

# 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 $\geq 1$ yr	All primary (i.e., first-time) vaccinees	Vaccinees aged $\geq 1$ yr
<b>Serious, but not life-threatening reactions</b>				
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
<b>Total number of serious, but not life-threatening reactions</b>	<b>48.8</b>		<b>935.3</b>	
<b>Life-threatening reactions</b>				
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
<b>Total number of life-threatening reactions</b>	<b>14.2</b>		<b>52.3</b>	
<b>Deaths</b>	<b>1.1</b>	<b>0.6</b>	<b>1.5</b>	<b>NR†</b>

\* Not available.

† None reported.

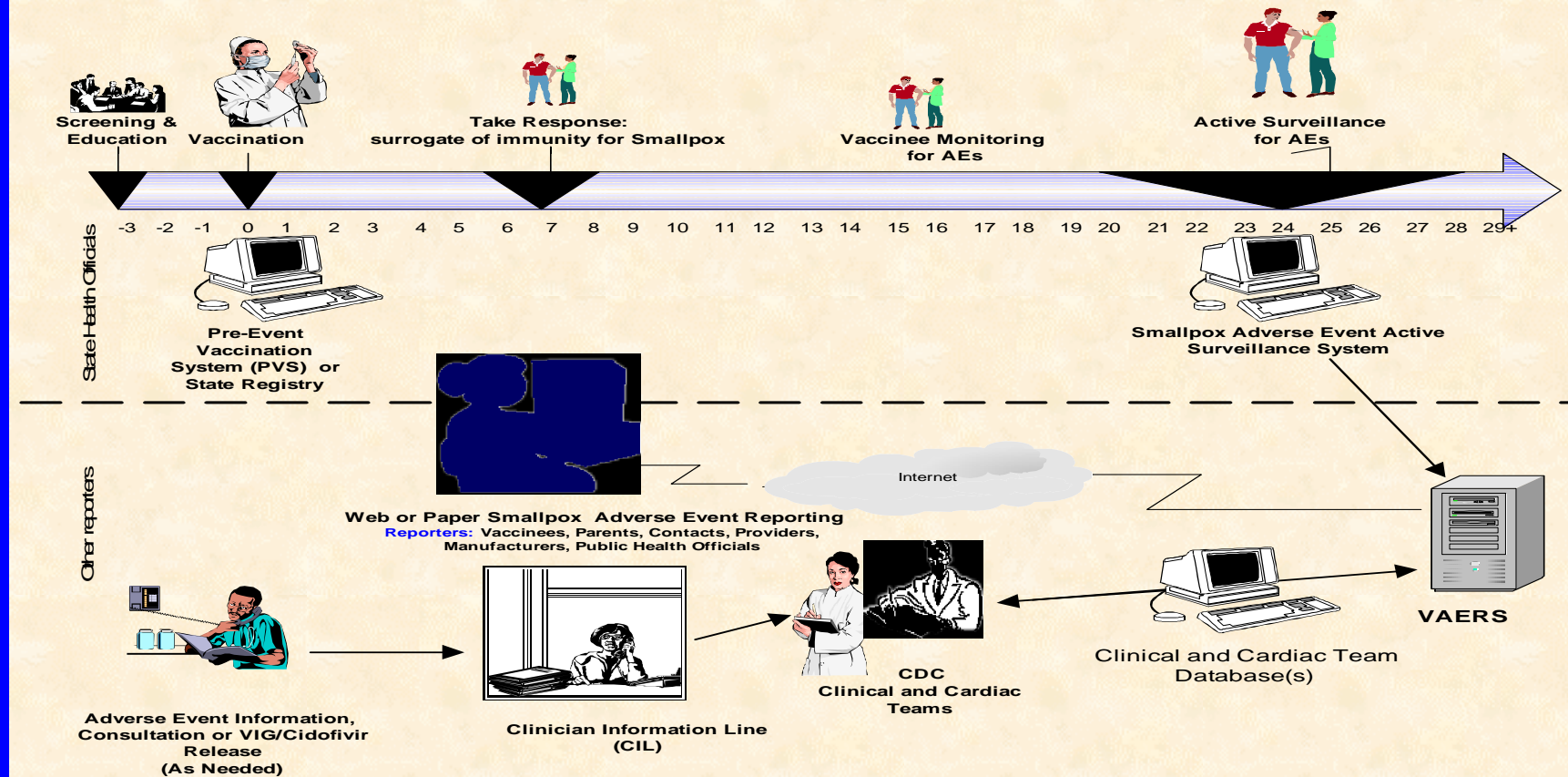
Source: CDC. Smallpox adverse event rates, 1968. Atlanta, GA: US Department of Health and Human Services, CDC, 2002. Available at <http://www.bt.cdc.gov/agent/smallpox/vaccine-safety/adverse-events-chart.asp>.



