DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
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AFEB

FEB 9 2004

MEMORANDUM FOR Assistant Secretary of Defense (Health Affairs)

SUBJECT: Sentinel Case Review 2004 - 03

1. References:

a. Advisory Committee on Immunization Practices (ACIP) - Armed Forces Epidemiological Board (AFEB) Smallpox Vaccine Safety (SVS) Working Group (WG) Sentinel Case Review for Signal Clarification Process, dated February 2, 2004 – Preliminary Report.

b. Advisory Committee on Immunization Practices (ACIP) - Armed Forces Epidemiological Board (AFEB) Smallpox Vaccine Safety (SVS) Working Group (WG) Sentinel Case Review for Signal Clarification Process, dated November 5, 2003 - Final.

c. Memorandum, Deputy Assistant Secretary of Defense, Clinical and Program Policy, 8 January 2003, Collaboration with Advisory Committee on Immunization Practices to Evaluate Smallpox Vaccination Program.

d. Memorandum, Executive Secretary, Armed Forces Epidemiological Board, 8 January 2003, Smallpox Vaccination Evaluation Workgroup.

e. Memorandum, Armed Forces Epidemiological Board, 20 June 2003, DoD Immunization Program for Biological Warfare Defense 2003 - 11.

f. Memorandum, Armed Forces Epidemiological Board, 4 October 2003, Draft Clinical Policy Guidance – Smallpox Vaccination 2003 - 02.

2. Beginning in January 2003, a select subcommittee of the Armed Forces Epidemiological Board (AFEB) has been working with a similar select subcommittee of the Advisory Committee on Immunization Practices (ACIP) through a combined Working Group (WG) evaluating smallpox vaccine safety data and the vaccine safety monitoring and treatment systems. This evaluation has encompassed both the civilian National Smallpox Vaccination Program and the Department of Defense Smallpox Vaccination Program. This group has been meeting weekly or more often as required since formation. The attached materials reflect part of the work product of this group. Specifically, these materials relate to a newly developed Sentinel Case Review Process established to closely monitor individual morbidity or mortality events associated in time with smallpox vaccination.

3. Sentinel cases identified for review underwent a systematic review for signal clarification by designated subgroups of the ACIP-AFEB SVS WG. This process was designed to assess evidence supporting or refuting the likelihood that the identified individual cases were part of a series representing varying manifestations of a common syndrome, as well as whether identified cases and syndromes might be causally associated with vaccination. The process adapts and incorporates useful elements of processes previously developed that were tailored to meet other specific programmatic goals. These include aspects of the Health Resources and Services Administration (HRSA) Anthrax Vaccine Expert Committee (AVEC) review process, Health Canada's Advisory Committee on Causality Assessment (ACCA) review process, and the Institute of Medicine's (IOM) Immunization Safety Review Committee process. This process also benefits from information culled from other published critiques of prior efforts at systematic review for purposes of signal identification and clarification, and specific critiques offered by expert consults on the ACIP-AFEB SVS WG proposed process. Pre-review, Re-review, and Cluster Evaluation forms were developed for use in this process. These forms ensure that a systematic thought process is followed by all reviewers, and facilitate the development of written reports communicating the best assessment of the reviewers. The first 2 subgroups, reviewing case series characterized by Chest Pain/Dyspnea/Fever and Unreviewed Deaths respectively, released their reports to the working group on 7 November 2003 where the reports were approved and forwarded for consideration by the full committees of the ACIP and AFEB. The AFEB considered the findings from the ACIP-AFEB SVS WG and unanimously approved these reports.

4. The current report, preliminary in nature, was released on 2 February 2004 from the ACIP-AFEB SVS WG. It discusses five cases of dilated cardiomyopathy (DCM), in individuals who had received smallpox vaccine several months earlier. For the military population, 3 DCM cases were identified among more than 560,000 smallpox vaccinees. To support this review, the DoD provided data on the rate of DCM among military personnel and follow-up data on patients that have developed myopericarditis following smallpox vaccination. The Board reviewed the data submitted by DoD regarding the observed versus expected occurrence of DCM among active duty service members as recorded in DoD databases. This analysis found a lower rate of DCM than expected, and does not suggest a strong relationship exists between DCM and smallpox vaccination. Although the accuracy and completeness of the data can be questioned, even if a significant degree of under-ascertainment occurred it would be unlikely to alter the basic conclusion. While the military data cannot definitely refute an association between smallpox vaccine and DCM, it certainly does not support it. The clinical follow-up of patients with myopericarditis following vaccination is also relevant. On follow-up of 64 patients at a mean of 18±11 weeks post-onset, none have developed cardiomyopathy. The Board considers it essential to continue clinical evaluation of existing cases to determine whether there will be any long-term morbidity associated with post-vaccinial myopericarditis and to conduct future vaccination programs in a way that allows for education, screening, and appropriate clinical follow-up to ensure evaluation, diagnosis, and treatment of suspected post-vaccinial myopericarditis cases.

5. The ACIP-AFEB SVS WG was charged with responsibility for safety oversight of the national smallpox vaccination programs and have provided their services in support of this national effort without compensation. The AFEB would like to express its sincere appreciation to the members of the ACIP-AFEB SVS WG who have given voluntarily of their time over these past many months in support of the national smallpox vaccination programs. In particular, the Board would like to recognize the outstanding contributions of Dr. Robert E. Shope, a member of the AFEB and ACIP-AFEB SVS WG, who passed away on 19 January 2004. The ability to seek timely independent scientific advice from a committee of noted experts has and will continue to be both essential and critical in the Nation's efforts to meet our national obligation to protect and conserve the freedom and health of our citizens.

6. The AFEB has considered the findings from the ACIP-AFEB SVS WG and the enclosed preliminary report has been unanimously approved.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

STEPHEN M. OSTROFF, MD
AFEB President

JAMES R. RIDDLE, DVM, MPH
Colonel, USAF, BSC
AFEB Executive Secretary

4 Enclosures
1. SV SWG, Cardiac Sentinel Case Review Subgroup Preliminary Report
2. Clinical Summary of Reviewed Cases
3. Sentinel Review Process
4. DoD DCM Epidemiological Analysis

ACIP-AFEB Smallpox Vaccine Work Group
Cardiac Sentinel Case Review Subgroup Preliminary Report
02-02-04

The Cardiac Sentinel Case Review Subgroup reviewed 5 cases of smallpox vaccine recipients who subsequently developed Dilated Cardiomyopathy (DCM).

Each patient had one or more risk factors for cardiac disease, none of which appeared, in the opinion of the group, likely to represent a primary etiologic factor for the cardiomyopathy. Several patients did have prior illnesses that can lead to myocardial dysfunction: obesity and borderline hypertension in one; hypertension, hypercholesterolemia and diabetes in a second; borderline hypertension and mild proteinuria in a third; childhood asthma, emphysema, and minimal alcohol use in a fourth; mitral valve prolapse in a fifth (Table 1.). However, these illnesses and conditions are common in the general population in this age group, and none appeared to be severe enough or long standing enough to account for the development of DCM.

