United States Smallpox Vaccine Safety: Past, Present and Future

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Smallpox Vaccination Timeline

- **1960s:** US: Landmark Neff/Lane Surveys
- **1972:** US: Routine Childhood vaccination stopped
- **1976**: US: Routine HCW vaccinations stopped
- **1977:** Global: Last naturally occurring smallpox case (Somalia)
- **1980**: Global: WHO declared Smallpox eradicated

Smallpox Vaccination Timeline (2)

- **1982:** Global: Int'l travel req lifted
  US: vaccine production halted
- **1984:** US: Military program restricted to basic training settings
- **1990:** US: Military recruit immunization discontinued
- **1990-pres** US: Laboratorians targeted





Smallpox Vaccination Timeline (3)

- **2001 (June)** – ACIP recommendations updated for laboratorians and included new guidelines for bioterrorism preparedness
- **2002 (June)** – ACIP updated recommendations for Smallpox Response Teams
- **2002 (Dec)** - Military vaccination program began: HCW, response teams and operational personnel
- **2003 (Jan)** – Civilian voluntary program began: smallpox response teams

Routine US Smallpox Immunization: 1960s

- ~14 million vaccinees / year
  - **Childhood, International Travelers, HCW, military**
- Setting of frequent revaccinations and limited screening
- Passive reporting: Lane/Neff National surveys
    - **VIG release**
- Active Surveillance: Lane (10) / Neff (4) State surveys
    - **provider questionnaires, telephone interview**
- Risk / benefit assessment led to cessation of routine childhood SP vaccination program

Neff/Lane Landmark Surveys

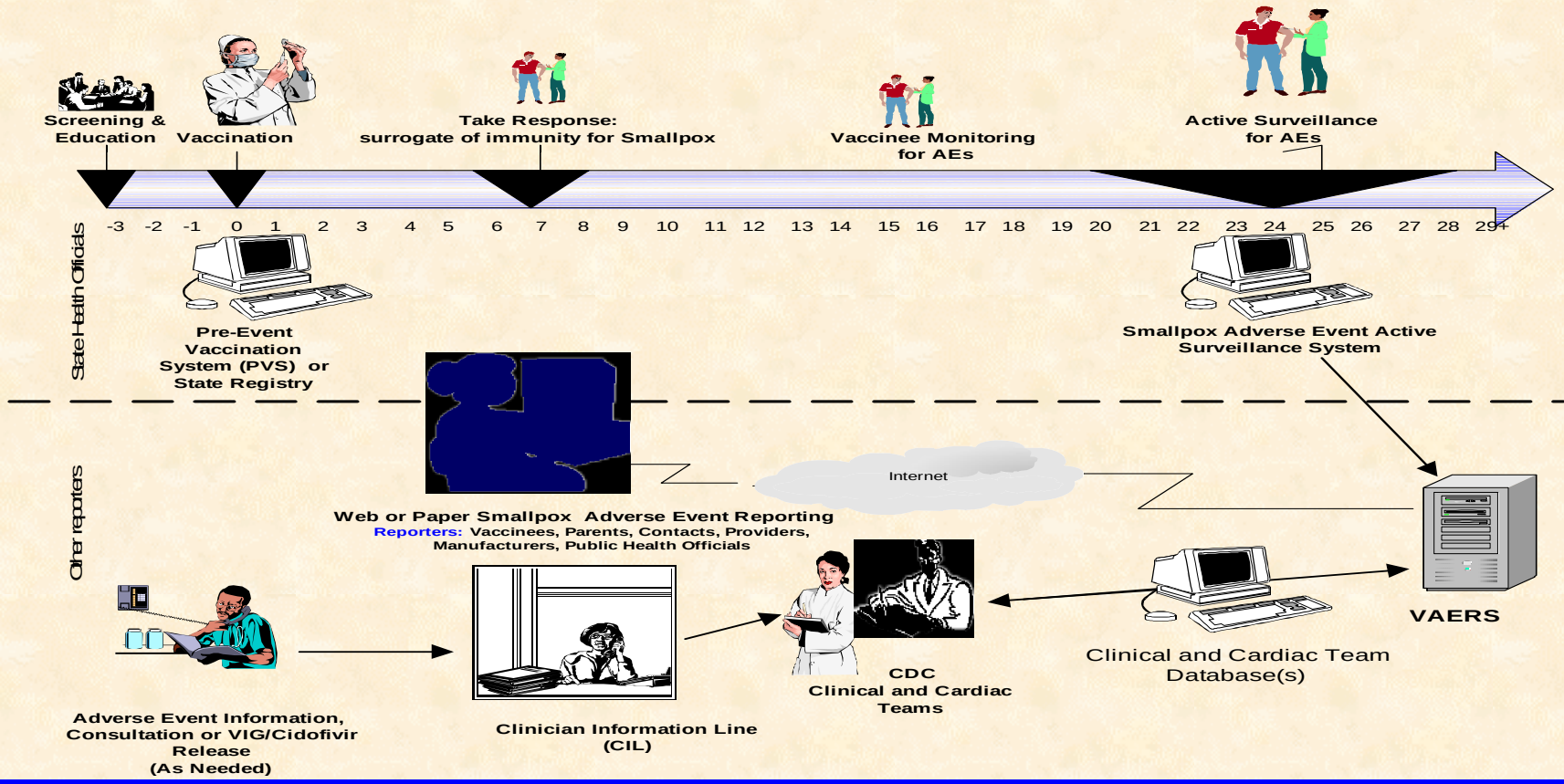
TABLE 1. Smallpox vaccine adverse event rates (number per million vaccinees) — United States, 1968

	National survey		10-state survey	
	All primary (i.e., first-time) vaccinees	Vaccinees aged ≥1 yr	All primary (i.e., first-time) vaccinees	Vaccinees aged ≥1 yr
Serious, but not life-threatening reactions				
Inadvertent inoculation	25.4	27.1	529.2	532.0
Generalized vaccinia	23.4	17.7	241.5	222.8
Erythema multiforme	NA*	NA	164.6	131.3
Total number of serious, but not life-threatening reactions	**48.8**		**935.3**	
Life-threatening reactions				
Postvaccinal encephalitis/encephalomyelitis	2.9	2.4	12.3	8.6
Progressive vaccinia (vaccinia necrosum)	0.9	1.0	1.5	1.7
Eczema vaccinatum	10.4	10.6	38.5	41.5
Total number of life-threatening reactions	**14.2**		**52.3**	
Deaths	1.1	0.6	1.5	NR†

* Not available.
† None reported.