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# US Smallpox Vaccine Adverse Events: Surveillance system overview



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# 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



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# 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)



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## **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]



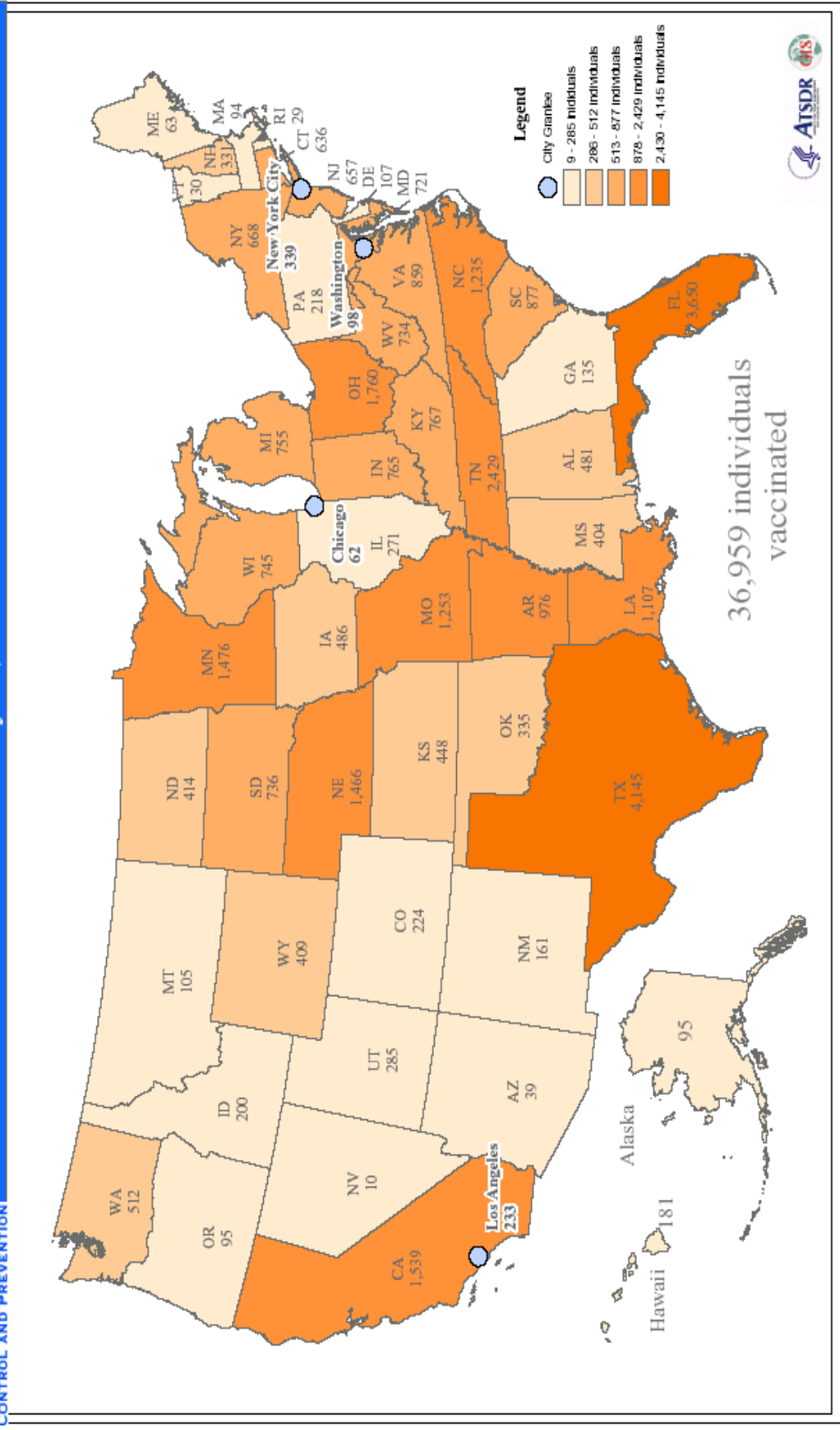


CENTERS FOR DISEASE CONTROL AND PREVENTION

National Immunization Program

# Number of Individuals Vaccinated

As of May 23, 2003

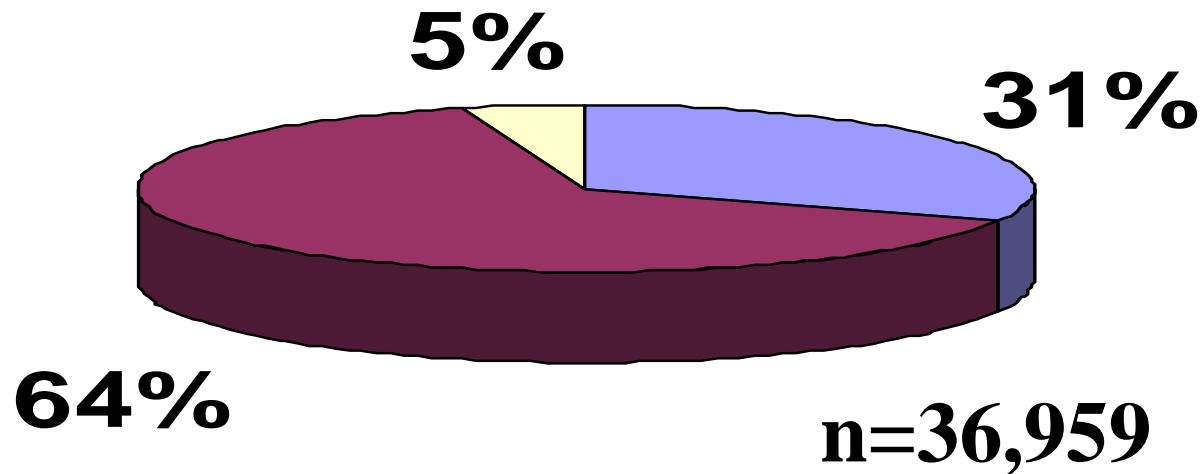


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# Cumulative Count of Civilian Smallpox Vaccinations (by type of response team) Jan 24-May 23, 2003