The five clinical courses varied in the type of symptoms, the timing of the onset of relevant symptoms or of diagnosis of DCM following smallpox vaccination, in the clinical course following diagnosis, and in the evidence of recovery to date. Some have improved considerably and appear likely to recover completely, while one has developed severe left ventricular dysfunction and markedly symptomatic heart failure with no sign of recovery. This patient is currently on the cardiac transplant list. It is noted that the other cases had a more benign and self-limited course. Variability of clinical course is common in patients who develop DCM from any cause.

The documentation of DCM was obtained at a time after vaccination ranging from 30 to 163 days (mean 106 days, median 99 days). However, patients had frequently reported symptoms prior to this documentation including fatigue and dyspnea.. The earliest symptoms noted in the materials available for review that were potentially referable to a cardiac cause were described as occurring between 5 and 141 days after vaccination (mean 35 days, median 9 days). (However, the history was very limited in some patients, and symptoms may have occurred earlier in some without documentation.) A number of patients reported symptoms that could have reflected pre-existing myocarditis, e.g., chest pain (Table 1.). At least one had evidence of elevated troponins, suggesting an active myocarditis at the time of onset of DCM. The others lacked this, but this may be due to variability in testing at the time of onset of symptoms or to the possibility that asymptomatic myocarditis preceded the symptoms of DCM. None of these patients had ever had cardiac symptoms prior to vaccination. While three of these patients received multiple simultaneous vaccinations, two did not, suggesting that the multiplicity of simultaneous immunizations per se is not etiologically implicated in this clinical outcome.

In all cases, diagnostic testing was performed to determine whether ischemia could be a cause of the DCM. Four of the five underwent cardiac catheterization, while the fifth underwent an adenosine pharmacologic stress test (Table 1.) In no instance was sufficient coronary artery disease (CAD) identified to suggest ischemia as a cause of DCM. One patient had normal coronary arteries and three had no more than minimal irregularities of the coronaries, with no obstruction. The adenosine stress test was negative for ischemia.

Despite the clinical variability among these individual cases, these five patients all represent cases of DCM, and therefore represent a common syndrome. It is frequently not possible to

definitively identify a specific cause for DCM, and this is true in these five cases. The available evidence is presently inadequate to accept or reject a definitive causal association between the smallpox vaccine and this clinical outcome. However, this group does present a pattern of five reasonably healthy people who, within a period of time following smallpox vaccination that is both temporally and mechanistically compatible with an etiologic association, developed DCM, a documented outcome of myocarditis. These observations suggest a possible causal association between smallpox vaccination and DCM that is worthy of further study.

Epidemiological evidence has documented a statistically significant excess of myocarditis among recent recipients of the smallpox vaccine (1). However, DoD data suggest no progression from myocarditis to DCM in the cases they have followed to date. While this is reassuring, symptoms of DCM following sub-clinical myocarditis may not be clinically apparent for many months. There are no published data regarding pathognomonic findings, positive challenge / re-challenge observations, or epidemiologic evidence of statistically significantly elevated rates of DCM among smallpox vaccinees as compared to comparable but non-vaccinated persons in the general population. Based upon data reported to VAERS as of December 30, 2003, if there is an association between smallpox vaccination and the development of dilated cardiomyopathy, it would appear to be infrequent, in the range of 3 cases of DCM per 40,000 civilian vaccinees at one year of follow up. However, since there is not active follow-up of all vaccinees, it is not possible to be certain that all cases have been ascertained by this passive reporting system.

Without further evidence, the data remain insufficient to move clearly away from neutrality to favor or reject a causal association between smallpox vaccination and DCM. Idiopathic cardiomyopathy is a rare event, making it hard to determine true statistical association. Epidemiologic data assessing the statistical frequency of DCM in smallpox vaccinees compared to the usual baseline rate of DCM observed in this population without vaccination would be valuable, but the expected rate of DCM in a population of this age range is unknown. This missing evidence could move our opinion toward or away from neutrality, if it were sufficiently different from what has been seen in smallpox vaccinees, but it is not available at present.

There are biologic mechanisms supporting the hypothesis that an association exists between smallpox vaccination and DCM, possibly via intervening myocarditis, and we feel that this should continue to be evaluated. A history of smallpox vaccination should be sought in all cases of apparent idiopathic DCM, and symptoms that may represent DCM in smallpox vaccinees should be vigorously investigated, regardless of the duration of time that has passed between vaccination and onset of symptoms. If subsequent epidemiologic evidence suggested that the occurrence of this number of cases within this time period following vaccination exceeded the usual range by statistically significant amounts, this evidence would favor acceptance of a causal relationship with smallpox vaccination. If we are to continue to vaccinate substantial numbers of individuals, consideration should be given to providing funding to support further epidemiologic studies to evaluate the possible association between smallpox vaccination and DCM.

**Since this report was prepared, we have become aware of one additional potential case reported to VAERS. There is insufficient information available at present to allow us to review and include this case in our considerations, though these data are being actively pursued. When these and/or other data become available, we will plan to update this report.*

1. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naïve US military personnel. JAMA 2003; 289:3283-9.

Table 1.

						Mean, median
Age	37 y	42 y	44 y	53 y	55 y	46, 44
Sex	M	M	M	F	F	
1st symptoms (days post vaccine)	5	141	14	7	9	35, 9
Symptom(s)	Chest pain with "slight fever", felt like band across chest, prevented push ups	Nausea, fatigue, dyspnea, Sharp left chest pain, intermittent to continuous	Chest tightness, dyspnea, fatigue	Fatigue, dyspnea, progressing to chest pain, palpitations	Myalgias, fatigue, palpitations,	
Symptom pattern continuous?	Days 5 – 8 after vaccine, "take check" clinic told him was normal reaction to vaccine; 3 months of intermittent light headedness preceding Dx DCM	Sharp left chest pain with SOB, intermittent progressing to continuous for unclear time prior to onset nausea & fatigue. Nausea & fatigue x 3 days prior to first ECHO;	Intermittent for 2 weeks (~9/26 – 10/11/03); persist and worsen until diagnosis, with development of shortness of breath as prominent presentation	Onset fatigue day 7; fatigue & dyspnea continue with onset URI symptoms day 21. fatigue continued with increasing dyspnea noted by day 50. Symptoms persist to Dx.	Myalgias, arthralgias and fever onset day 9 – resolved within 4 days. Day 28 reported continuing fatigue. Day 82 had episodes palpitations. Day 99 complained of intermittent fatigue since vaccination.	
DCM Dx (days post vaccine)	163	151	30	85	99	106, 99
Symptom or finding precipitating diagnostic evaluation	collapsed while running	fatigue, SOB, later chest pain	Inability to complete work shift	New onset heart murmur	New onset heart murmur	
Primary vs. re-vaccinee (? If history only on VAER report)	?	?Re-vaccinee (1 prior dose on VAER report)	?Re-vaccinee (DoD 15 jabs & 1 prior dose on VAER report)	Re-vaccinee	Re-vaccinee	
History of risk factors for cardiac disease	HTN, elevated HDL	Childhood asthma, ETOH 1-3 drinks/month,	Mitral valve prolapse, possible mild	HTN, mild obesity	DM, controlled HTN, hyper-lipidemia,	

		possible mild emphysema	interstitial lung disease		mild obesity	
Ischemia evaluation	Cath – no significant CAD	Cath – non-obstructive CAD	Cath – non-obstructive CAD	Cath – no CAD	Adenosine pharmaco-logic stress test - neg	
Left Ventricular Function	Mild LV dysfunction ; LVEF 0.45	Severe lV dysfunction; LVEF <0.20; ICD advised; referred for transplant	Severely depressed LV function; LVEF 0.20	Moderate LV dysfunction; LVEF 0.35	Moderate to Severely depressed LV function; LVEF 0.25-0.30	
Elevated troponin?	No	0.6 (upper limit normal = 0.5)	No	No	No	
Outcome at last follow up	Stable	Stable	On transplant list	Stable	Improved	
Treatment?	Beta blocker, ACE inhibiter	Carvedilol, aldactone, digoxin, lisinopril, lasix	Lasix, ramiprel, CoReg, lanoxin, AcipHex, Flonase, Dobutamine	HCTZ started prior to DCM Dx; Ramiprol & metoprolol started after DCM Dx	Lisinopril, HCTZ, atovastatin, feofibrate, metformin, Dose of CoReg increased during follow up	