Source: CDC. Smallpox adverse event rates, 1968. Atlanta, GA: US Department of Health and Human Services, CDC, 2002. Available at http://www.bt.cdc.gov/agent/smallpox/vaccine-safety/adverse-events-chart.asp.

US Smallpox Vaccine Adverse Events: Surveillance system overview



Surveillance System Overview

Pre-event Vaccination System (PVS)

- Vaccination clinic or hospital based monitoring system of the vaccination process
- Entry point into Surveillance system for all civilian vaccinees
- Collects vaccine information, and smallpox vaccinee demographics, vaccination history and take response.
- Web-based or reported through existing state registries

Surveillance System Overview (2)

Vaccine Adverse Event Reporting System (VAERS)

- An established national passive surveillance system for AEs following vaccination co-managed by the CDC and Food and Drug Administration (FDA)
- Stimulated reporting via state-based adverse events surveillance coordinators
- Standardized review of all smallpox AE reports
- Web or paper based

Surveillance System Overview (3)

Clinician Information Line (CIL)

- A new CDC bioterrorism initiative to provide smallpox AE consultation to clinician and public health officials
- Collects reports via telephone (24 hours/day 7days/week); refers complex cases to the CDC Clinical Team
- Data stored in Clinical team database; matched with VAERS reports
- Potential for expansion to other bioterrorism agents or emerging infectious diseases (e.g., SARS)

Surveillance System Overview (4)

Active Surveillance System

- State based monitoring system for all smallpox civilian vaccinees
- Collects potential adverse events information
  - **Vaccinees and contacts, Contraindications, Cardiac risk factors**
- Monitoring system recommended by the Institute of Medicine [January 2003]
- Web-based data entry at vaccination clinic/hospital monitoring sites and/or state AE coordinator between day 21-28 post-vaccination.

Surveillance System Overview (5)

- Pregnancy registry: inadvertent exposure to smallpox vaccine
  - Vaccination
  - Contact transmission
  - Pregnant within 28 d of vaccination or contact
- Voluntary hospital-based site care surveillance [HSVMS]
- Telephone Survey: 10 and 21 day follow-up (8 states, controls included)

SMALLPOX PRE-EVENT VACCINATION PROGRAM EXTERNAL REVIEWERS





Institute of Medicine

- Advises CDC and program managers on selected aspects of pre-event smallpox vaccination program implementation
  - **Screening, AEs, Data Collection**
  - **Informed Consent, Training, Communication**
  - **Implementation plans and goal milestones**
- Called for Active Surveillance (Jan 2003)
- Called for program pause (June 2003)

Joint Smallpox Vaccine Safety Working Group (SVS WG) of the Advisory Committee on Immunization Practices (ACIP) and the Armed Forces Epidemiology Board (AFEB)

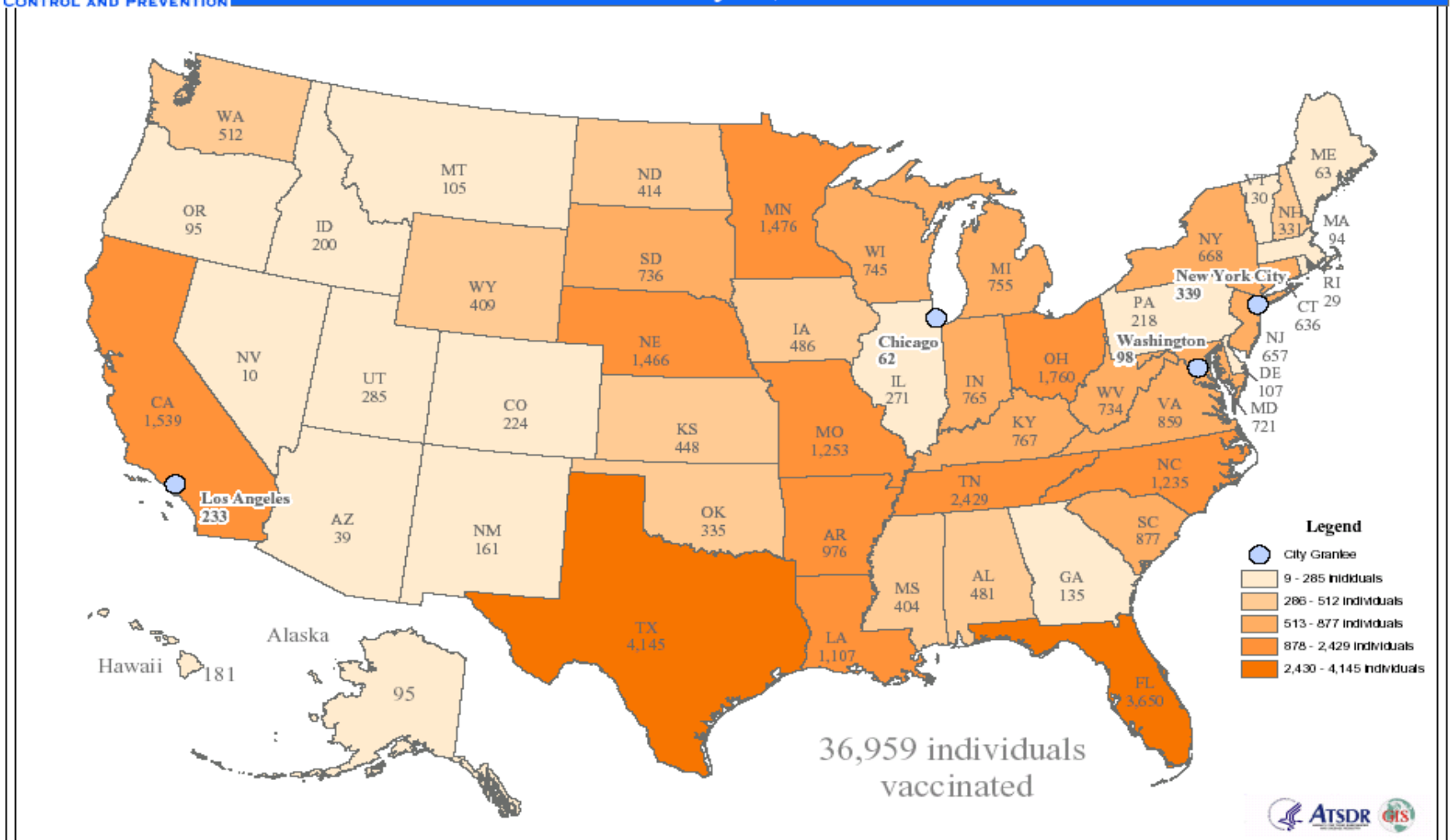
- Responsible for joint military-civilian safety oversight
  - Weekly review of AE monitoring and reports
  - Case definitions
  - VIG or cidofovir release under IND
- Identifies action "trigger thresholds" and appropriate response
  - Cardiac events [March 2003]
  - Options for ACIP consideration regarding program continuance [June 18, 2003]