Public Health Healthcare Other

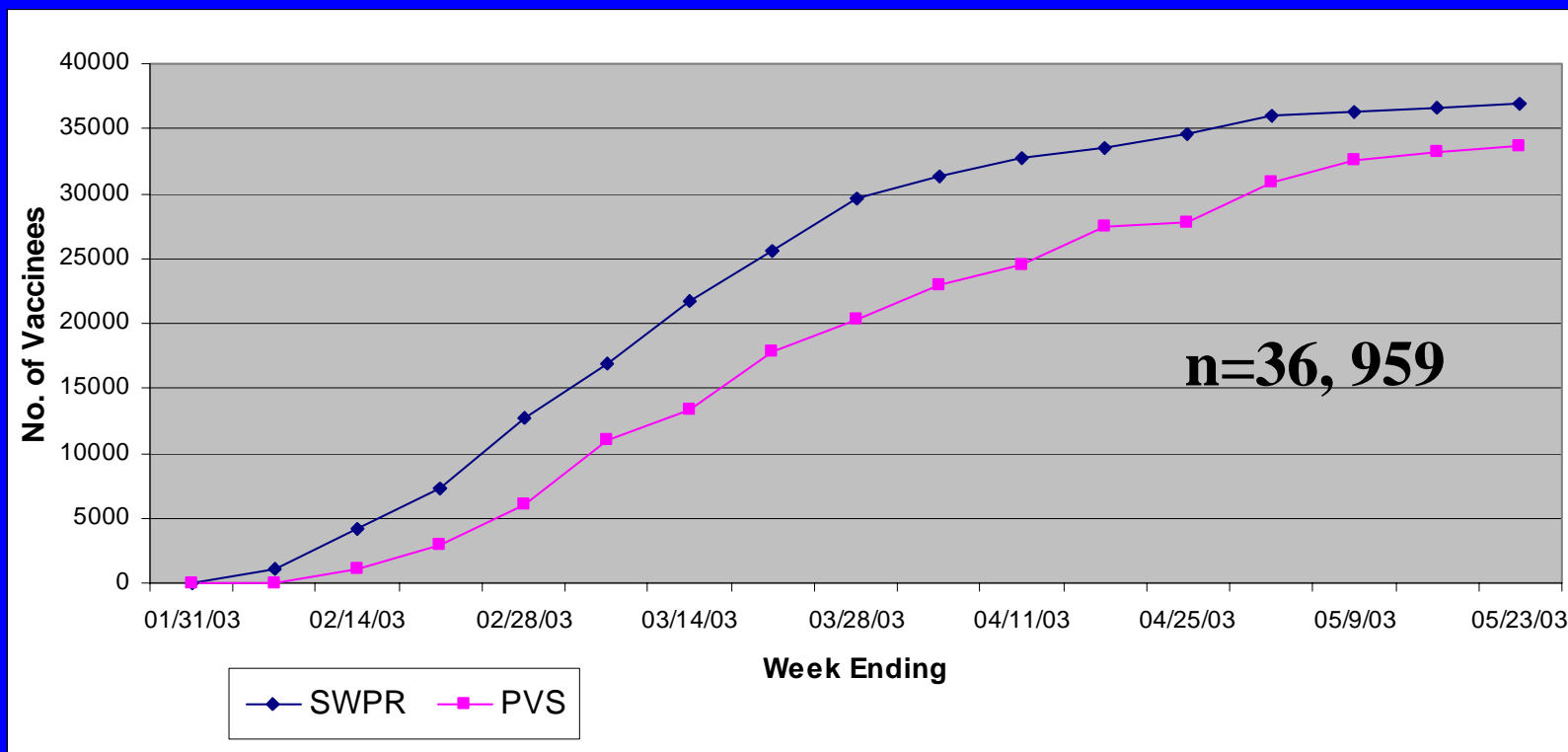


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# Cumulative Count of Smallpox Vaccinations by Data Source

[Jan 24- May 23, 2003]