Advisory Committee on Immunization Practices (ACIP)- Armed Forces Epidemiology Board (AFEB) Smallpox Vaccine Safety (SVS) Working Group (WG) Sentinel Case Review for Signal Clarification Process

Sentinel cases identified for review underwent a systematic review for signal clarification by designated subgroups of the ACIP-AFEB SVS WG. This process was designed to assess evidence supporting or refuting the likelihood that the identified individual cases were part of a series representing varying manifestations of a common syndrome, as well as whether identified cases and syndromes might be causally associated with vaccination. The process was not intended to serve as a general model for signal clarification. Rather, it was specifically designed to meet the needs of the US smallpox vaccination program at this time.

The process adapts and incorporates useful elements of processes previously developed that were tailored to meet other specific programmatic goals. These include aspects of the HRSA Anthrax Vaccine Expert Committee (AVEC) review process, Health Canada's Advisory Committee on Causality Assessment (ACCA) review process, and the Institute of Medicine's (IOM) Immunization Safety Review Committee process. This process also benefits from information culled from other published critiques of prior efforts at systematic review for purposes of signal identification and clarification and specific critiques offered by expert consults on our proposed process.

Pre-review, Re-review, and Cluster Evaluation forms were developed for use in this process. These forms incorporate language adapted from forms used in the HRSA Anthrax Vaccine Expert Committee (AVEC) review process, Health Canada's Advisory Committee on Causality Assessment (ACCA) review process, and the Institute of Medicine's (IOM) Immunization Safety Review Committee process. These forms ensure that a systematic thought process is followed by all reviewers, and to facilitate the development of a written report communicating the best assessment of the reviewers. Both the process and the interpretation are guided by, but neither is bound by, the process, language, format, and interpretations used by these prior review processes.

The pre-reviews are performed by government staff. These reviews serve only to facilitate the work of the reviewers. Only private sector members, and not CDC or DoD staff, function as reviewers. The reviewers independently review the clinical material and may disagree with the pre-reviewers. A government staff serves to coordinate the review process and assists with preparation of preliminary draft reports. However, reports are finalized by the members of the Working Group, coordinated by the Working Group Chair, without input from the government staff coordinator. Only the thoughts of the reviewers are reflected in the final report.

The following process was followed:

(1.) The Sentinel Case Review process is coordinated by the CDC staff person responsible for management of the ACIP-AFEB SVS WG, which is Louisa Chapman. Pre-Review (Appendix 1), Re-Review (Appendix 2), and Cluster

Evaluation (Appendix 3) forms were developed to facilitate the review process.

(2.) Clinically trained CDC or DoD staff collected and collated all relevant available medical information on each case selected for review.

(3.) CDC or DoD staff complete a Sentinel Case Pre-Review assessment form for each case. Specifically, Louisa Chapman MD completed a Sentinel Case Pre-Review assessment form for four cases selected for review that had been vaccinated by DHHS and for 2 cases vaccinated by DoD. John Grabenstein Pharm.D, either alone or in association with LC Collins MD, completed a Sentinel Case Pre-Review assessment form for four additional cases selected for review that had been vaccinated by DoD.

(4.) The collated medical information for each case, along with a completed Pre-Review Form (Appendix 1) and a blank Re-Review form (Appendix 2) for each case, are provided to the re-reviewers. In addition, each re-reviewer receives one blank Cluster Evaluation form (Appendix 3) for the entire subgroup of cases.

(5.) Prior to receipt of any unredacted medical records, reviewers sign and return a NIP Non-disclosure agreement and a VAERS Rules of Behavior form. These signatures are kept on file at CDC.

(6.) Each reviewer completes a Re-Review form for each case, and one Cluster Evaluation form for the entire subgroup and faxes a copy of each completed form to the coordinator, Dr. Chapman at CDC.

(7.) The coordinator copies the results of all 3 reviews, along with the results of the pre-reviews onto one Re-review form, identifying areas of concurrence and disagreement among reviewers. Copies of this form, containing the collated findings of the reviewers, are provided to each reviewer as well as to the Chair. This allows each reviewer and the Chair to have access to the comments of the other reviewers when critiquing written draft reports or participating in teleconference discussions of the reviews.

(8.) The Chair of the ACIP-AFEB SVS WG does not participate as a reviewer of the individual cases. Instead the Chair is responsible for ensuring that the final report developed by each subgroup clearly and accurately reflects the opinions and consensus of the reviewers. The Chair is also responsible for communicating the consensus of the subgroup reviewers to the ACIP-AFEB SVS WG and facilitating the ACIP-AFEB SVS WG review and discussion of the subgroup reports. Finally, the Chair is responsible for communicating the subgroup reports and any appropriate commentary from the ACIP-AFEB SVS WG to the Chairs and Executive Secretaries of the parent committees (ACIP and AFEB).

(9.) The coordinator develops a draft report based on the written comments of the reviewers. A draft version of this report is provided to each of the reviewers and the Chair. This draft is critiqued serially in written form and/or verbally by the reviewers. Further, reviewers will have opportunity to discuss their impressions and the draft report at least once by teleconference.

(10.) As a final step, the subgroup will decide whether to issue their review and report as final, or to request broader review of individual cases (or of the entire subset) by additional members of the ACIP-AFEB SVS WG membership.

(11.) To ensure that the final report reflects the thought of the reviewers alone and not the coordinator, the ACIP-AFEB SVS WG Chair, with the reviewers, will finalize each subgroup report without input from the coordinator.

(12.) No DoD or CDC staff other than the coordinator will review or edit these reports at any point in the process. No CDC or DoD staff, including the coordinator, receive or edit the reports between the time that the draft is provided to the Chair and Subgroup reviewers for final critique and the release of the final subgroup report to the ACIP-AFEB SVS WG membership by the Chair.

(13.) The final subgroup report will be confidentially shared with the ACIP-AFEB SVS WG membership by the Chair for review and discussion. The ACIP-AFEB SVS WG cannot edit the final subgroup report. However, the ACIP-AFEB SVS WG can, if it wishes, decide that no fewer than three selected members will also review individual cases regardless of whether this was recommended by the subgroup itself.

(14.) If the ACIP-AFEB SVS WG chooses to review selected cases, the process described above will be repeated and a report developed using the same process.