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

National Immunization Program

Number of Individuals Vaccinated

As of May 23, 2003



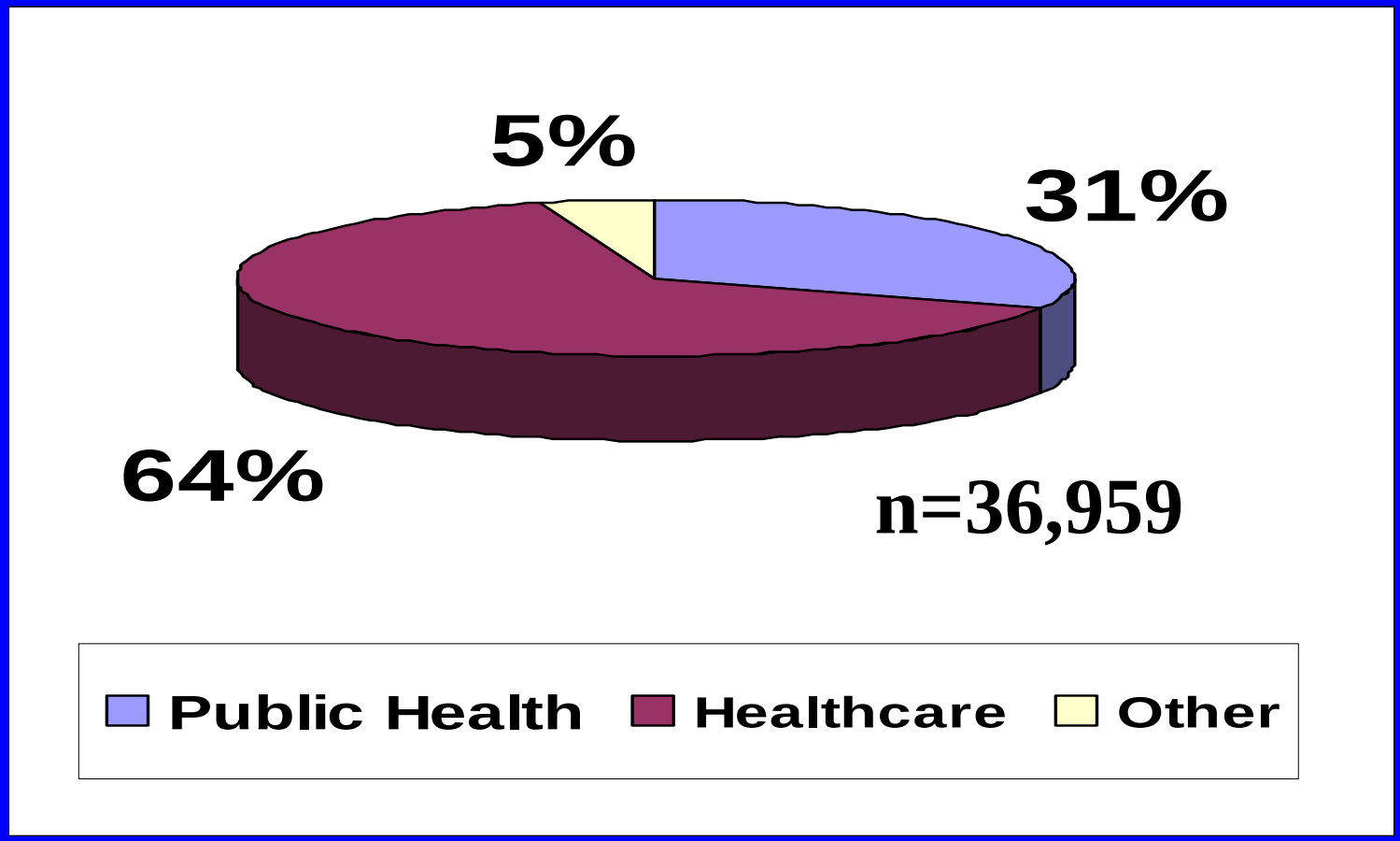
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

