

# Establishing Safety Surveillance for Smallpox Vaccine



- This presentation will discuss monitoring needs for adverse events associated with smallpox vaccine

## Objectives for Safety Monitoring

- Detect program errors
- Correlate with specific lot or brand
- Identify non-correlated events
- Maintain confidence in immunization programs
- Generate new hypotheses
- Compare rates with known data



•According to the World Health Organization's guidelines on immunization safety monitoring, the major goal of immunization safety monitoring is early detection and appropriate quick response to adverse events in order to lessen the negative impact on the health of individuals and on the immunization program.

Potential objectives of immunization safety surveillance include:

- Detecting, correcting, and preventing program errors
- Identifying unusually high rates or types of adverse events associated with specific vaccine lots or brands
- Ensuring that coincidental events are not falsely blamed on immunization
- Maintaining confidence in the immunization program and properly responding to community concerns about immunization safety while increasing awareness about vaccine risks
- Generating new hypotheses about vaccine reactions that are specific to the population
- And, estimating adverse event rates in the population compared with trial and international data

## General Steps to Establishing Vaccine Safety Surveillance



- Many countries already have existing adverse events surveillance that could be utilized to monitor for smallpox related adverse events in a pre- and post-event setting. But if you don't, here is a quick summary of what steps should be taken to establish a system.

## Steps to Establishing a System

1. Roles of Regulatory and Epi
2. Identify resources available
3. Appoint or designate assessors
4. Establish expert committee
5. Distribute list of events to be reported
6. Train staff at all levels
7. Inform healthcare workers of need to report
8. Consider compensation scheme



If there is no system in place for monitoring adverse events that could handle the addition of surveillance for smallpox, VIG, and Cidofovir, the following activities should be taken:

- Clarify the roles of the national regulatory authority and the public health epidemiology and agree on objectives for the system
- Identify the resources available and needed and establish political commitment to immunization safety surveillance
- Appoint or designate regional and/or national assessors for immunization safety
- Establish an expert panel on immunization safety
- Develop and disseminate a list of events to be reported and their case definitions; a standard investigation procedure; and report and investigation forms
- Designate and train staff to prepare the reports, complete the report forms, investigate adverse events, and conduct analyses of the data as appropriate
- Inform all healthcare workers and clinicians of the need to report an adverse event immediately and clarify which ones should be reported
- Consider the establishment of a compensation scheme for specified adverse events

## What to Report?

- Serious adverse events
- Certain moderate events
- See “Immunization Safety Surveillance” guidelines from WHO



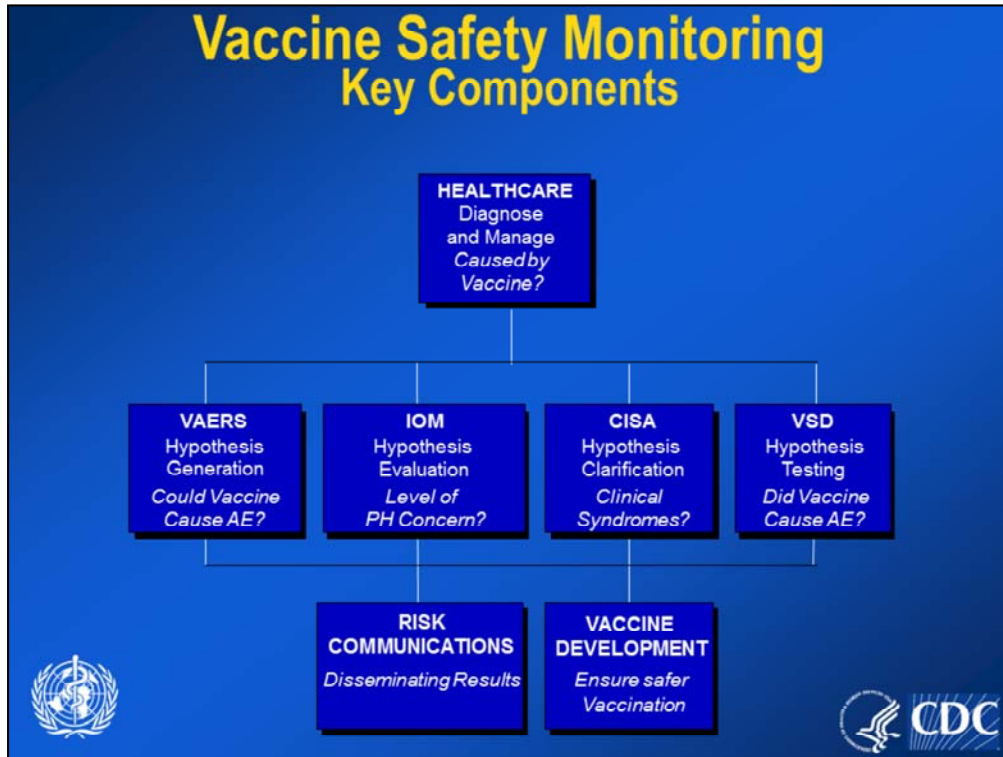
•Reportable adverse events must include any deaths or serious adverse events believed by the public or healthcare workers to be caused by immunization. Some events like abscess, toxic shock syndrome, and sepsis, are indicators of program error and need to be monitored at a minimum to identify and correct program errors. In addition, providers must be encouraged to report even if the causality of the adverse event is uncertain (i.e., temporal association is sufficient for reporting).