(15.) When each subgroup review is complete, the ACIP-AFEB SVS WG Chair will present a written report of the Sentinel Review findings to the Executive Secretary and the Chair of both the ACIP and the AFEB simultaneously. This report will consist of the final report prepared by each subgroup, as well as any reports resulting from review of selected cases by additional members of the ACIP-AFEB SVS WG.

(16.) The reports from the Chair, ACIP-AFEB SVS WG to the Chairs, ACIP and AFEB will be shared confidentially with the membership of the ACIP and the AFEB. The ACIP and AFEB members will have 6 days to review and comment on these reports. Assuming the reports are released to the committee

members prior to 12 midnight EST on Friday November 7, comments must be returned to the Chair of the respective parent committee no later than 12 noon EST on Thursday, November 13, 2003.

(17.) Immediately following release of the report to the memberships of the ACIP and AFEB, the ACIP and AFEB Chair should, in a coordinated fashion, confidentially share the reports with the Assistant to the Director for Immunization Policy, Epidemiology and Surveillance Division, NIP, CDC (Louisa Chapman) and to the appropriate counterpart at DoD for transmission up the chains of command to the Director, CDC and the Office of the Undersecretary for Health, DoD.

(18.) Any public release of the findings of the Working Group Sentinel Review process should be coordinated between the Office of the Director, CDC, the Office of the Undersecretary for Health, DoD in collaboration with the Chairs of the ACIP and the AFEB. No public release of information will occur until these entities have had opportunity to review the report and to confidentially share the contents of the reviews with other appropriate parties, which may include in select instances the families of cases under review or others.

Appendix 1.

SENTINEL CASE PRE-REVIEW FORM

1. Identifying information:

1.1. Case VAERS # ☐☐☐☐☐☐-☐ 1.2. Date of pre-review: ____/___/___
MM / DD / YY

1.3. Pre-Reviewer Name: _____ CDC ☐
Last, First initial DoD ☐

1.4. Date of Smallpox vaccination: ____/___/___ (MM / DD / YY)

1.5. Primary event reported: _____
VAERS serious? ☐ Yes ☐ No

1.6. Onset date: ____/___/___ Duration: _____
MM / DD / YY

1.7. Current status:
☐ Recovered to baseline ☐ Partially recovered ☐ Permanently disabled ☐ Dead

1.8. Do you agree with reported diagnosis? ☐ Yes ☐ No ☐ Insufficient data to assess
If no, your diagnosis: _____

1.9. Is this case part of a syndrome cluster? ☐ Yes ☐ No If yes:

1.9.1. Sentinel Case Cluster Identification #: ☐☐☐

1.9.2. number of cases in cluster ☐☐☐

2. Questions regarding the primary event reported:

2.1. Frequency of occurrence of adverse event?
☐ Rare ☐ Intermediate ☐ Common

2.2. Similar events known to occur with other disease?
☐ Yes ☐ No ☐ Insufficient data

2.3. Event is known to be related to this vaccine?
☐ Yes ☐ No ☐ Insufficient data

2.4. Event is explainable by the biological properties of the vaccine?
☐ Yes ☐ No ☐ Insufficient data

2.5. Vaccination-event interval compatible with the event?
☐ Yes ☐ No ☐ Insufficient data

2.6. The patient had similar symptoms in the past:
2.6.1. not associated with vaccination? ☐ Yes ☐ No ☐ Insufficient data
2.6.2. associated with other vaccinations?
☐ Yes ☐ No ☐ Insufficient data
2.6.3. associated with smallpox vaccination?
☐ Yes ☐ No ☐ Insufficient data

2.7. Concomitant / preceding drug therapy? ☐ Yes ☐ No ☐ Insufficient data
If yes, list: _____

2.8. Concomitant / preceding medical condition? ☐ Yes ☐ No ☐ Insufficient data
If yes, list: _____

2.9. Other vaccines received within 4 weeks prior to event onset? ☐ Yes ☐ No ☐ Insufficient data
If yes, list vaccines / dates: _____

2.10. Other contributing factors? ☐ Yes ☐ No ☐ Insufficient data
If yes, list factors: _____

3. Causal Interpretations: Beginning from a position of neutrality, does the weight of available clinical and epidemiologic evidence allow you to shift to one of the following positions?

3.1. No evidence *(Complete absence of clinical and epidemiological evidence)*
☐ Yes ☐ No

3.2. Evidence is inadequate to accept or reject a causal association *(Evidence is not reasonably convincing either in support of or against causality; evidence is sparse, conflicting, of weak quality, or just suggestive)(Cases in which medical information available is insufficient to allow adequate assessment of causal association should be placed in this category).* ☐ Yes ☐ No

3.3. Evidence favors rejection of a causal relationship (*Evidence does not support a causal relationship)*
☐ Yes ☐ No

3.4. Evidence favors acceptance of a causal relationship *(Causal evidence is strong and generally convincing but not definitive)* ☐ Yes ☐ No
If yes, basis for decision:
3.4.1. Epidemiologic study demonstrating statistical significance ☐ Yes ☐ No
3.4.2. Epidemiologic study suggesting association ☐ Yes ☐ No
3.4.3. Pathognomonic clinical or laboratory finding ☐ Yes ☐ No
3.4.4. Challenge – Re-challenge observations ☐ Yes ☐ No

3.5. Evidence establishes a causal relationship *(Causal link is unequivocal)*
☐ Yes ☐ No
If yes, basis for decision:
3.5.1. Epidemiologic study demonstrating statistical significance combined with additional criteria identified below ☐ Yes ☐ No
3.5.2. Epidemiologic studies demonstrating statistical significance ☐ Yes ☐ No
3.5.3. Pathognomonic clinical or laboratory finding ☐ Yes ☐ No
3.5.4. Positive Challenge – Re-challenge observations ☐ Yes ☐ No

4. Evidence of biological mechanisms consistent with a proposed relationship:

Evidence regarding biological mechanisms can never prove causality. However, such evidence can assist in assessing whether associations demonstrated by epidemiological analysis are consistent with or implausible in the light of current biological understandings. Further, when demonstrated

epidemiological associations are absent, identification of sound biological mechanisms may influence the development of research agendas.

4. Are biological mechanisms identifiable that might be consistent with a relationship between the vaccine exposure and the adverse clinical outcome? ☐ Yes ☐ No

If yes, category of evidence:

4.1. Theory only *(a reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles)* ☐ Yes ☐ No

4.2. Experimental evidence exists that the mechanism operates in animal models, *in vitro* systems, or humans: ☐ Yes ☐ No

4.3. Experimental evidence that the mechanism results in known disease in humans: ☐ Yes ☐ No

4.4. Summary judgment of body of evidence supporting presence of identifiable biological mechanisms that could be operational:

☐ weak ☐ moderate ☐ strong

5. Assessment of Sufficiency of Available Information:

5. Were the judgments above made on the basis of complete and sufficient clinical information? ☐ Yes ☐ No

If No, describe:

5.1. Key portions of existing medical records were unavailable ☐ Yes ☐ No

5.2. Appropriate diagnostic tests not performed, or inappropriately timed ☐ Yes ☐ No

5.3. Medical record inadequately records history of illness ☐ Yes ☐ No

5.4. Other: ☐ Yes ☐ No

Describe: _____

6. Comments:

SENTINEL CASE RE-REVIEW FORM

1. Identifying information:

1.1. Case VAERS # ☐☐☐☐☐☐-☐ 1.2. Date of re-review: ____/___/___
MM / DD / YY

1.3. Re-Reviewer Name: _____
Last, First initial

1.4. Date of Smallpox vaccination: ____/___/___ (MM / DD / YY)

1.5. Primary event reported: _____
VAERS serious? ☐ Yes ☐ No

1.6. Onset Date and Duration: ☐ Concur with pre-review ☐ Disagree
If disagree: Onset date: ____/___/___ Duration: _____
MM / DD / YY

1.7. Current status: ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Recovered to baseline ☐ Partially recovered ☐ Permanently disabled ☐ Dead

1.8. Do you agree with reported diagnosis? ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Yes ☐ No ☐ Insufficient data to assess
If no, your diagnosis: _____

2. Questions regarding the primary event reported:

2.1. Frequency of occurrence of adverse event? ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Rare ☐ Intermediate ☐ Common

2.2. Similar events known to occur with other disease? ☐ Concur with pre-review ☐ Disagree
I If disagree: ☐ Yes ☐ No ☐ Insufficient data

2.3. Event is known to be related to this vaccine? ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Yes ☐ No ☐ Insufficient data

2.4. Event is explainable by the biological properties of the vaccine? ☐ Concur w pre-review ☐ Disagree
If disagree: ☐ Yes ☐ No ☐ Insufficient data

2.5. Vaccination-event interval compatible with the event? ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Yes ☐ No ☐ Insufficient data

2.6. The patient had similar symptoms in the past: ☐ Concur with pre-review ☐ Disagree
If disagree:
2.6.1. not associated with vaccination? ☐ Yes ☐ No ☐ Insufficient data
2.6.2. associated with other vaccinations? ☐ Yes ☐ No ☐ Insufficient data
2.6.3. associated with smallpox vaccination? ☐ Yes ☐ No ☐ Insufficient data

2.7. Concomitant / preceding drug therapy? ☐ Concur with pre-review ☐ Disagree

If disagree: ☐ Yes ☐ No ☐ Insufficient data
If yes, list: _____

2.8. Concomitant / preceding medical condition? ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Yes ☐ No ☐ Insufficient data
If yes, list: _____

2.9. Other vaccines received within 4 weeks prior to event onset? ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Yes ☐ No ☐ Insufficient data
If yes, list vaccines / dates: _____

2.10. Other contributing factors? ☐ Concur with pre-review ☐ Disagree
If disagree: ☐ Yes ☐ No ☐ Insufficient data
If yes, list factors: _____

3. Causal Interpretations: Beginning from a position of neutrality, does the weight of available clinical and epidemiologic evidence allow you to shift to one of the following positions?

☐ Concur with pre-review ☐ Disagree with pre-review If disagree:

3.1. No evidence *(Complete absence of clinical and epidemiological evidence)*
☐ Yes ☐ No

3.2. Evidence is inadequate to accept or reject a causal association *(Evidence is not reasonably convincing either in support of or against causality; evidence is sparse, conflicting, of weak quality, or just suggestive)(Cases in which medical information available is insufficient to allow adequate assessment of causal association should be placed in this category).* ☐ Yes ☐ No

3.3. Evidence favors rejection of a causal relationship *(Evidence does not support a causal relationship)*
☐ Yes ☐ No

3.4. Evidence favors acceptance of a causal relationship *(Causal evidence is strong and generally convincing but not definitive)* ☐ Yes ☐ No
If yes, basis for decision:
3.4.1. Epidemiologic study demonstrating statistical significance ☐ Yes ☐ No
3.4.2. Epidemiologic study suggesting association ☐ Yes ☐ No
3.4.3. Pathognomonic clinical or laboratory finding ☐ Yes ☐ No
3.4.4. Challenge – Re-challenge observations ☐ Yes ☐ No

3.5. Evidence establishes a causal relationship *(Causal link is unequivocal)*
☐ Yes ☐ No
If yes, basis for decision:
3.5.1. Epidemiologic study demonstrating statistical significance combined with additional criteria identified below ☐ Yes ☐ No
3.5.2. Epidemiologic studies demonstrating statistical association ☐ Yes ☐ No
3.5.3. Pathognomonic clinical or laboratory finding ☐ Yes ☐ No
3.5.4. Positive Challenge – Re-challenge observations ☐ Yes ☐ No

4. Evidence of biological mechanisms consistent with a proposed relationship:

Evidence regarding biological mechanisms can never prove causality. However, such evidence can assist in assessing whether associations demonstrated by epidemiological analysis are consistent with or implausible in the light of current biological understandings. Further, when demonstrated epidemiological associations are absent, identification of sound biological mechanisms may influence the development of research agendas.

☐ Concur with pre-review ☐ Disagree with pre-review If disagree:

4. Are biological mechanisms identifiable that might be consistent with a relationship between the vaccine exposure and the adverse clinical outcome? ☐ Yes ☐ No

If yes, category of evidence:

4.1. Theory only *(a reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles)* ☐ Yes ☐ No

4.2. Experimental evidence exists that the mechanism operates in animal models, *in vitro* systems, or humans: ☐ Yes ☐ No

4.3. Experimental evidence that the mechanism results in known disease in humans: ☐ Yes ☐ No

4.4. Summary judgment of body of evidence supporting presence of identifiable biological mechanisms that could be operational:

☐ weak ☐ moderate ☐ strong

5. Assessment of Sufficiency of Available Information:

☐ Concur with pre-review ☐ Disagree with pre-review If disagree:

5. Were the judgments above made on the basis of complete and sufficient clinical information? ☐ Yes ☐ No

If No, describe:

5.1. Key portions of existing medical records were unavailable ☐ Yes ☐ No

5.2. Appropriate diagnostic tests not performed, or inappropriately timed ☐ Yes ☐ No

5.3. Medical record inadequately records history of illness ☐ Yes ☐ No

5.4. Other: ☐ Yes ☐ No

Describe: _____

6. Comments:

7. Recommendations:

Appendix 3.

SENTINEL CASE REVIEW FOR SIGNAL CLARIFICATION
CLUSTER ASSESSMENT FORM

1. Identifying information:

1. Date of Cluster Assessment: ____/___/___
   MM / DD / YY
2. Cluster Assessment Reviewer Name: ____________________________
   Last, First initial
3. Sentinel Case Cluster Identification #: ☐☐☐ 3.1. identifying feature of cluster: ______________

   3.2. number of cases in cluster ☐☐☐
4. Do these cases appear to be presentations of a common syndrome?
   ☐ No ☐ Yes ☐ Only the indicated cases appear to belong to a common syndrome
5. VAERS numbers of cases in cluster:

VAERS numbers of cases in cluster:	Checked cases belong to common syndrome:
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐
Case VAERS # ☐☐☐☐☐☐-☐	☐

If a cluster is identified, proceed to questions 6 & 7. Otherwise, skip to question 8.

6. Causal Interpretations with regard to possible association between the perceived syndrome and vaccine: Beginning from a position of neutrality, does the weight of available clinical and epidemiologic evidence allow you to shift to one of the following positions?