CDC Immunization

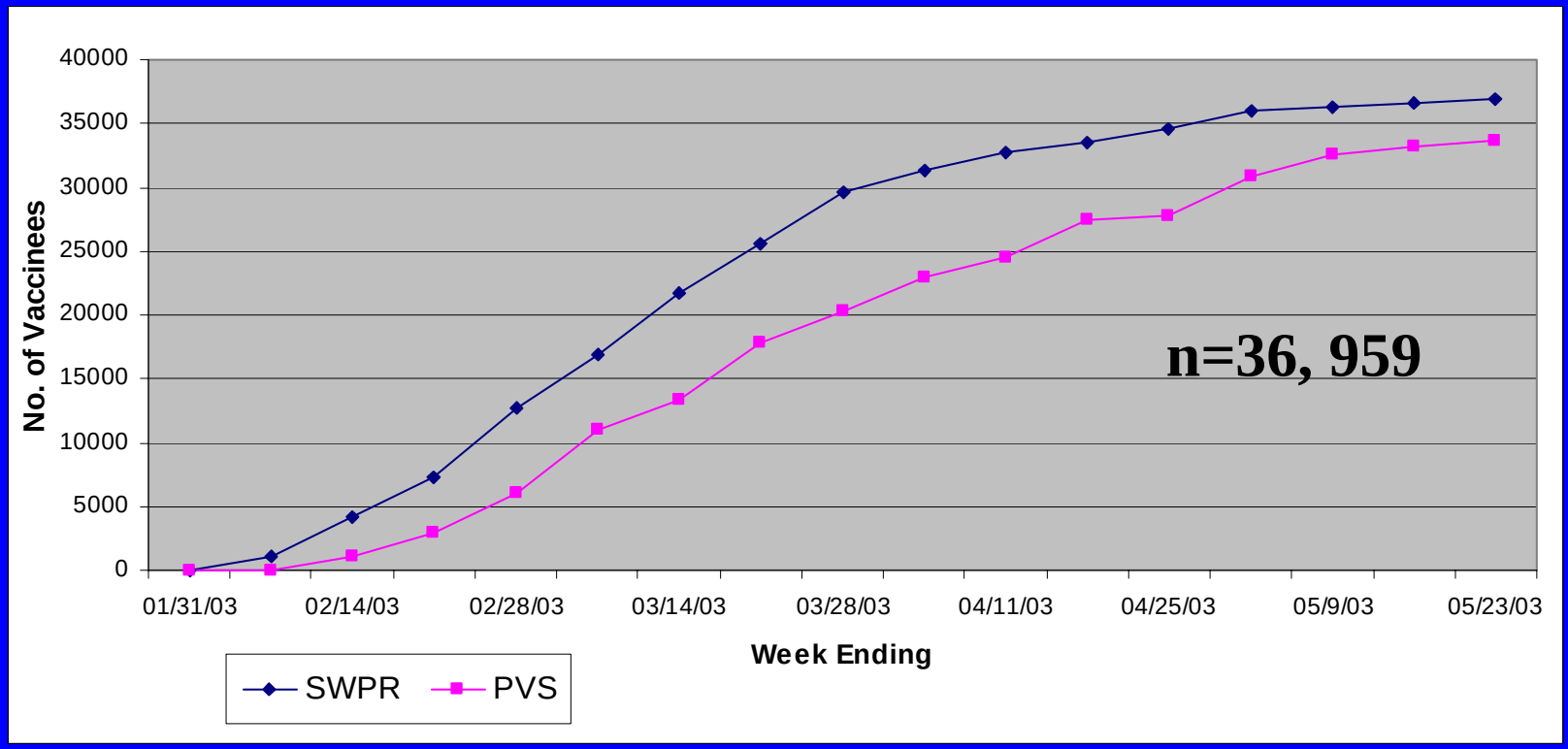
Cumulative Count of Civilian Smallpox Vaccinations (by type of response team)