SWPR: smallpox weekly progress report

PVS: Pre-event Vaccination System

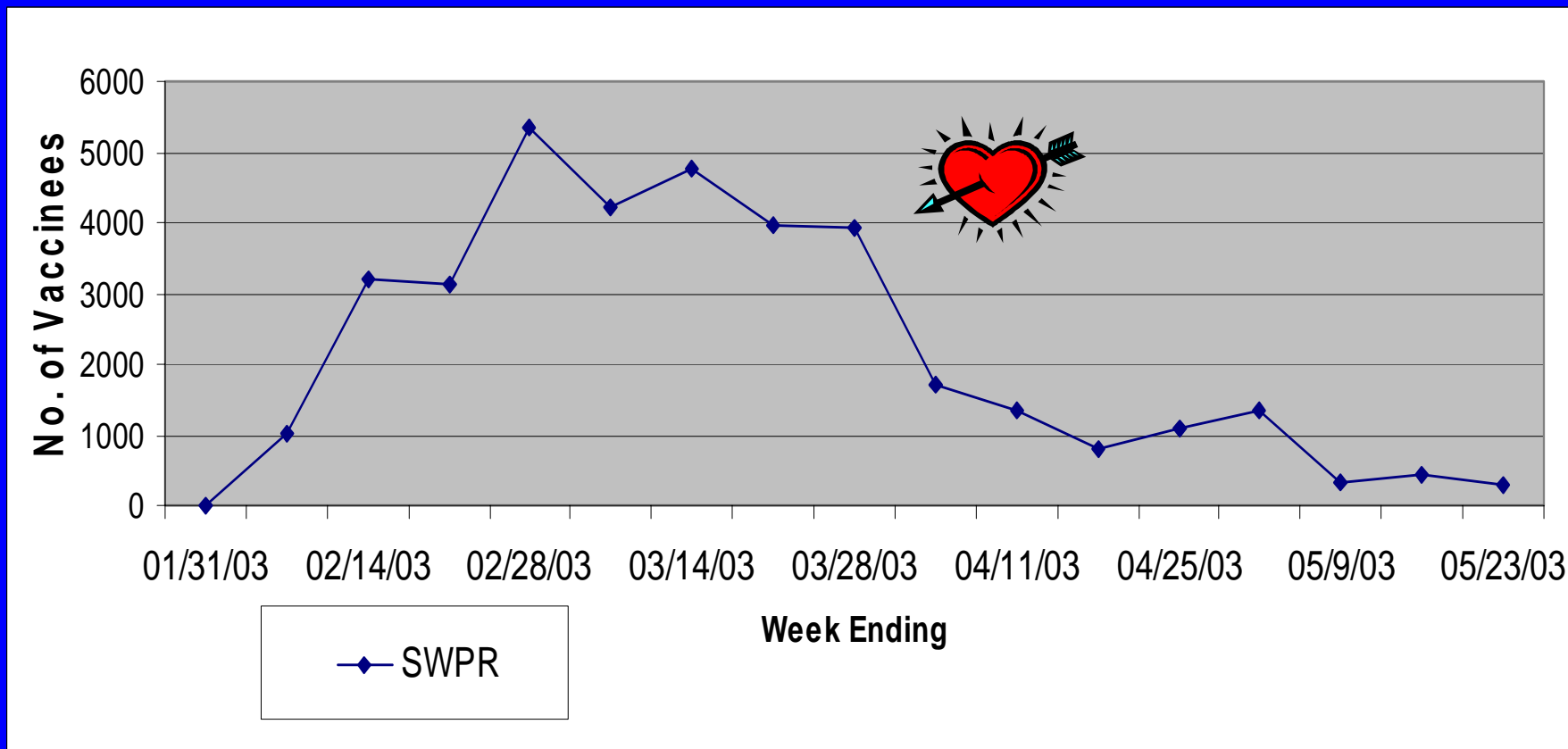


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# Smallpox Vaccinations by week

[Jan 24-May 23, 2003]