6.1. No evidence *(Complete absence of clinical and epidemiological evidence)*

☐ Yes ☐ No

6.2. Evidence is inadequate to accept or reject a causal association *(Evidence is not reasonably convincing either in support of or against causality; evidence is sparse, conflicting, of weak quality, or just suggestive))(Cases in which information available is insufficient to allow adequate assessment of causal association should be placed in this category).* ☐ Yes ☐ No

6.3. Evidence favors rejection of a causal relationship *(Evidence does not support a causal relationship)*

☐ Yes ☐ No

6.4. Evidence favors acceptance of a causal relationship *(Causal evidence is strong and generally convincing but not definitive)* ☐ Yes ☐ No

If yes, basis for decision:

6.4.1. Epidemiologic study demonstrating statistical significance ☐ Yes ☐ No

6.4.2. Epidemiologic study suggesting association ☐ Yes ☐ No

6.4.3. Pathognomonic clinical or laboratory finding ☐ Yes ☐ No

6.4.4. Challenge – Re-challenge observations ☐ Yes ☐ No

6.5. Evidence establishes a causal relationship *(Causal link is unequivocal)*

☐ Yes ☐ No

If yes, basis for decision:

6.5.1. Epidemiologic study demonstrating statistical significance combined with additional criteria identified below ☐ Yes ☐ No

6.5.2. Epidemiologic studies demonstrating statistical significance ☐ Yes ☐ No

6.5.3. Pathognomonic clinical or laboratory finding ☐ Yes ☐ No

6.5.4. Positive Challenge – Re-challenge observations ☐ Yes ☐ No

7. Evidence of biological mechanisms consistent with a proposed relationship:

Evidence regarding biological mechanisms can never prove causality. However, such evidence can assist in assessing whether associations demonstrated by epidemiological analysis are consistent with or implausible in the light of current biological understandings. Further, when demonstrated epidemiological associations are absent, identification of sound biological mechanisms may influence the development of research agendas.

7. Are biological mechanisms identifiable that might be consistent with a relationship between the vaccine exposure and the adverse clinical outcome? ☐ Yes ☐ No

If yes, category of evidence:

7.1. Theory only *(a reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles)* ☐ Yes ☐ No

7.2. Experimental evidence exists that the mechanism operates in animal models, *in vitro* systems, or humans: ☐ Yes ☐ No

7.3. Experimental evidence that the mechanism results in known disease in humans: ☐ Yes ☐ No

7.4. Summary judgment of body of evidence supporting presence of identifiable biological mechanisms that could be operational:

☐ weak ☐ moderate ☐ strong

8. Assessment of Sufficiency of Available Information:

8. Were the judgments above made on the basis of complete and sufficient clinical information?

☐ Yes ☐ No

If No, describe:

8.1. Key portions of existing medical records were unavailable ☐ Yes ☐ No

8.2. Appropriate diagnostic tests not performed, or inappropriately timed ☐ Yes ☐ No

8.3. Medical record inadequately records history of illness ☐ Yes ☐ No

8.4. Other: ☐ Yes ☐ No

Describe: _____

9. Comments:

10. Recommendations:

CDC Chain of Distribution for Reports from the Chair, ACIP and Chair, AFEB

The Chair, ACIP will release reports from ACIP-AFEB joint Smallpox Vaccine Safety Working Group to the Assistant to the Director for Immunization Policy, Office of the Director (OD), Epidemiology and Surveillance Division (ESD), National Immunization Program (NIP), Centers for Disease Control and Prevention (CDC) who is responsible for internal communication of these reports within CDC.

The Assistant to the Director for Immunization Policy will transmit such reports to the Director, ESD, who is responsible for transmission of such reports to the Office of the Director, NIP and for internal distribution to ESD staff as appropriate.

The Director, ESD will transmit the reports to the Director, NIP and the Director, Smallpox Preparedness and Response Activity, NIP, as well as to ESD staff as appropriate.

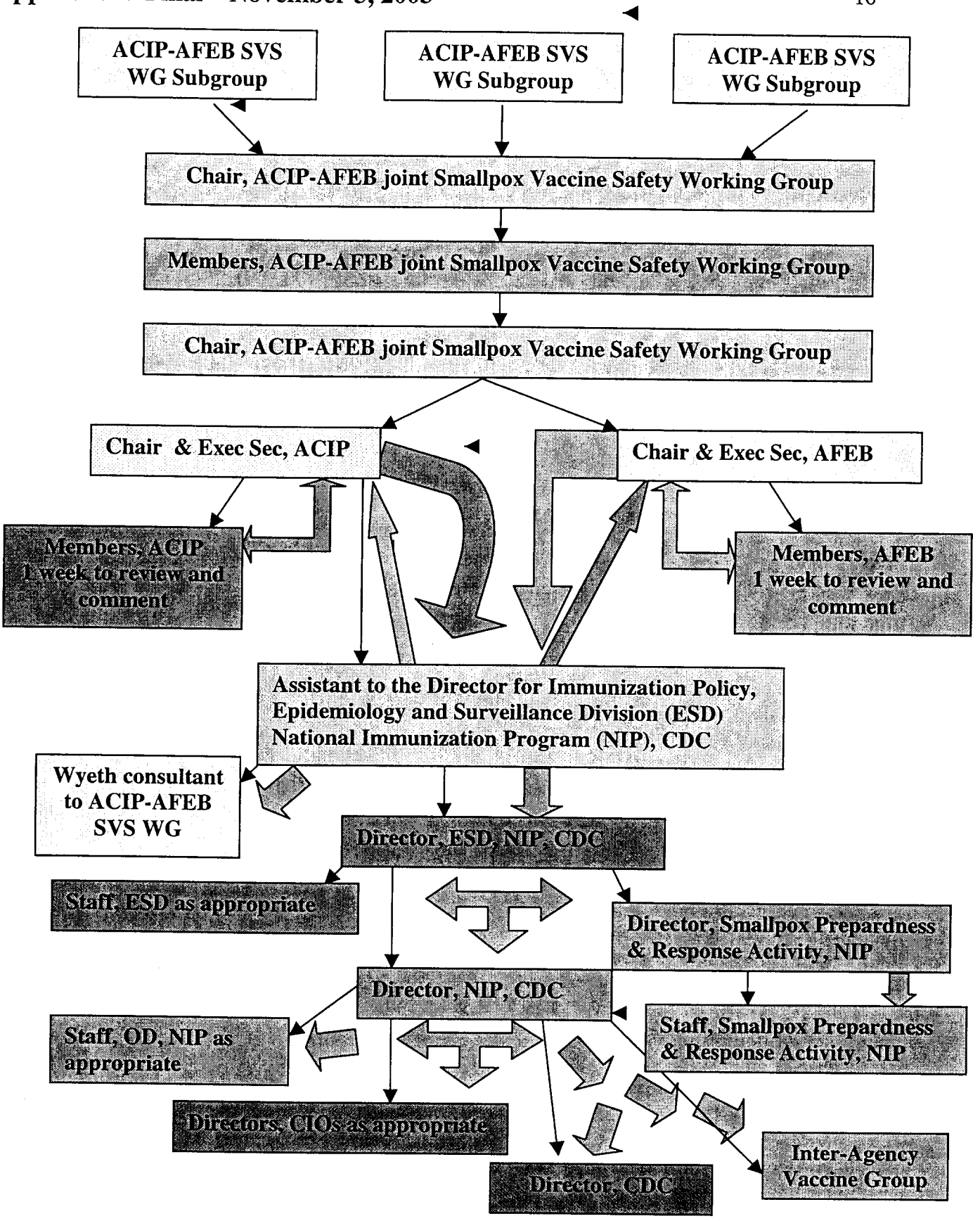
The Director, Smallpox Preparedness and Response Activity, NIP will transmit the reports to Activity staff as appropriate.