•More information can be found in the World Health Organization guidelines on “Immunization Safety Surveillance.”

# Current General Vaccine Safety Infrastructure USA



- The following is a description of the current vaccine safety infrastructure in the United States



•This diagram represents an overview of the regular process for reporting vaccine adverse events in the United States. As you can see, there are several groups and organizations involved in the process including:

- Healthcare system
  - Vaccine Adverse Event Reporting System
  - Institute of Medicine
  - Clinical Immunization Safety Assessment Network
  - Vaccine Safety Datalink project
- Will go into more detail with each group later in the presentation

# The Vaccine Adverse Event Reporting System

## What is VAERS?


- National passive surveillance system for medical events temporally associated with U.S. licensed vaccines
- Co-managed by CDC and FDA
- Established in 1990
- Certain reporting mandated by law
- Delivery point for smallpox adverse event reports



- VAERS is the national surveillance system for adverse events following the administration of U.S. licensed vaccines.
- VAERS is administered by CDC and the Food and Drug Administration (FDA).
- VAERS data are routinely analyzed by CDC and the FDA to identify:
  - new or rare vaccine side effects;
  - increases in rates of known side effects;
  - associations with specific vaccine lots;
  - and patient risk factors.
- All smallpox adverse event reports are also delivered to this system.



# VAERS Reporting Form



**VACCINE ADVERSE EVENT REPORTING SYSTEM**  
 24 Hour Toll-free Information Line 1-800-822-7987  
 P.O. Box 1100, Rockville, MD 20849-1100  
**PATIENT IDENTITY KEPT CONFIDENTIAL**

**VAERS**

**For CDC/OPD Use Only**  
 VAERS Number \_\_\_\_\_  
 Date Received \_\_\_\_\_

Form completed by (Name): \_\_\_\_\_  
 Relationship to Patient:  Vaccine Provider  Patient's Spouse  Other \_\_\_\_\_  
 Address (if different from patient or provider): \_\_\_\_\_

Vaccine administered by (Name): \_\_\_\_\_  
 Responsible Physician: \_\_\_\_\_  
 Facility Name/Address: \_\_\_\_\_

Patient Name: \_\_\_\_\_  
 Last First M.I. \_\_\_\_\_  
 Address: \_\_\_\_\_  
 City State Zip \_\_\_\_\_  
 Telephone no. ( ) \_\_\_\_\_

1. Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ 2. County where administered: \_\_\_\_\_ 3. Date of birth: \_\_\_\_/\_\_\_\_/\_\_\_\_ 4. Patient age: \_\_\_\_ y \_\_\_\_ m \_\_\_\_ d  
 5. Sex:  M  F 6. Date form completed: \_\_\_\_/\_\_\_\_/\_\_\_\_

7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any: \_\_\_\_\_  
 8. Patient received:  YES  NO  UNKNOWN  
 9. Adverse event onset: \_\_\_\_/\_\_\_\_/\_\_\_\_ Time: \_\_\_\_:\_\_\_\_:\_\_\_\_  
 10. Date of vaccination: \_\_\_\_/\_\_\_\_/\_\_\_\_ Time: \_\_\_\_:\_\_\_\_:\_\_\_\_

11. Check all that apply:  
 Life threatening illness  Required emergency room/doctor visit  
 Required hospitalization (\_\_\_\_ days)  
 Resulted in prolongation of hospitalization  
 Resulted in permanent disability  
 None of the above

12. Relevant diagnostic test/laboratory data: \_\_\_\_\_

13. Enter all vaccines given on date listed in no. 10:  

Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses
a. _____	_____	_____	_____	_____
b. _____	_____	_____	_____	_____
c. _____	_____	_____	_____	_____
d. _____	_____	_____	_____	_____

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10:  

Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a. _____	_____	_____	_____	_____	____/____/____