**Cardiac Events, societal influences**

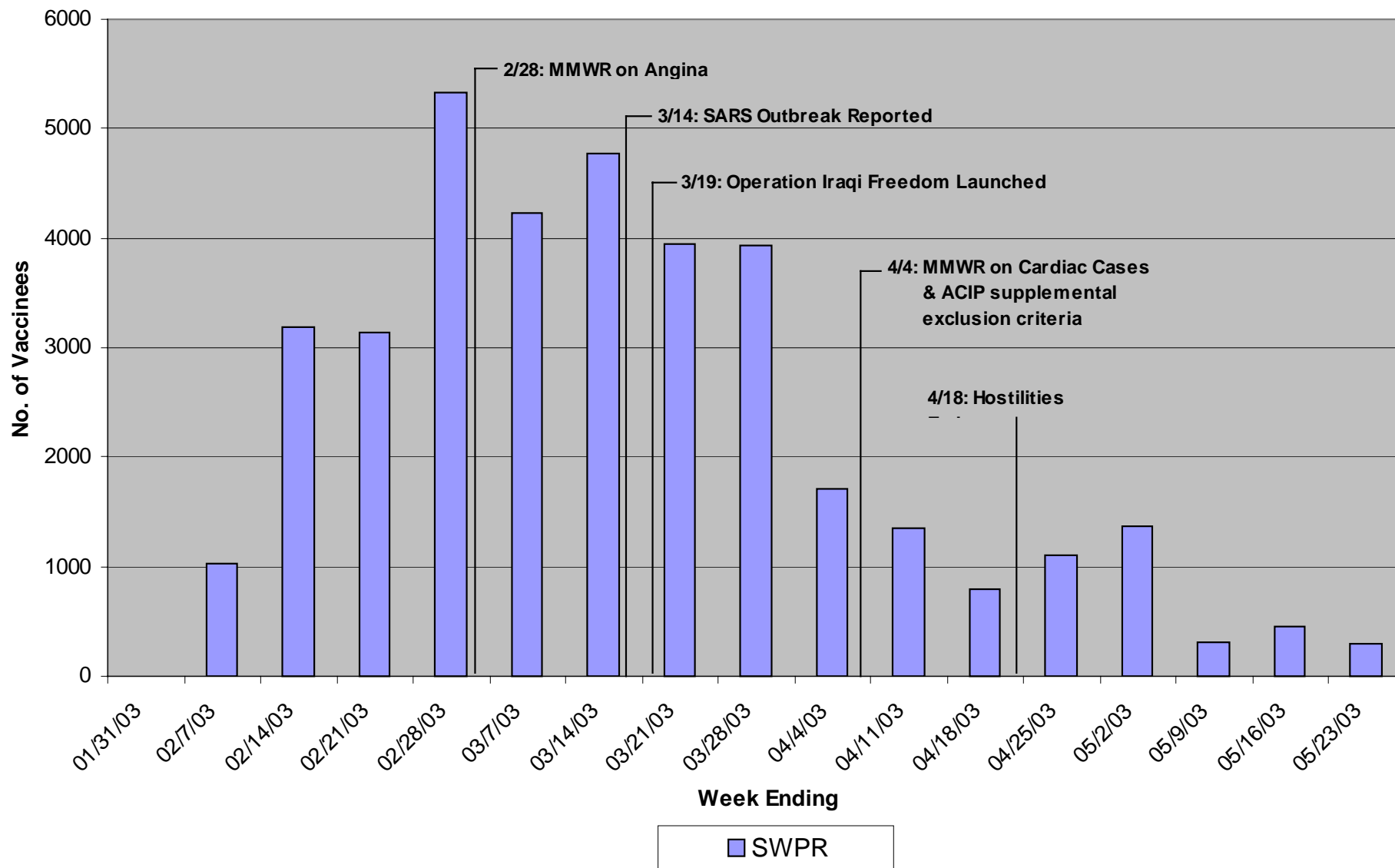
**SWPR: smallpox weekly progress report**



