.9**	**1515.2**	**1253.8**

Adapted from Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys, J Infect Dis. 1970 Oct;122(4):303-9 and ACAM2000 package insert.

Smallpox Vaccine (Dryvax) Adverse Events Revaccination

Rates of reported complications from revaccination (cases per 1,000,000 vaccinations)					
Age (yrs)	<1	1-4	5-19	≥20	Overall Rates
Inadvertent Inoculation	0.0	109.1	47.7	25.0	42.1
Generalized Vaccinia	0.0	0.0	9.9	9.1	9.0
Eczema Vaccinatum	0.0	0.0	2.0	4.5	3.0
Progressive Vaccinia	0.0	0.0	0.0	6.8	3.0
Postvaccinial Encephalitis	0.0	0.0	0.0	4.5	2.0
Death	0.0	0.0	0.0	0.0	0.0
Total	0.0	200.0	85.5	113.6	108.2

Adapted from Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys, J Infect Dis. 1970 Oct;122(4):303-9 and ACAM2000 package insert.

Smallpox Vaccine (Dryvax) Adverse Event Rates 2002-2005

Adverse event	Department of Defense Program (n = 730,580[a]) as of 1/4/2005		Department of Health and Human Services (n = 40,422[b]) as of 1/31/2004	
	N	Incidence / million	N	Incidence / million
Eczema vaccinatum	0	0.0	0	0.0
Progressive vaccinia	0	0.0	0	0.0
Fetal vaccinia	0	0.0	0	0.0
Contact transmission	52	71.2	0	0.0
Auto-inoculation (non-ocular)	62	84.9	20	494.8
Ocular vaccinia	16	21.9	3	74.2
Generalized vaccinia	43	58.9	3	74.2
Post-vaccinial encephalitis	1	1.4	1	24.7
Myo/pericarditis	86	117.7	21	519.5

[a] 71% primary vaccination; 89% male; median age 28.5 yr

[b] 36% primary vaccination; 36% male; median age 47.1 yr

Adapted from Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. Vaccine 2005, Mar 18;23(17-18):2078-81 and ACAM2000 package insert.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Steps

- Develop policy question
- Identify and assess importance of outcomes
- Literature review
- Summarize evidence for critical outcomes
- Evaluate quality of evidence for outcomes

Policy Question

- Should administration of ACAM2000 be recommended routinely to persons at risk for orthopoxviral disease?
- Population: Persons at risk for exposure to orthopoxviruses
- Intervention: Vaccination with ACAM2000
- Comparison: Vaccination with Dryvax

Outcome Assessment

Outcome	Importance	Include in Evidence Profile	Data Available
Benefits			
Vaccine Efficacy to Prevent Orthopoxviral Disease	Critical	Yes	No
Cutaneous Response	Important	Yes	Yes
Neutralizing Antibody Response	Important	Yes	Yes
Harms			
Serious Adverse Events	Critical	Yes	Yes
Myo/pericarditis Resolved with Sequelae	Critical	Yes	Yes
Myo/pericarditis Resolved without Sequelae	Important	Yes	Yes
Inadvertent Inoculation	Important	Yes	Yes
Mild Adverse Events	Important	Yes	Yes

Literature Review

Outcome	Design (# Studies)
Benefits	
Cutaneous Response	RCT (5)
Neutralizing Antibody Response	RCT (5)
Harms	
Serious Adverse Events	RCT (4)
Myo/pericarditis Resolved with Sequelae	RCT (4)
Myo/pericarditis Resolved without Sequelae	RCT (4)
Inadvertent Inoculation	RCT (4)
Mild Adverse Events	RCT (4)

Summary of Critical Benefits Outcomes Cutaneous Response

Cutaneous Response (Vaccination Success)	Study Population / Treatment Group			
	Study 1 Vaccinia-Naïve Subjects		Study 2 Previously Vaccinated Subjects	
	ACAM2000	Comparator (Dryvax)	ACAM2000	Comparator (Dryvax)
Size of Evaluable Population	776	257	1189	388
Number of Vaccination Successes (%)	747 (96%)	255 (99%)	998 (84%)	381 (98%)
Non-Inferiority to Comparator	Yes		No	

Adapted from ACAM2000 package insert.