Jan 24-May 23, 2003



Cumulative Count of Smallpox Vaccinations by Data Source

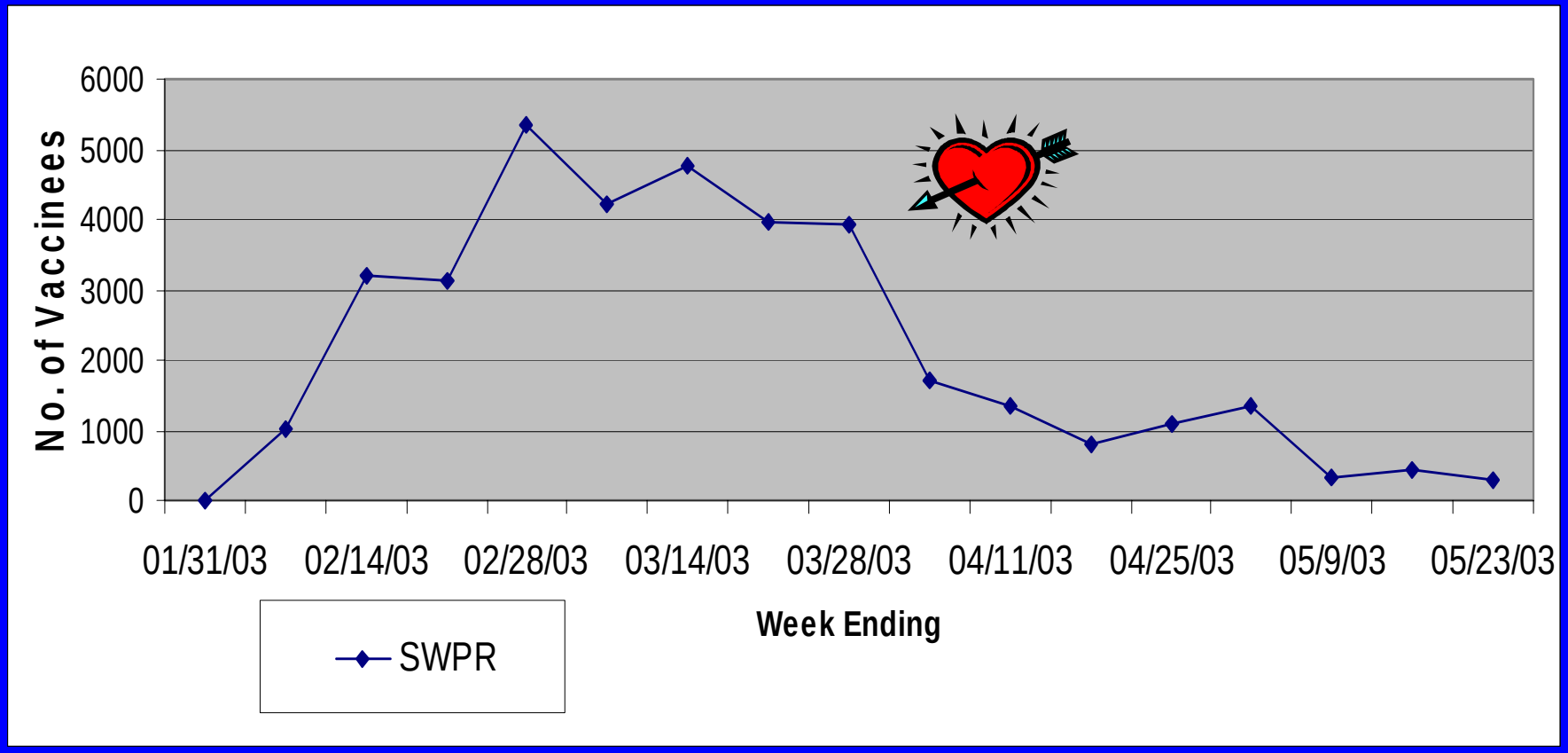
[Jan 24- May 23, 2003]



SWPR: smallpox weekly progress report
PVS: Pre-event Vaccination System

Smallpox Vaccinations by week

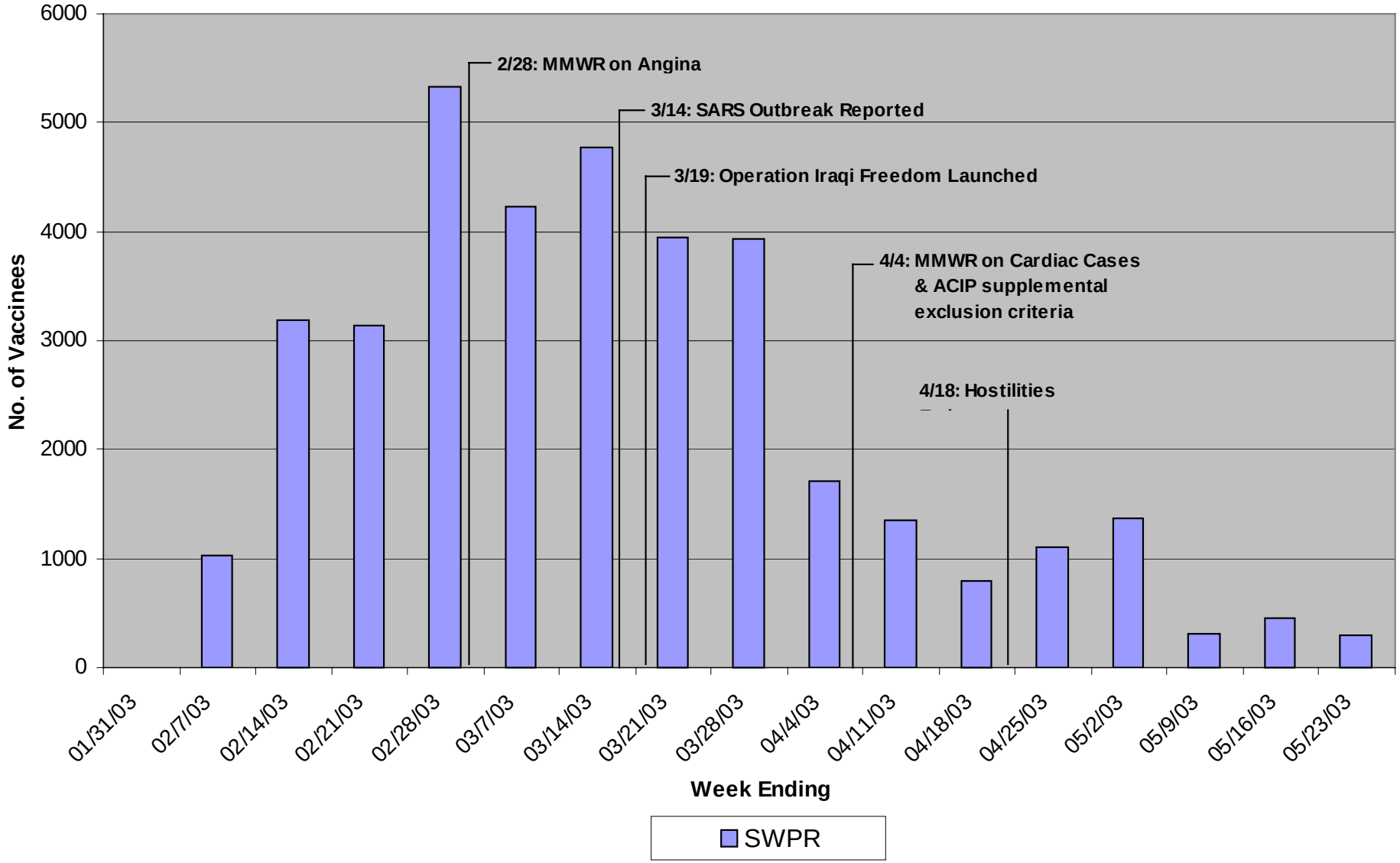
[Jan 24-May 23, 2003]