15. Vaccinated at:  Private doctor's office/hospital  Military clinic/hospital  Public health clinic/hospital  Other/unknown  
 16. Vaccine purchased with:  Private funds  Military funds  Public funds  Other/unknown  
 17. Other medications: \_\_\_\_\_

18. Stress at time of vaccination (specify): \_\_\_\_\_  
 19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify): \_\_\_\_\_

20. Have you reported this adverse event previously?  No  Yes  
 If Yes: To health department \_\_\_\_\_ To doctor \_\_\_\_\_ To manufacturer \_\_\_\_\_  
 21. Adverse event following prior vaccination: (Date of event, specify Adverse Event, Type of vaccine, Dose no. at series)  
 In patient: \_\_\_\_\_ In brother: \_\_\_\_\_ In sister: \_\_\_\_\_  
 22. Birth weight: \_\_\_\_ lb \_\_\_\_ oz 23. No. of brothers and sisters: \_\_\_\_\_  
 24. MFR / mmr prep report no.: \_\_\_\_\_ 25. Date received by MFR / mmr prep: \_\_\_\_/\_\_\_\_/\_\_\_\_  
 26. 14 day report?  Yes  No 27. Report open?  YES  NO  Follow-Up

Health care providers and manufacturers are required by the CDC. Dates do not report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary. Report only reactions to a condition of immunization given records.

VAERS 02/02

- Here is an example of the VAERS reporting form.
- Can be downloaded from the internet for physician or patient access and reporting
- The next slide will show the information requested from each person reporting a vaccine associated adverse event.

## VAERS Reporting Form

- Date of birth, age, sex
- Description of adverse event
- Outcome (recovery status)
- Date of vaccination
- Adverse event onset
- All vaccines administered
- Source of report, vaccine purchase/ admin
- Pre-existing illness, medications
- Relevant diagnostic tests/lab data



- Form is designed to obtain basic information about the adverse event and its management.
- Additional follow-up is done to determine long-term sequelae.

## VAERS Role in Smallpox Vaccine Response

- Single locus for reporting Vaccine Adverse Events (VAEs):
  - National in scope
  - Known to health care providers
  - Electronic reporting as of January 1, 2002
- Established mechanisms and trained staff for enhanced follow up of serious reports
- BUT VAERS:
  - Not able to determine causality
  - Does not provide clinical case investigation



- The VAERS system is useful as a mechanism for monitoring smallpox vaccine adverse events because it's national and known to healthcare providers.
- It allows the CDC to get an indication of what is occurring with the vaccine.
- Electronic, web-based reporting since January, 2002 allows more rapid reporting and thus more rapid evaluation
- However, since it is simply a gathering point of information, it cannot determine whether or not a vaccine caused the adverse events.
- While VAERS provides useful information on vaccine safety, the data are somewhat limited.
  - judgments about causality (whether the vaccine was truly responsible for an adverse event) cannot be made from VAERS reports because of incomplete information.
  - VAERS reports often lack important information such as laboratory results. As a result, researchers have turned more recently to large-linked databases (LLDBs) in order to further study vaccine safety. LLDBs provide scientists with access to the complete medical records of millions of individuals receiving vaccines (all identifying information is deleted to protect the confidentiality of the patient).

## Institute of Medicine

- Review VAERS data
- Public health significance?
- Review hypotheses



- As concerns about vaccine safety or a particular AE association are raised by VAERS data or by other studies, the Institute of Medicine can convene expert committees to review the hypotheses and supporting information to determine their significance to public health.
- The mission of the Institute of Medicine is to advance and disseminate scientific knowledge to improve human health. The Institute provides objective, timely, authoritative information and advice concerning health and science policy to government, the corporate sector, the professions and the public.
- The Institute of Medicine has been convened on a number of occasions to assess the potential causal associations between some vaccines and selected VAEs. For example, encephalopathy following DTP and, more recently, autism following MMR vaccine.

## Clinical Immunization Safety Assessment (CISA) Network

Academic centers of excellence (4) in partnership with CDC serving as a source of clinical expertise in adverse events following immunization.

- Johns Hopkins with University of Maryland.
- Boston Medical Center.
- Kaiser Research Institute Foundation with Stanford University and Vanderbilt University.
- New York Presbyterian-Columbia.



•The Clinical Immunization Safety Assessment Network, or CISA, was established to provide clinical evaluation of the data collected by VAERS in order to help determine whether or not a particular vaccine caused an adverse event. Many of the top academic centers in the US are part of this network.