Summary of Critical Benefits Outcomes Neutralizing Antibody Response

Neutralizing Antibody Response (based on vaccinia 50% plaque reduction neutralization test titer on day 50)	Study Population / Treatment Group			
	Study 1 Vaccinia-Naïve Subjects		Study 2 Previously Vaccinated Subjects	
	ACAM2000	Comparator (Dryvax)	ACAM2000	Comparator (Dryvax)
Size of Evaluable Population	565	190	734	376
Geometric Mean Neutralizing Antibody Titer	166	255	286	445
Log_{10} mean	2.2	2.4	2.5	2.6
Non-Inferiority to Comparator	No		Yes	

Adapted from ACAM2000 package insert.

Summary of Critical Harms Outcomes

- **Serious Adverse Events**
  - No incidents of death, eczema vaccinatum, progressive vaccinia, or postvaccinial encephalitis were reported
- **Myo/pericarditis**
  - 7 cases of suspected myocarditis were reported among 2983 of clinical trial participants who received ACAM2000
  - 5.7 cases per 1000 vaccinees thought to be best estimate of risk based on detection of 5 cases among 873 vaccinees during Phase 3 clinical trials incorporating active monitoring for myocarditis and pericarditis
  - One case with sequelae (persistent abnormal echocardiogram)

Summary GRADE Table

Outcome	Design (# studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Evidence Type
Benefits							
Cutaneous Response	RCT (5)	No serious	No serious	Serious	No serious	None	2
Neutralizing Antibody Response	RCT (5)	No serious	No serious	Serious	No serious	None	2
Harms							
Serious adverse events	RCT (4)	No serious	No serious	No serious	Serious	None	2
Myo/pericarditis Resolved with Sequelae	RCT (4)	No serious	No serious	No serious	No serious	None	1
Myo/pericarditis Resolved without Sequelae	RCT (4)	No serious	No serious	Serious	No serious	None	2
Inadvertent inoculation	RCT (4)	No serious	No serious	No serious	Serious	None	2
Mild Adverse Events	RCT (4)	No serious	No serious	No serious	No serious	None	1

Indirectness

- **The outcome that was assessed may differ from that of primary interest**
  - Cutaneous response and neutralizing antibody response were surrogates for the outcome of primary interest (vaccine efficacy to prevent orthopoxviral disease)
  - Clinical significance of myo/pericarditis resolved without sequelae is unclear => myo/pericarditis resolved with sequelae assessed to be outcome of primary interest

Imprecision

- Clinical trials were not adequately powered to detect serious adverse events (i.e. eczema vaccinatum, progressive vaccinia, postvaccinial encephalitis, death) or inadvertent inoculation

	Rates of AEs in vaccinated population (# cases / million vaccinations)*		% Chance You Would NOT see SAE in ACAM2000 RCTs		Sample Size Needed to Detect Twice the AE Rate (Power 0.8)	
	Naïve	Previously Vaccinated	Naïve	Previously Vaccinated	Naïve	Previously Vaccinated
Eczema vaccinatum	38.5	3	95.5%	99.5%	611,565	7,848,844
Progressive vaccinia	1.5	3	99.8%	99.5%	15,697,723	7,848,844
Post-vaccinial encephalitis	12.3	2	98.5%	99.6%	1,914,325	11,773,284
Inadvertent inoculation	529.2	42.1	52.8%	95.0%	44,459	559,267
Death	1.5	NA	99.8%	NA	15,697,723	NA
ACAM2000 RCT participants:	Naïve: n = 1207					
	Previously vaccinated: n = 1670					

* Rates of SAEs from Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. The Journal of infectious diseases. 1970 Oct;122(4):303-9.

Overall Quality of Evidence

Outcome	Design (# Studies)	Evidence Type	Overall Evidence
Benefits			**2**
Cutaneous Response	RCT (5)	2	
Neutralizing Antibody Response	RCT (5)	2	
Harms			
Serious Adverse Events	RCT (4)	2	
Myo/pericarditis Resolved with Sequelae	RCT (4)	1	

Next Steps

- Work group will begin updating and revising recommendations
- Present recommendations to ACIP
- Publish ACIP Policy Note summarizing recommendations

Questions?

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