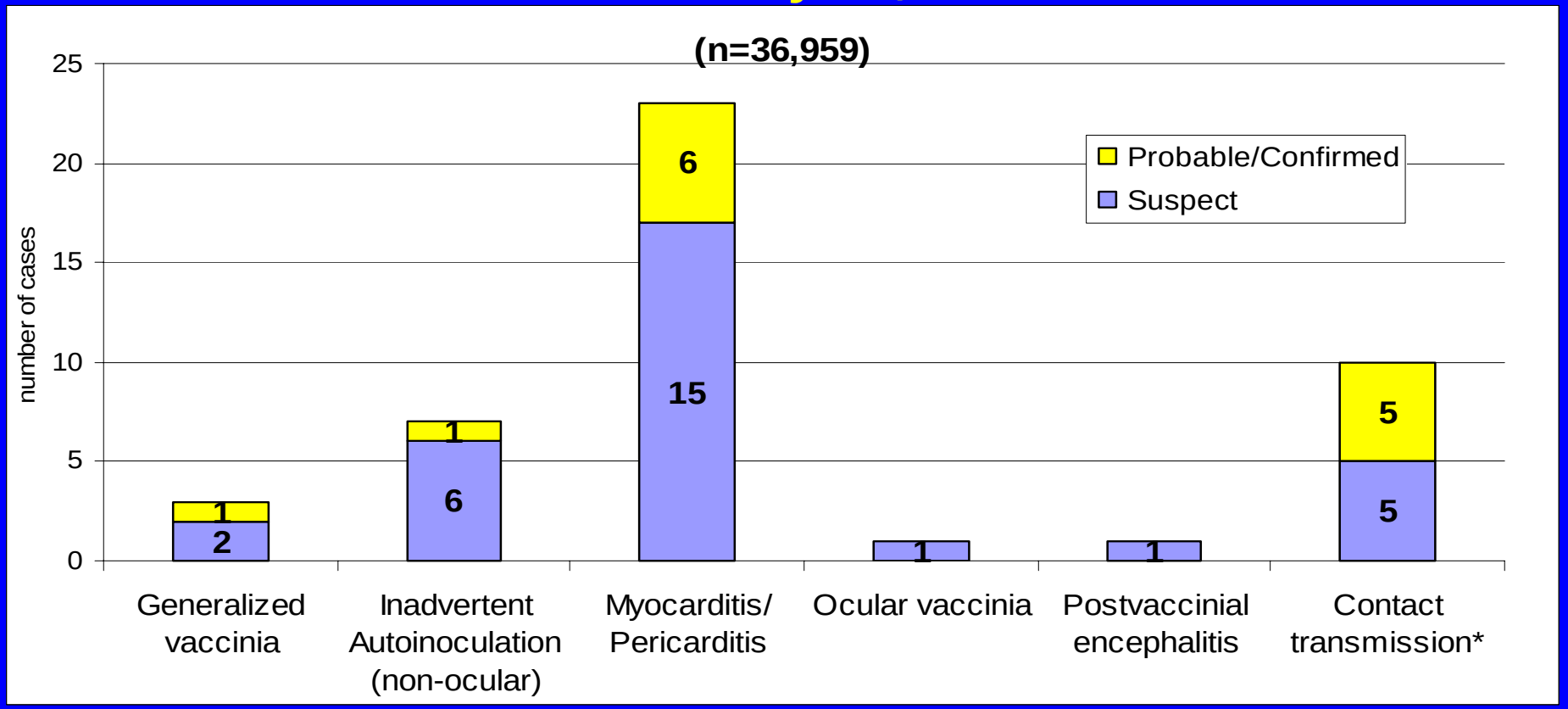
: Cardiac Events, societal influences

SWPR: smallpox weekly progress report

Smallpox Weekly Progress Report (SWPR)
Weekly Count of Vaccinations



DRAFT: Numbers of Smallpox Adverse Events reported to VAERS and CDC Clinical team Jan 24-May 23, 2003



*all reported contact transmission cases are military to civilian (includes two confirmed ocular cases)

There are no reports of Eczema Vaccinatum, Erythema Multiforme Major (SJS), Fetal Vaccinia, or Progressive Vaccinia

DRAFT: Inadvertent inoculation, non-ocular: breakdown civilian / military

- 12 suspected:
  - 7 autoinoculation (all civilian)
  - 5 contact transmission (all military to civilian)
- 6 confirmed:
    - 1 autoinoculation
    - 5 contact transmission (all military to civilian)
- No reported cases of civilian-to-civilian contact transmission
- No reported cases of nosocomial transmission

DRAFT: Adverse events after smallpox vaccination among US civilians Jan 24–May 23 (n=36,959)

Other events of concern	Total no. of cases
Other serious adverse events	66
Other non-serious adverse events	557
Vaccinia immune globulin release	1
Vaccinia transmission to contacts	0

US Military Smallpox Vaccination Program (through 3 Jun 03):

- Vaccinated: 457, 598 (screened: 549,118)
  - 71% Primary 29% Revaccinees
  - 96% Major reaction for both groups
  - Male: 87%. Female: 13%
- Exemption
  - Personal: 4.9-7.8%.
  - Personal + household: 11% to 34%
- Sick leave (average 1.5 days)
  - Hospital staff: 3%.
  - In theater: 0.5%.