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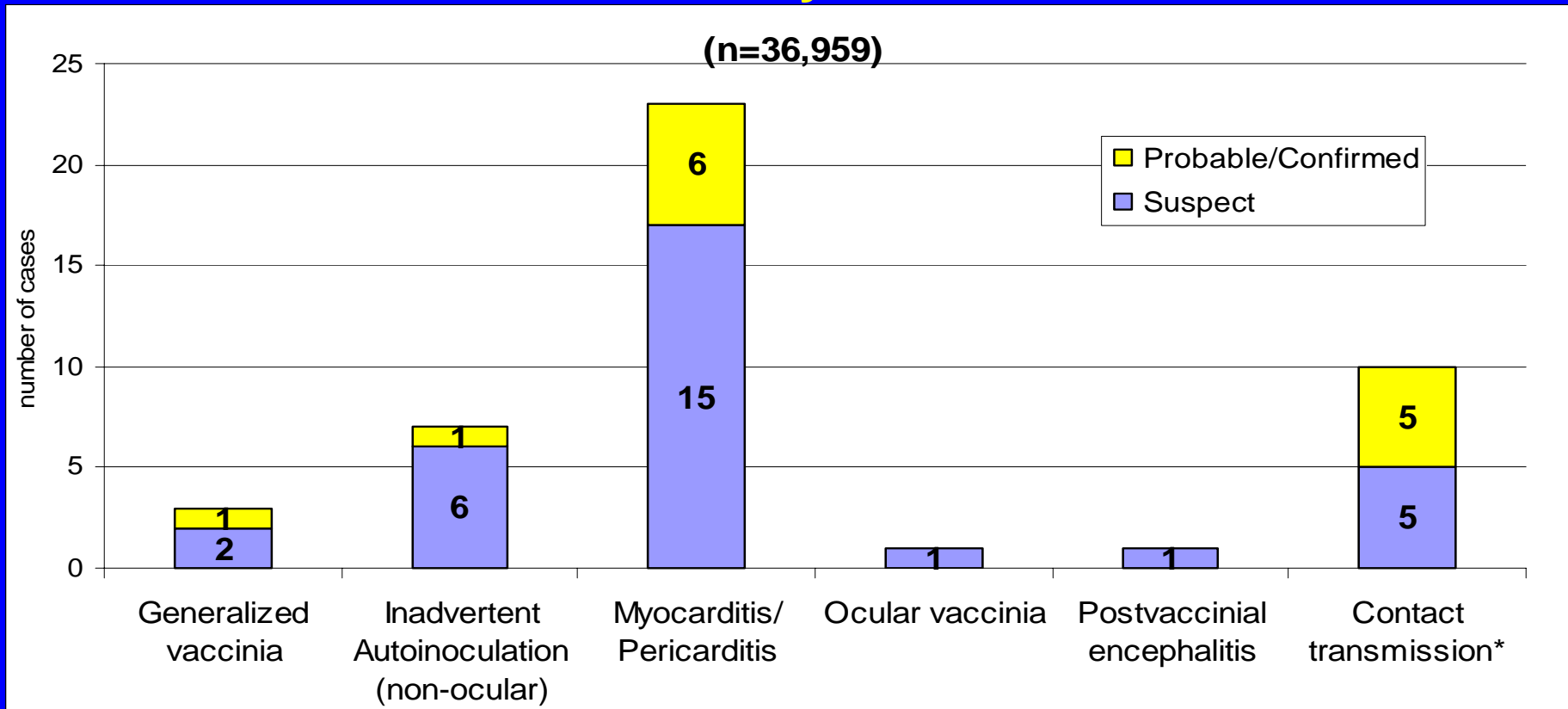
## Smallpox Weekly Progress Report (SWPR) Weekly Count of Vaccinations



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# 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



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# **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)**

<b><u>Other events of concern</u></b>	<b><u>Total no. of cases</u></b>
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**



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# 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**

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# 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

