Use of Smallpox Vaccine in Laboratory and Health-Care Workers at Risk for Occupational Exposure to Orthopoxviruses

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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

- 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

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 outcomes of interest
- 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 occupational exposure to orthopoxviruses?
- 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)	Vaccinia-Naïve Subjects		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)	Vaccinia-Naïve Subjects		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 2,325 of clinical trial participants who received ACAM2000 (3 cases of suspected myocarditis were reported among 816 clinical trial participants who received Dryvax), no statistically significant difference in rates
  - 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
  - Two cases with sequelae (persistent abnormal echocardiogram), one ACAM2000 recipient and one Dryvax recipient

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	

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)

Summary of Laboratory-related Orthopoxvirus Exposures Reported to CDC during 2004–2014

- **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)

Workgroup Conclusions and Recommendations

- ACAM2000 is comparable to Dryvax in providing protection against orthopoxviruses (Overall evidence type 2)
- Workgroup proposes extending current ACIP recommendations for use of smallpox vaccine among laboratory and healthcare workers at risk for occupational exposure to orthopoxviruses

Proposed Recommendations

- "Routine vaccination with ACAM2000 is recommended for laboratory workers who directly handle a) cultures or b) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains, or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola) (recommendation category: A, evidence type 2)."

Proposed Recommendations

- "Vaccination with ACAM2000 is not recommended for persons who work only with replication-deficient strains of vaccinia virus (e.g., MVA, NYVAC, TROVAC, and ALVAC) (recommendation category: A, evidence type 2)."

Proposed Recommendations

- "Health-care workers (e.g., physicians and nurses) whose contact with replication-competent vaccinia viruses is limited to contaminated materials (e.g., dressings) and persons administering ACAM2000 smallpox vaccine who adhere to appropriate infection prevention measures can be offered vaccination with ACAM2000 (recommendation category: B, evidence type 2)."

Proposed Recommendations

Contraindication	Primary Vaccinees	Revaccinees	Household Contacts*
History or presence of atopic dermatitis	X	X	X
Other active exfoliative skin conditions†	X	X	X
Conditions associated with immunosuppression±	X	X	X
Pregnancy	X	X	X
Aged <1 year§	X	X	X
Breastfeeding	X	X	
Serious vaccine component allergy	X	X	
Known underlying heart disease	X	X	
≥3 known major cardiac risk factors**	X		

* Household contacts include persons with prolonged intimate contact with the potential vaccinee (e.g. sexual contacts) and others who might have direct contact with the vaccination site.

† Conditions include eczema, burns, impetigo, varicella zoster, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease (keratosis follicularis).

± Conditions include HIV/AIDS, leukemia, lymphoma, generalized malignancy, solid organ transplantation, or therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor (TNF) inhibitors, or high-dose corticosteroids, hematopoietic stem cell transplant recipients <24 months post transplant or ≥24 months but have graft-versus-host disease or disease relapse, or autoimmune disease with immunodeficiency as a clinical component

§ Vaccination of infants aged <1 year is contraindicated. Additionally, the Advisory Committee on Immunization Practices does not recommend vaccinating children and adolescents aged <18 years

** Major cardiac risk factors include hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking.

Dissenting view on level of recommendation for workers handling vaccinia virus

- **The risk-benefit ratio for routine smallpox vaccination of laboratory workers handling vaccinia virus has changed significantly**
  - As opposed to the ACIP recommendations in 1980, today vaccination of most workers is no longer a boost vaccination, but a primary vaccination that carries more risk
  - This change in risk likely should have been addressed in 2001 when the recommendations were revised
  - This change in risk at least needs to be acknowledged
- **How can the level of evidence and the risk/benefit ratio for lab workers handling vaccinia virus be the same as for those working with variola and monkeypox viruses?**
  - Variola & monkeypox would cause a more serious infection after a lab accident and have public health implications. Thus there is an acceptable risk-benefit ratio when recommending routine vaccination for these viruses.
  - The same cannot be said for those working with vaccinia virus
- **Therefore, the strength of recommendation for all workers handling vaccinia virus needs to be adjusted**

Alternative language

- A careful assessment of the type of work being done with vaccinia virus should be made and those at high risk of an accidental exposure should be vaccinated
- Alternatively, as opposed to "recommendation category: A, evidence type 2" a lower level be assigned to the recommendation to vaccinate workers who handle vaccinia virus
  - An argument can be made for a lower recommendation category since it is difficult to quantify the risk of occupational exposure to vaccinia virus

Next Steps

- Questions and discussion
- Proposed vote on extending current ACIP recommendations for use of smallpox vaccine among laboratory and healthcare workers at risk for occupational exposure to orthopoxviruses

Questions?

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