US Military Smallpox vaccine AEs: Summary Data through June 3, 2003

Auto-inoculation	48 cases (10 ocular)
Contact Transmission	19 cases (2 ocular)
Generalized vaccinia	36 cases
Treatments with vaccinia immune globulin (VIG)	2 cases [prophylactic burn and ocular]
Post-vaccinial encephalitis/encephalopathy	1 case (recovered)
Severe reactions (e.g., eczema vaccinatum, progressive vaccinia)	0 cases
Myopericarditis	1-suspect; 35-probable; 1-confirmed

Cardiac Events following smallpox vaccination: March 2003

- ACIP SVS wg reviewed military data for myo/pericarditis which indicated observed rate exceeded background rate [March 2003]
- Ischemic events initially not thought to exceed expected background rates
- Interim ACIP recommendations for vaccination deferral for known cardiac disease or >3 cardiac risk factors *(see CDC patient education fact sheet)*
- No ischemic cases have occurred after interim ACIP recommendations

Smallpox Vaccination: Summary of Cardiac Events*

- M/P following SP vaccination is consistent with previous reports describing a likely causal relationship
- M/P Civilian rate > M/P military rate but approximates (1:36,000) when comparing only cases with elevated cardiac enzymes
- The association between ischemic cardiac events and SP vaccination is unclear

*** MMWR 2003 52(21);492-496**

US Civilian Cardiac Events: Myo/pericarditis*

- Suspect/Probable myo/pericarditis [M/P] for known data:
  - symptom onset within 1-42 days post-vaccination: median 12 days
  - 90% revac; 71% female
  - 29% ECHO had positive findings
  - 29% ER evaluation; 52% hospitalized

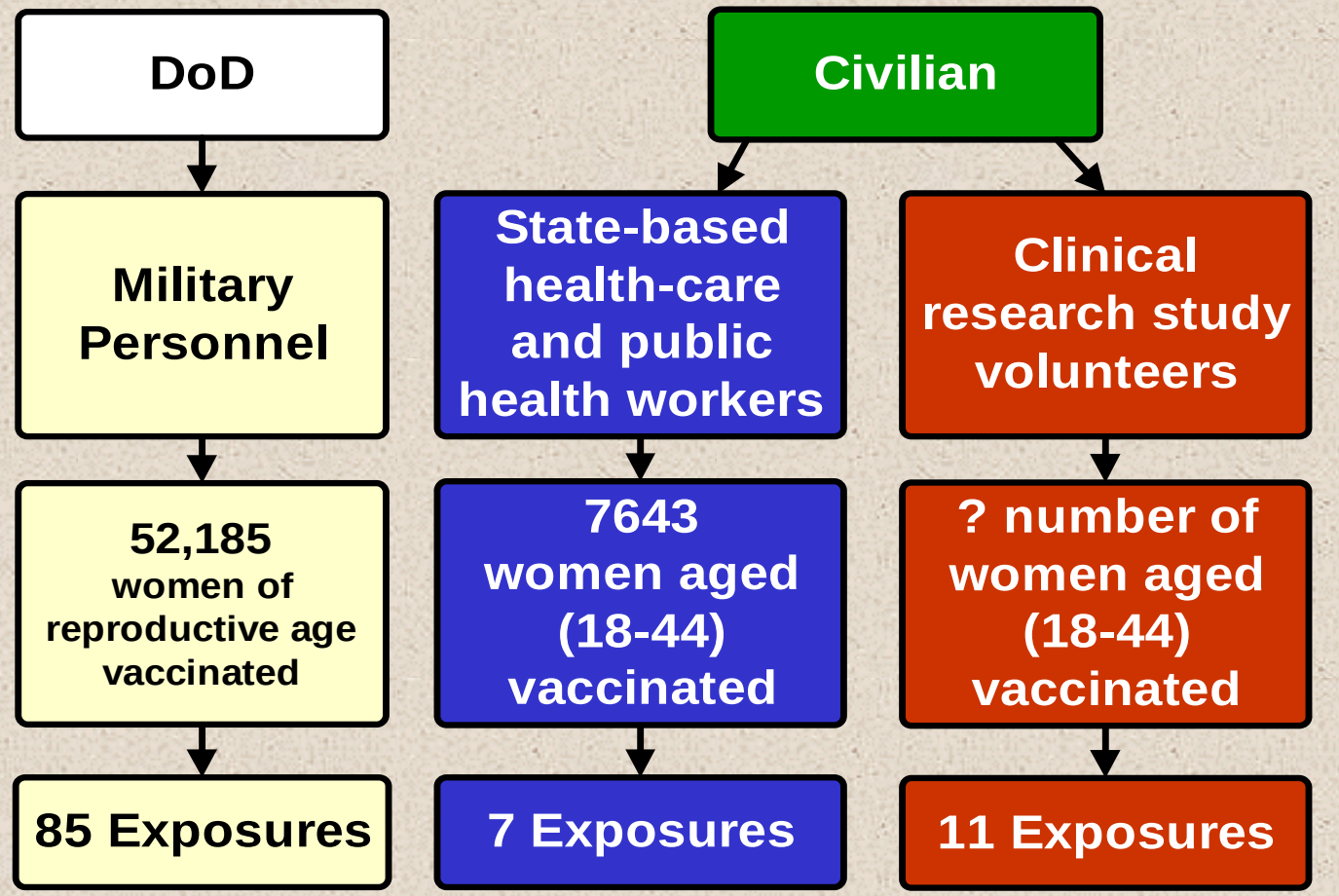
* MMWR 2003 52(21);492-496

US Civilian Cardiac Events: Ischemia*

- 9 cases: (six MI and three angina)
- Age range 46-56 (median 57)
- 2 deaths (females 57 yrs)
- Median symptom onset: 10 days
- 67% would have been excluded from vaccination by new deferral criteria
- No significant statistical difference between observed MI / angina rates and expected baseline rates for equivalent population