The Director, NIP will transmit the reports to OD, NIP staff as appropriate. The Director, NIP will also transmit the reports to other CDC CIO directors, to the OD, CDC, and to the Interagency Vaccine Group (IAVG).

Immediately following distribution within CDC, the Assistant to the Director for Immunization Policy ESD NIP CDC will transmit a confidential report to the Wyeth consultant to the ACIP-AFEB SVS WG.

At the end of the 6 days allowed for review and comment by the members of ACIP and AFEB, the Chair, ACIP and the Chair, AFEB will transmit any additional comments or reports from the memberships of these two committees to the Assistant to the Director for Immunization Policy, ESD, NIP, CDC. The Assistant to the Director for Immunization Policy will again be responsible for internal communication of these reports within CDC, as well as distribution to the Chairs & Ex Sec of both parent committees, and to the Wyeth consultant as outlined above and in Figure 1 below.

Figure 1. CDC Chain of Distribution for Reports


ACIP-AFEB SVS WG Subgroup
ACIP-AFEB SVS WG Subgroup
ACIP-AFEB SVS WG Subgroup
Chair, ACIP-AFEB joint Smallpox Vaccine Safety Working Group
Members, ACIP-AFEB joint Smallpox Vaccine Safety Working Group
Chair, ACIP-AFEB joint Smallpox Vaccine Safety Working Group
Chair & Exec Sec, ACIP
Chair & Exec Sec, AFEB
Members, ACIP 1 week to review and comment
Members, AFEB 1 week to review and comment
Assistant to the Director for Immunization Policy, Epidemiology and Surveillance Division (ESD) National Immunization Program (NIP), CDC
Wyeth consultant to ACIP-AFEB SVS WG
Director, ESD, NIP, CDC
Staff, ESD as appropriate
Director, Smallpox Prepardness & Response Activity, NIP
Director, NIP, CDC
Staff, OD, NIP as appropriate
Staff, Smallpox Prepardness & Response Activity, NIP
Directors, CIOs as appropriate
Director, CDC
Inter-Agency Vaccine Group

Summary: The Army Medical Surveillance Activity analyzed DoD worldwide inpatient and outpatient medical encounter data[1] looking at age group-specific incidence rates of cardiomyopathy among active duty members of the US Armed Forces from January 2002 through September 2003.

The analysis was based on ICD-9-CM codes 425.4 (Other primary cardiomyopathies: cardiomyopathy NOS, congestive, constrictive, familial, hypertrophic, idiopathic, nonobstructive, obstructive, restrictive, cardiovascular collagenosis) and 429.3 (Cardiomegaly: cardiac dilatation, hypertrophy, ventricular dilatation).
Age group-specific "background rates" were estimated by identifying incident reports of relevant ICD-9-CM codes among US service members (unvaccinated) during the surveillance period: 1 Jan 2002 - 30 September 2003. Incident cases were distributed in relation to the ages of the affected service members. Age-specific rates were then calculated by dividing the incident cases in each age stratum by the total active military service (in years) served by all unvaccinated service members during the surveillance period. Expected cases were then estimated by multiplying age-specific background rates by the total military service after vaccination served by service members in the relevant age-strata. Observed numbers of cases were compared against "expected cases" based on estimated background rates. By this estimation method, there did not appear to be excess cardiomyopathy cases post-smallpox vaccination.

Any medical encounter

Age group	Number of observed cases	Rate per 100,000 py	Total person years	Person years after smallpox immunization	Expected cases	Observed cases among vaccinees	Ratio of observed:expected
Total	1,397	58.8	2,375,347.2	186,949.1	116.7	55	0.5
17-19	59	31.2	189,351.9	13,474.7	4.2	0	0.0
20-24	242	31.2	776,637.3	59,520.5	18.5	12	0.6
25-29	185	41.4	446,429.2	30,630.9	12.7	7	0.6
30-34	174	54.9	316,760.8	36,497.7	20.0	6	0.3
35-39	273	91.4	298,579.2	28,953.5	26.5	16	0.6
40-44	269	165.9	162,157.7	12,641.9	21.0	9	0.4
45-49	126	233.1	54,056.3	4,178.9	9.7	5	0.5
50-54	51	345.9	14,742.8	867.8	3.0	0	0.0
55-59	15	535.3	2,802.4	151.5	0.8	0	0.0
60-64	2	534.6	374.1	26.2	0.1	0	0.0
65-69	1	2217.3	45.1	1.5	0.0	0	0.0
70-74	0	0.0	7.2	0.0	0.0	0	0.0
75-79	0	0.0	2.0	0.0	0.0	0	0.0