## Clinical Immunization Safety Assessment (CISA) Network

Overall Goals relating to VAEs:

- Develop clinical evaluation and management protocols
- Improve understanding of VAEs' pathophysiology at the individual patient level
- Identify genetic or risk factors for predisposed groups
- Provide expert advice for supervised immunization and clarify valid contraindications for reimmunization in high-risk groups
- Serve as regional referral center for safety inquiries
- Conduct formal causality assessment and case review



•The goal of the CISA centers is to help improve the knowledge of how to clinically evaluate and manage possible adverse events associated with most vaccines monitored through the VAERS system and to help improve our understanding of the underlying causes and risk factors for vaccine adverse events. They also act as a referral center for healthcare providers to consult on regarding vaccine associated adverse events.

•

## Vaccine Safety Datalink

- Study rare vaccine side effects
- Seven large HMOs
- Six million people monitored
- Planned studies
- Timely investigations



- The gaps that exist in the scientific knowledge of rare vaccine side effects prompted the CDC to develop the Vaccine Safety Datalink (VSD) project in 1990.
- This project involves partnerships with seven large health maintenance organizations (HMOs) to continually monitor vaccine safety.
- VSD is an example of a large-linked database (LLDB) and includes information on more than six million people. All vaccines administered within the study population are recorded. Available data include vaccine type, date of vaccination, concurrent vaccinations (those given during the same visit), the manufacturer, lot number, and injection site. Medical records are then monitored for potential adverse events resulting from immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypotheses. At present, the VSD project is examining potential associations between vaccines and a number of serious conditions. The database is also being used to test new vaccine safety hypotheses that result from the medical literature, VAERS, changes in the immunization schedule, or from the introduction of new vaccines. This project is a powerful and cost-effective tool for the on-going evaluation of vaccine safety.<sup>1,10</sup>

## Why Monitor Smallpox Vaccine Safety?

- Vaccine not used on large scale in today's society
- More altered immunity
- More organ transplants
- Unknown safety profile today
- Unknown treatment resource needs with limited availability (VIG and other potential treatments, e.g. Cidofovir)



- Although we have a great deal of information already on the expected adverse events associated with smallpox vaccine, monitoring for these and other adverse events is still essential (in both a pre- and post- event vaccination campaign)
- Several issues arise that support the need for organized monitoring for adverse events:
  - smallpox vaccination hasn't been used on a large scale in quite some time, therefore, primary vaccine recipient populations will generally be older than during the eradication period
  - More people exist today with disease or medication altered immune systems than existed when the vaccine was used on a wide-scale.
  - Because the make-up and health status of today's population is different than previously, while we can make intelligent guesses as to what to expect in terms of adverse events, we really do not have a modern day safety profile
- In addition, it is extremely important to actively track serious vaccine adverse events that may require specialized and/or limited treatment resources in order to gauge and address these resource needs to support vaccination



## Smallpox Vaccine AE Monitoring Needs

- Monitoring needs for vaccine programs will differ depending upon the circumstances
- Pre-outbreak programs
  - Focus on safest possible use of vaccine
- Post-outbreak programs
  - Emergency response
  - Focus on identifying serious AEs that require medical resources



- Monitoring for vaccine adverse events in a pre-outbreak responder vaccination program versus a post-event outbreak control emergency vaccination program will be different
- Different primary goals for monitoring
- Pre-outbreak program should focus on assuring the best possible safety profile for the vaccine, characterize non-serious and serious AE profiles to assist with post-event response planning, education, etc., identify all unexpected AEs, instill confidence in program by assuring that careful monitoring is being done and enhancing strategies to screen for persons with contraindications to vaccination.
- Post-event outbreak AE monitoring may have to be adjusted to accommodate large numbers of people being vaccinated in a short period of time
  - Emergency response mode, limited resources, must focus on immediate needs such as identifying most serious AEs that require medical resources

## Pre-Outbreak Smallpox Vaccine AE Monitoring

- Safest program possible
  - Increased screening
  - More active monitoring and investigation of AEs
  - Quickly identify and respond to unexpected AEs to maintain confidence in vaccine/program
- Studies to evaluate full scope of AE profile for vaccine
  - Use system to help define profile of vaccine use in current population
- Identify additional needs to address in larger-scale vaccination AE monitoring programs



- A pre-event program has to be as safe as possible as you are vaccinating people for a disease that doesn't exist naturally anymore and for an un-definable risk of future exposure
- Will screen out people who may have potential problems, even if you would normally allow vaccination in outbreak setting (e.g. people without definite risk factors but who may have questionable risk factors)
- At least in early stages of program, must have a timely and responsive system for monitoring in order to pick up problems quickly
  - Treat individuals with limited access medications (VIG) if needed
  - Maintain confidence in program that authorities are being as vigilant as possible to assure a safe program
- Additional studies to define full scope of AEs (common and minor to more serious) in current, older primarily vaccinated population so that will have a better idea of what to expect in a post-event emergency response vaccination program. Will also assist with training and education for post-event response
- Opportunity to “test-run” system in non-emergency setting to identify needs to address in larger-scale post-event monitoring system
- The pre-outbreak setting also provides the opportunity to monitor any adverse events resulting from the treatment of vaccine adverse events using VIG or Cidofovir. Thus, we would have a comprehensive safety profiles on the vaccine and

AE treatments.