*** MMWR 2003 52(21);492-496**

Women Reported to the National Smallpox Vaccine in Pregnancy Registry as of May 2003*



* MMWR 52(17)386-388

Preliminary Pregnancy Registry Data

Estimated rate of exposure to smallpox vaccine during pregnancy in the absence of screening among women of reproductive age*

Civilian vaccinees	General Population
8 per 1,000	12 per 1,000

Observed rate of inadvertent exposure to smallpox vaccine during pregnancy among vaccinated women of reproductive age*

Civilian vaccinees	Military vaccinees
1 per 1,000	1.5 per 1,000

*age 18-44

US Smallpox Vaccination Program: Summary

- Rates for Expected AEs are at or below the reported historical rates
- Cardiac events not previously reported in historical US surveillance surveys: need further investigation to assess causality, recommend standardized follow-up and new studies
- Evaluation of screening and educational efforts

NEXT STEPS

- Await ACIP recommendations
- CDC program
  - Analysis of active surveillance data for cardiac risk factors and AE outcome
  - Contraindications registry
  - VIG / Cidofovir release
  - VAERS reports
  - Continued Active Surveillance
- Military program
  - Maintenance vaccination
  - Continued prospective evaluation of myo/pericarditis cases

NEXT STEPS (2)

- Cardiac investigations
  - Continue case surveillance
  - Follow-up of known cases
  - Potential prospective myo/pericarditis study (serial ECGs, cardiac enzymes, cytokines)
  - Guidelines for prospective evaluation of persons with cardiac events

Lessons Learned

- Successful implementation of bioterrorism vaccination program on compressed timeline using existing resources
- Successful cooperation between US government entities
- Successful partnership with stakeholders (e.g., state health departments, specialty societies)

Lessons Learned (2)

- Novel use of established vaccine safety infrastructure (e.g., VAERS)
- Rapid creation and integration of multiple surveillance systems
- New national consultative service
- Rapid communication and implementation of interim recommendations for vaccination deferral

Lessons Learned (3)

- Signal detection (e.g., cardiac events) leading to programmatic response and policy formation
  - Cardiac events previously reported (Europe & Australia)
  - Not expected at this rate using NYCBOH strain
- Causality Assessment – pending
- Denominator dilemma
  - # vaccinated vs. % major reaction

Lessons Learned (4)

- Harmonized Training: CDC response teams, State AE Coordinators, CIL, CDC Clinical Team, VHC, DoD Providers
- Interpretation of Vaccination Response – initially problematic
- Recommended interval of revaccination in the setting of an equivocal reaction

Interesting Clinical Observations: Potential for future study

- Local reactions at vaccination site:
  - Pustules at vaccination site (typically >2-4 weeks after scab separation)
  - Keloid formation
- Delayed scab separation: >8 weeks
- Diagnosis of malignancy post-vaccination
- Reactivation of HSV / VZV
- Provider empiric antibiotic treatment for robust take
- Post-vaccination headache common, sometimes severe

Website resources

CDC:

http://www.bt.cdc.gov/agent/smallpox/index.asp

DoD:

www.smallpox.mil

IOM:

http://www.iom.edu/IOM/IOMHome.nsf/Pages/Smallpox+Vaccination

ACIP:

http://www.cdc.gov/nip/ACIP/default.htm

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- Centers for Disease Control and Prevention
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- Food and Drug Administration
- National Institute of Health
- Department of Defense
  - Military Vaccine Agency
  - Armed Forces Epidemiology Board
  - Vaccine Health Care Centers
  - Walter Reed Army Medical Center, Departments of Dermatology, Cardiology and Neurology
  - US Army Medical Research Institute of Infectious Diseases
- State Health Departments
- Smallpox Eradication Experts
- Epidemiology, Public Health and Clinical Specialty Societies
- US Government Contractors





Legend for Acronyms

ACIP-Advisory Committee for Immunization Practices

AE-Adverse Event

AFEB-Armed Forces Epidemiology Board

BPRP-Bioterrorism Preparedness and Response Program (CDC)

CDC-Centers for Disease Control and Prevention

DoD-Department of Defense

ECG-electrocardiogram

ECHO-echocardiogram

ER-Emergency Room

HCW-Health Care Workers

HSV-Herpes Simplex Virus

Legend for Acronyms (2)

HSVMS-Hospital Smallpox Vaccine Monitoring System

IOM-Institute of Medicine

IRMO-Information Resources and Management Organization (CDC)

JIC-Joint Information Center (NIP and OPTER)

M/P-myo/pericarditis

MI-Myocardial Infarction

NICD-National Center for Infectious Diseases (CDC)

NIP-National Immunization Program (CDC)

NYCBOH-New York City Board of Health: vaccinia strain

OC-Office of Communications

Legend for Acronyms (3)

OTPER-Office of Terrorism Preparedness and Emergency Response (CDC)

PVS-Pre-event Vaccination System

SP-Smallpox

SWPR-Smallpox Weekly Progress Report

SVS wg- Joint Smallpox Vaccine Safety work group

US-United States

VAERS-Vaccine Adverse Event Reporting System

VHC-Vaccine Healthcare Centers

VIG-Vaccinia immune globulin

VZV-Varicella virus

WHO-World Health Organization