1. Incidence rates = incident events per 100,000 person-years
2. ICD-9-CM codes: 425.4, 429.3

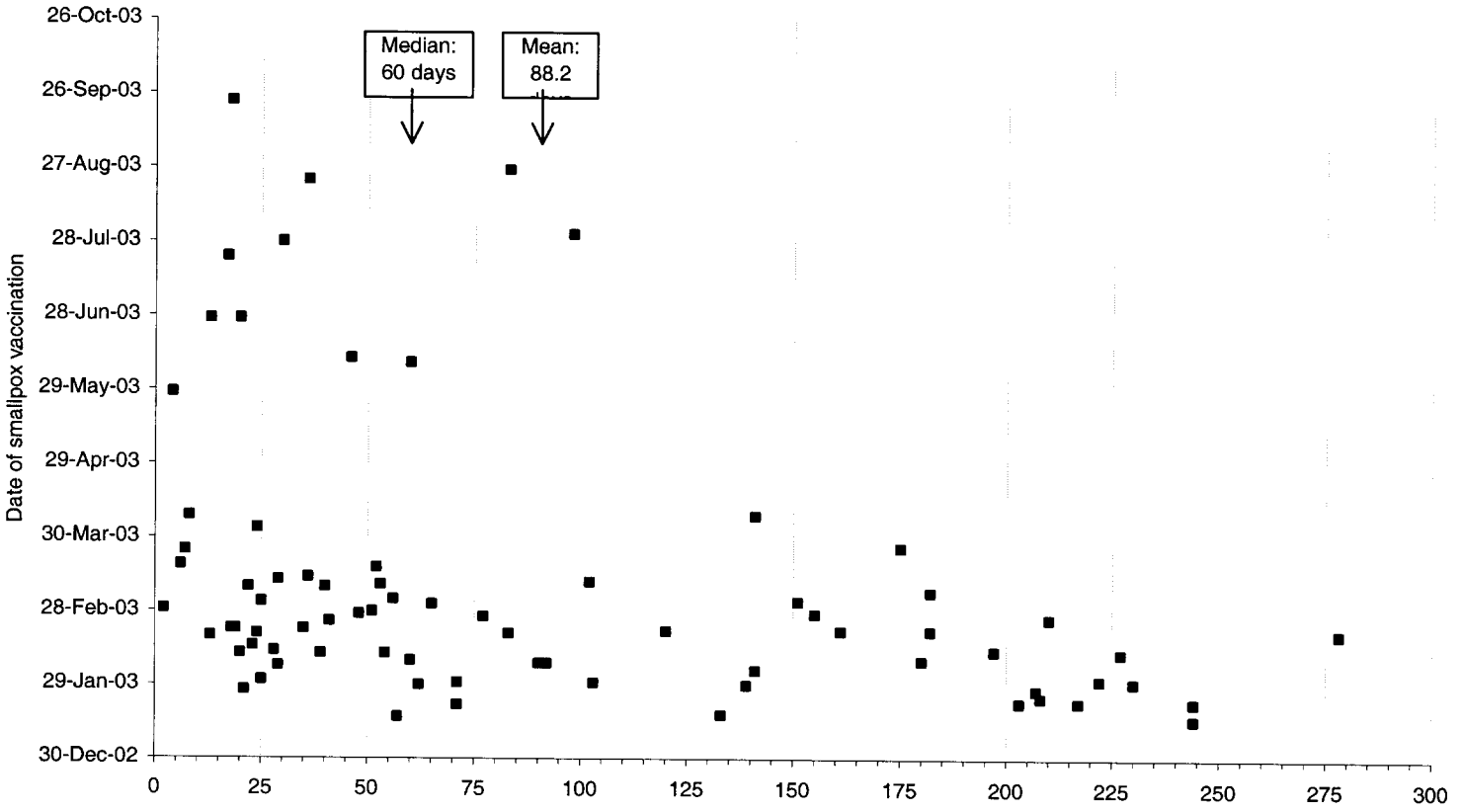
Source: DMSS

December 24, 2003

[1] Defense Medical Surveillance System – DMSS - This system integrates data from sources worldwide in an expanding relational database of military and medical experiences of personnel throughout their careers. It allows prompt morbidity assessments of those who share common characteristics such as vaccinations. Personnel data in DMSS are obtained from the Defense Manpower Data Center (Monterey Bay, CA), including demographic data (age, gender, race) and service-related data (such as date of entry into service, date of separation from service, and occupation).

DMSS records were searched to identify servicemembers with reported diagnoses of cardiomyopathy (n=1390); and among them, those who had records of smallpox vaccination prior to their first diagnoses of cardiomyopathy (n=82; 6% of the total). Among those who had first diagnoses after a smallpox vaccination, intervals (days) were calculated between the two events. The mean interval was 303 days. These data are skewed by four cases among individuals vaccinated prior to the current vaccination program (mean interval 4,502 days). When these four cases are excluded (smallpox vaccination after 1 January 2003), the mean interval from vaccination to diagnosis is 88.2 and the median is 60 days. Results are summarized in graphical form below.

Days from smallpox vaccination (after 1 January 2003) to first diagnosis of "dilated cardiomyopathy", active duty, US Armed Forces



Source: AMSA/DMSS, 6 Jan 2004

For three service members identified by report to the Vaccine Adverse Events Reporting System (VAERS) who were known to have dilated cardiomyopathy after smallpox vaccination, hospitalization and ambulatory records in the electronic database were reviewed to identify relevant medical encounters. These data are provided below. Importantly, for the two cases, which had records available, the diagnosis was recorded as ICD-9-CM 425.4, one of the ICD-9-CM codes used in this analysis. As of the date of the review, one of the individuals did not have a record of cardiomyopathy diagnosis – perhaps due to the lag in reporting of hospitalization records to the Army Medical Surveillance Activity.

Abstracts of records of medical encounters of selected patients

Initials Last 4	Date of smallpox vaccination	Type of care	Date of med care	Primary diagnosis
	3/6/2003	Hospitalization	8/11/2003	4254 (oth primary cardiomyopathy)
		Hospitalization	8/14/2003	4280 (congestive heart failure)
		Hospitalization	8/17/2003	4254 (oth primary cardiomyopathy)
	3/14/2003	Ambulatory	8/28/2003	7802 (syncope and collapse)
		Ambulatory	9/2/2003	78659 (chest pain, other)
		Ambulatory	9/5/2003	78650 (chest pain, unspec)
		Ambulatory	9/8/2003	7802 (syncope and collapse)
		Ambulatory	9/9/2003	4254 (oth primary cardiomyopathy)
		Ambulatory	10/20/2003	4259 (second'y cardiomyopathy, unspec)
	9/12/2003	Ambulatory	11/3/2003	79431(abn ECG)

Source: AMSA, DMSS (6 Jan 2004)

From review of the medical literature, the most common causes of dilated cardiomyopathy are idiopathic origin (47%), idiopathic myocarditis (12%) and coronary artery disease (11%). The other identifiable causes of dilated cardiomyopathy make up 31% of the total cases.[2] The published risk factors associated with dilated cardiomyopathy include diabetes, asthma, atopic diseases, hypertension, obesity, cigarette smoking and moderate alcohol consumption.[3] The prevalence of dilated cardiomyopathy is estimated at 36.5 per 100,000

[2] The causes of dilated cardiomyopathy: A clinicopathologic review of 673 consecutive patients. Kasper EK, Agema WR, Hutchins GM, Deckers JW, Hare JM, Baughman KL. Division of Cardiology, Johns Hopkins Medical Institutions, Baltimore, Maryland.

[3] Prevalence and etiology of idiopathic dilated cardiomyopathy (summary of a National Heart, Lung, and Blood Institute workshop. Manolio TA, Baughman KL, Rodeheffer R, Pearson TA, Bristow JD, Michels VV, Abelmann WH, Harlan WR. Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20892.

with an incidence estimated at 8 cases per 100,00 per year. The prevalence of DCM in persons less than 55 years old is estimated at 17.9 per 100,000.[4]

It is not unexpected to find the observed:expected age-stratified group-specific ratios of cardiomyopathy among smallpox vaccinees of 0.0 to 0.6. The vaccinees are likely healthier than non-vaccinees (the previously described "healthy warrior effect"). The data presented above support a conclusion that there does not appear to be an elevated incidence of cardiomyopathy after smallpox vaccination among US Armed Forces personnel who received smallpox vaccine (136,478.7 person-years of observation) compared to US Armed Forces personnel who did not receive smallpox vaccine (2,375,347.2 person-years of observation).

This conclusion is limited by both diagnostic accuracy and recording and 4-digit ICD-9-CM code analysis (cases include all diagnosis of ICD-9-CM 429.3, cardiomegaly and ICD-9-CM 425.4, other primary cardiomyopathies). Additional limitations include reporting lag, the global migration of over 200,000 troops to a theater of war, potential limited electronic capture of ambulatory visits within that theater, and incomplete electronic recording of vaccinations administered in that theater.

Strengths of this analysis include a median follow-up of 11 months (for more than 225,000 smallpox-vaccinated individuals), follow-up of at least 6 months (for more than 470,000 vaccinated individuals), and follow-up of at least 3 months (for more than 500,000 vaccinated individuals.

[4] Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984. Codd MB, Sugrue DD, Gersh BJ, Melton LJ 3rd. Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905.