## Safety Steps at Time of Vaccination

- Screen for vaccine contraindications
- Obtain consent
- Distribute VIS with VAERS and Health Department contact information
- Distribute Vaccine Adverse Event Information and instructions to vaccinees
- Distribute instructions on care of vaccination site



- In order to help prevent adverse events from occurring in the first place, participants should be carefully screened for contraindications.
- Participants should be given extensive instructions on contraindications, adverse events and where to seek evaluation, and site care before vaccination.

## Recognition of a Problem Individual

- Unexpected symptoms or serious side effects
- Vaccination site different (worse) than pictures of expected vaccine take
- Vaccine recipient develops more than fever, malaise, enlarged/tender lymph nodes, and expected site reaction
- Potential contact points for follow up: clinic, private MD, HD, hospital, VAERS, public health vaccination staff



- Given the lack of experience with smallpox vaccine in most healthcare communities, even recognizing people who are having adverse events may be difficult. The key for the pre-outbreak monitoring system is to be overly sensitive.
- Told to have any unexpected symptoms or serious side effects evaluated by a physician
- Vaccine recipients should be encouraged to report to the vaccination clinic or healthcare provider if the vaccine site looks worse than the pictures they are given of the expected vaccine take.
- Anyone who develops more than the expected mild systemic illness expected is also encouraged to call in.

## Response to a Problem Individual

- Response team safety member to investigate
- VAERS form submitted
- Possible consultation with CDC Clinical Team, neurology, or dermatology consultants
- CDC Physician helps determine need for VIG or Cidofovir:
  - Distribution mechanism (NPS) contacted
- CDC/state follows up vaccine reaction cases:
  - Resolution of VAE, response to VIG or Cidofovir, complications from Cidofovir



•When a significant individual problem is identified/reported, vaccine safety team personnel should begin an investigation; ensuring that a VAERS form has been submitted and is filled out completely.

•More serious adverse events would be referred to the established CDC Clinical Consultation Team. This team is made up of infectious disease and vaccine safety specialists who can consult on various aspects of vaccine adverse events. The vaccine recipient is followed until the adverse event has resolved and then for as long as a year after depending upon the vaccine complication.

## Recognition of a Problem Population

### Population: unusual reactions or high rates

- Daily review of submitted VAERS forms and follow up information
- Frequent calculation of rates of VAEs:
  - Dependent on frequent submission of age and gender specific dose administered data from the field
- Review and analysis of VAE Report Card data
- Calls from clinicians
- Adverse event reports evaluated for:
  - Common, usually mild expected reactions
  - Rare, serious VAEs
  - Vaccination of persons with contraindications
  - Transmission of vaccinia to contacts



- At the national level, the CDC and the FDA reviews all the VAERS forms submitted for smallpox vaccine. The CDC also reviews the follow-up information obtained by the Clinical Consultation team.
- The CDC routinely calculates rates and monitors for unusual reactions.
- This data is further monitored by an expert committee composed of the Advisory Committee on Immunization Practices (ACIP), Department of Defense (DoD) members, and smallpox experts..
- The vaccination program overall is monitored by the Institute of Medicine.

## Recognition of a Problem Population Response

- Identify groups at risk for VAE:
  - ? New contraindications
  - ? Screening for contraindications not consistent.
  - ? Unavoidable VAEs (e.g., person with contraindication was also high-risk contact in post-outbreak setting)
- Determine if VAEs differ by lot, clinic, etc.
- Determine if AE resulted from treatment of vaccine reaction (e.g., renal failure from Cidofovir)
- Investigate pathophysiology of VAE
- Develop new, safer vaccine



•If a problem is identified, the CDC will be conducting an investigation to determine if this indicates a previously unknown contraindication, or some issue with screening criteria.

•This is also an opportunity to review other possible causes of the condition and to possibly improve the vaccine.