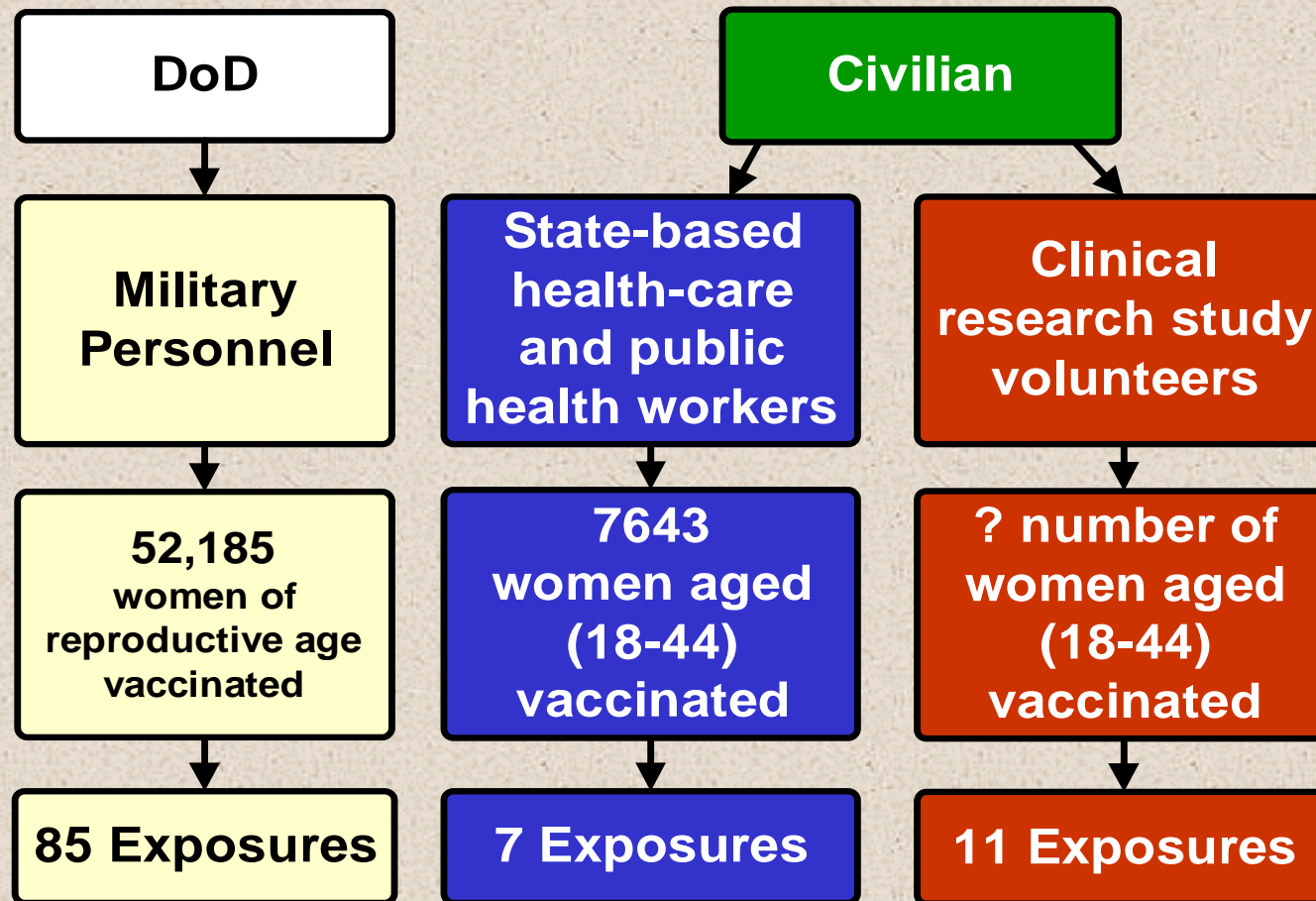
\* **MMWR 2003 52(21);492-496**



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



\* MMWR 52(17)386-388



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# 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](http://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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# Acknowledgements

- Centers for Disease Control and Prevention
  - NIP, NCID, OTPR, BPRP, IRMO, OC
- 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



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# 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