## Smallpox Vaccine Safety Workgroup Advisory Committee on Immunization Practices

- Standing committee of clinical and public health experts from the CDC's immunization advisory group, DoD's Armed Forces Epidemiology Board and other designated smallpox experts and specialty consultants
- Function as medical monitor for smallpox vaccine program and IND protocols (VIG and Cidofovir):
  - Review and assess VAE data from multiple sources:
    - VAERS
    - Diary Cards
    - Epidemiology Studies
  - Review and assess and AEs associated with IND medications for treatment of smallpox vaccine AEs



•To provide an additional level of oversight, a committee of clinical experts can review data on a regular basis in order to monitor the program and help to formulate medical policy.

## Post-Outbreak Smallpox Vaccine AE Monitoring

- Adapt pre-existing monitoring system to meet increased demands and post-event priorities
  - More familiar with existing systems
- Establish monitoring system priorities
  - Identification/immediate reporting of serious, known AEs,
    - Requiring hospitalization and/or treatment (VIG)
  - Identification and immediate reporting of serious, unexpected AEs
- Establish method and frequency of data communication
  - Web-based
  - Publications
  - Daily or weekly totals



- The ability to monitor AEs in a post-event emergency setting will most likely be limited and must focus on the more serious adverse events that require utilization of medical resources
- If possible, figuring out how to adapt an existing system that medical providers already use would be easiest as they are already familiar with that system
- Must establish reporting priorities for the providers
  - Serious AEs
  - Unexpected serious AEs
- Determine how and how often the public health system will communicate AE data

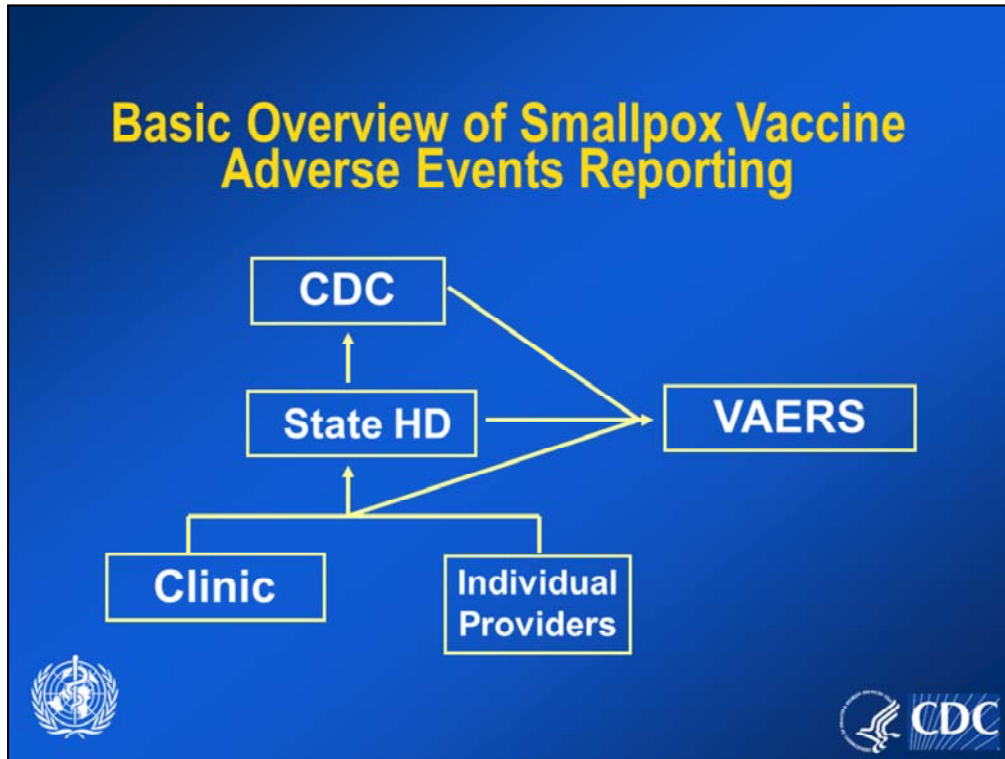
# Smallpox Vaccine Safety System

United States, Early Vaccination Phases



- The following is a more detailed description of the current, pre-outbreak responder smallpox vaccine safety monitoring program in the United States

## Basic Overview of Smallpox Vaccine Adverse Events Reporting



- During the early phases of smallpox vaccination, vaccination clinics and healthcare providers should report clinically significant and unexpected adverse events to their state health department.
- The state health department will, in turn, report such adverse events to the CDC. A VAERS report should also be filed for clinically significant and unexpected adverse events; the VAERS report can be submitted by the clinic, provider, vaccinee, or state health department.

## Reporting Adverse Events Following Smallpox Vaccine

- What to report to VAERS:
  - All clinically significant or unexpected AEs
- When to report:
  - Clinically significant/unexpected AEs within 48 hours
  - Other AEs within 7 days



- Although any adverse event can be reported to VAERS, it is most important to report the clinically significant or unexpected adverse events, ideally within 48 hours.
- What is meant by clinically significant? Of course, serious adverse events, events that result in death, hospitalization, permanent disability, or are life-threatening are considered clinically significant.
- Adverse events that prompt a visit to a healthcare provider may also be considered clinically significant; however, that is left to the judgment of the healthcare provider.
- Adverse events other than unexpected or clinically significant can be reported to VAERS within 7 days.

## Smallpox Adverse Events to Report

- Eczema vaccinatum
- Erythema Multiforme major/Steven Johnson
- Fetal vaccinia
- Generalized vaccinia
- Inadvertent inoculation
- Myocarditis/pericarditis
- Ocular vaccinia
- Post vaccinia encephalitis
- Progressive vaccinia
- Pyogenic infection of vaccination site
- Vaccinia transmission to contacts
- Vaccination of persons with a contraindication
- Other serious AEs and any AE of concern to a clinician/patient



Some of the items that can be encouraged for reporting include:

Eczema vaccinatum

Erythema Multiforme major/Steven Johnson

Fetal vaccinia

Generalized vaccinia

Inadvertent inoculation

Myocarditis/pericarditis

Ocular vaccinia

Post vaccinia encephalitis

Progressive vaccinia

Pyogenic infection of vaccination site

Vaccinia transmission to contacts

Vaccination of persons with a contraindication

Other serious AEs and any AE of concern to a clinician/patient

## Reporting Adverse Events Following Smallpox Vaccine

- Who can report to VAERS:
  - State Health Departments
  - Healthcare providers
  - Vaccine manufacturers
  - Anyone



- Anyone can report to VAERS: vaccinees, healthcare providers, vaccine manufacturers, and, of course, state health departments.
- For smallpox vaccine, state health departments should make sure that VAERS reports have been filed for the clinically significant and unexpected adverse events.
- Reports can be sent to VAERS via the web, FAX, or mail.

## Federal Health Authorities (CDC) Roles and Responsibilities

- Tabulate AEs
- Determine the frequency of known serious AEs
- Monitor for unexpected AEs
- Conduct special studies of AEs
- Make VIG and Cidofovir available under Investigational New Drug (IND) protocols



•Vaccine safety roles and responsibilities of the different participants in the vaccination program:

- At the Federal level, CDC is responsible for tabulating the reported adverse events, by number and type of adverse event, determining the reported frequency of known serious adverse events to estimate whether the reported rates are consistent with the historically reported rates, and reviewing VAERS reports and information from the states and providers on a daily basis to monitor for unexpected adverse events.
- If there are any unusual adverse events, such as type of event, geographic location, or population distribution, CDC will conduct special studies to further investigate any risk factors.
- CDC will make Vaccinia Immune Globulin or VIG and Cidofovir available under Investigational New Drug (IND) protocols for selected adverse events.



## Federal Health Authorities (CDC) Roles and Responsibilities

- Provide technical assistance to state health authorities to support safest possible use of smallpox vaccine
- Provide technical consultation to clinicians in diagnosis and management of adverse events after smallpox vaccination
- Work with regulatory agency (FDA) to monitor AE (VAERS) reports



- CDC provides technical assistance to state public health authorities to support the safest possible use of smallpox vaccine.
  - For example, CDC provides assistance for questions regarding screening, contraindications, vaccination technique, and adverse events.
  - CDC will provide technical consultation to clinicians in the diagnosis and management of adverse events after smallpox vaccination, especially if the adverse events are moderate to severe, unexpected, or are not following an expected clinical course.
  - And CDC works directly with the Food and Drug Administration (FDA) to closely monitor VAERS reports.

## State Health Authorities Roles and Responsibilities

- Develop a plan to assure monitoring of adverse events among public health smallpox response teams
- Identify an individual to oversee, establish, and coordinate vaccine safety monitoring



- State Health authorities are responsible for developing a plan to assure monitoring of adverse events among vaccinees (state-based response team members) in their state smallpox vaccination program.
- As part of that plan, State Health authorities must identify an individual to oversee, establish, and coordinate state vaccine safety monitoring.

## State Health Authorities Roles and Responsibilities

- Communicate with medical organizations
- Communicate with media on vaccine safety issues
- Inform medical providers about smallpox vaccination program



- Must communicate with medical organizations, media, and public on vaccine safety issues before, during, and after the vaccination program.
- Although states may designate or recommend certain medical facilities for the assessment of adverse events, in practice, vaccinees could enter the healthcare system at many points. Therefore, should make sure healthcare providers are aware of the vaccination program and know who to contact if they need to assess, refer, or treat a person with a potential vaccine adverse event.

## State Health Authorities Roles and Responsibilities

- Develop system for rapid reporting and assessment of AEs in vaccinees or their contacts:
  - Provide 24/7 coverage for answering questions
  - Ensure prompt reporting to Federal Health Authorities (CDC):
    - Clinically significant and unexpected AEs.
    - Vaccinia Immune Globulin (VIG) or Cidofovir requests.
    - Clinical outcome following treatment.



- At the state/local level a system should be developed for rapid reporting and local assessment of adverse events in vaccinees or their contacts.
- This system should provide coverage for answering questions posed by vaccinees and clinicians 24 hours a day, 7 days a week. This system should assure prompt reporting to Federal officials (CDC) for clinically significant and unexpected adverse events; VIG or Cidofovir requests; and for the clinical outcome following treatment.

## Hospital Roles and Responsibilities

- Provide follow-up of vaccinees, including 24/7 coverage
- Perform vaccination site care
- Identify subspecialists to assist with assessment of suspected AEs



- The hospitals with smallpox response teams must provide follow-up of their own team vaccinees, including 24/7 coverage for vaccine adverse event assessment.
- Hospitals should identify subspecialists to assist with assessment of suspected adverse events in other persons who may present for evaluation. Subspecialty categories would ideally include dermatology, infectious diseases, neurology, ophthalmology, and allergy/immunology.

## Hospital Roles and Responsibilities

- Promptly report clinically significant or unexpected AEs to state health departments.
- Submit case report forms to state health departments.



- Should know the system and requirements for reporting AEs to the state health authorities and requesting VIG and other treatments or recommendations for serious AEs
- Hospitals should promptly notify their state health department of any clinically significant or unexpected adverse events and should submit a case report to the health department.

## Vaccine Clinic Roles and Responsibilities

- Treat immediate AEs (i.e., anaphylaxis, syncope)
- Educate vaccinees on vaccination site care
- Ensure vaccinees have instructions for follow-up



- Vaccination clinics have a number of vaccine safety responsibilities.
- Vaccine clinics should be prepared to treat rare, immediate adverse events, such as anaphylaxis or syncope.
- The clinics should be able to educate vaccinees on vaccination site care, such as with written instructions.
- Vaccine clinics should assure that vaccinees have instructions for follow up, such as for vaccine take checks

## Vaccine Clinic Roles and Responsibilities

- Know the reporting process for AEs.
- Provide vaccinees with information on who to contact for suspected AEs
- Tabulate the number of persons vaccinated:
  - Facilitates calculating ratio of AEs
  - Assesses vaccine resources utilized/wastage



- The clinics should know the reporting process for adverse events for their own reporting purposes, and should also provide vaccinees with information on who to contact for suspected adverse events.
- Clinics should keep track of the number of persons vaccinated. This is helpful for evaluating clinic operations, monitoring vaccine use, and, for vaccine safety purposes, it facilitates calculating the rate of reported adverse events.



## Individual Providers Roles and Responsibilities

- Recognize possible AEs
- Manage and treat AEs
- Refer patients as clinically indicated to an appropriate specialist



- Individual health care providers should at least be able to recognize possible smallpox vaccine adverse events. Many of the adverse events will be mild and can be managed by primary care physicians.
- For moderate, severe, or unusual adverse events, healthcare providers should know how to refer patients as clinically indicated to an appropriate specialist

## Individual Providers Roles and Responsibilities

- Report AEs to state health department
- Comply with IND protocol requirements if VIG and Cidofovir used for treatment of AEs
- Report AEs to VAERS



- For clinically significant and unexpected adverse events, the provider must report to the state health department and to VAERS.
- If a provider needs to treat a vaccinee or contact with VIG or Cidofovir, the provider must seek consultation with Federal authorities and comply with the IND protocol requirements for the administration of these medications.

## Adverse Events Surveillance

- Important for confidence in program
- Will require organization at all levels
  - All levels should understand system
  - All levels should understand roles
- Use the system to modify program, as necessary



In summary, establishing an adverse events surveillance system will be key to maintaining public confidence in the vaccination program, as well as understanding new and unforeseen adverse events. The system will need to include all levels of the healthcare system and all its players will need to understand their roles in this system. And be sure to regularly use the information you gather to ensure you have the safest program possible.