Adverse Events Following Immunization: Surveillance in Clinical Practice

PIDSP Annual Convention 2010

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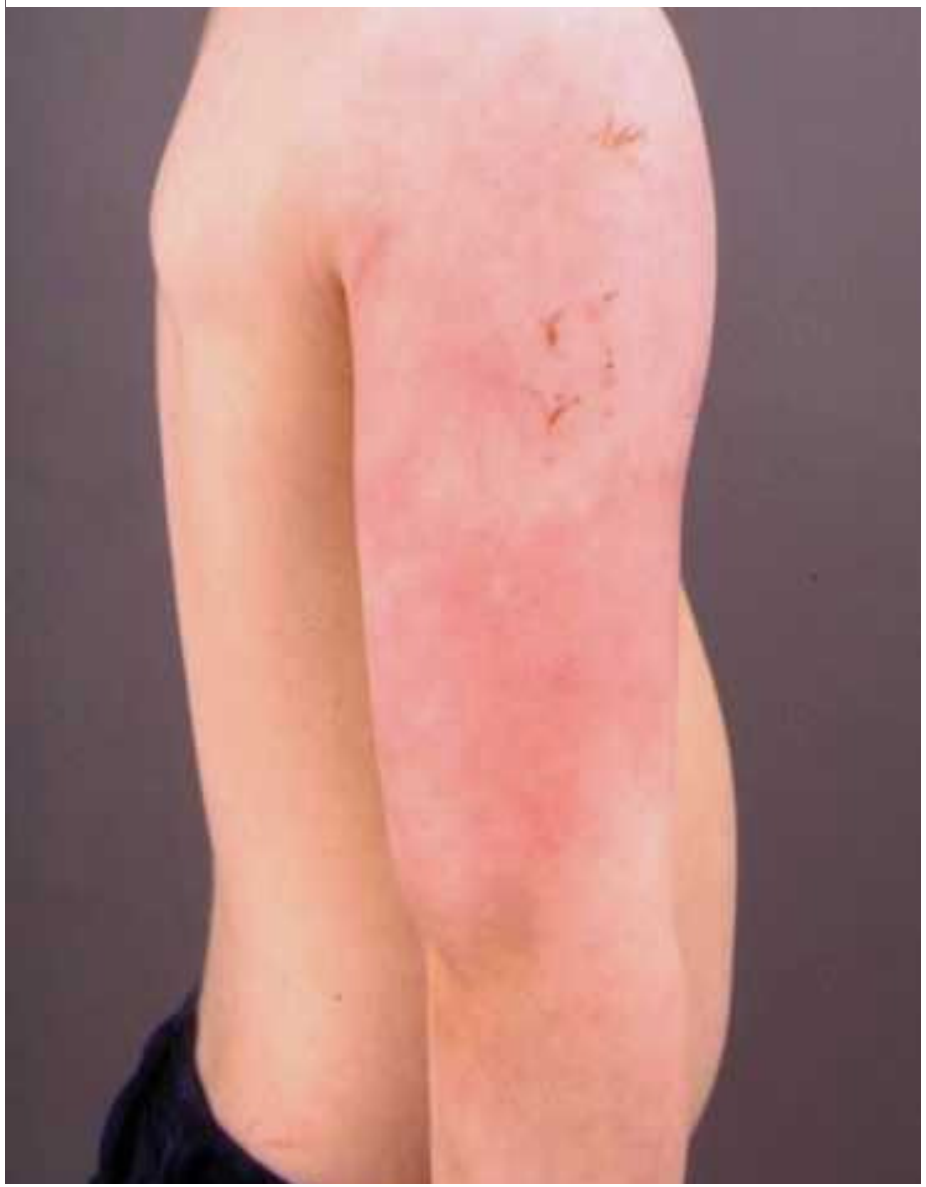
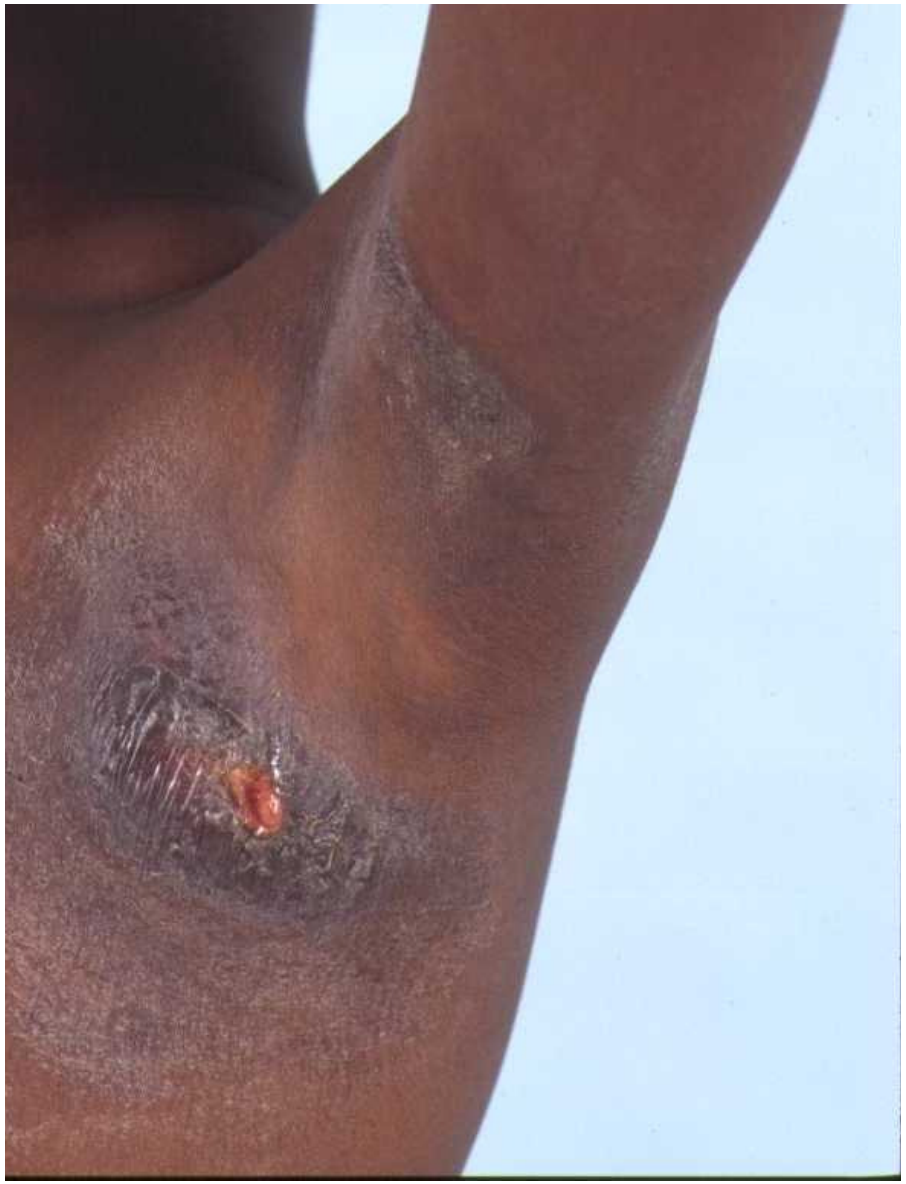
ATTRIBUTES OF A GOOD VACCINE

- **Appropriate immune response**
- **Long-term protection**
  - **(against the most pathogenic and prevalent strains)**
- **Safe**
- **Stable**
- **Affordable**
- **Minimum number of shots (injections)**
- Maximum number of antigens

Like all drugs, no vaccine is 100% safe



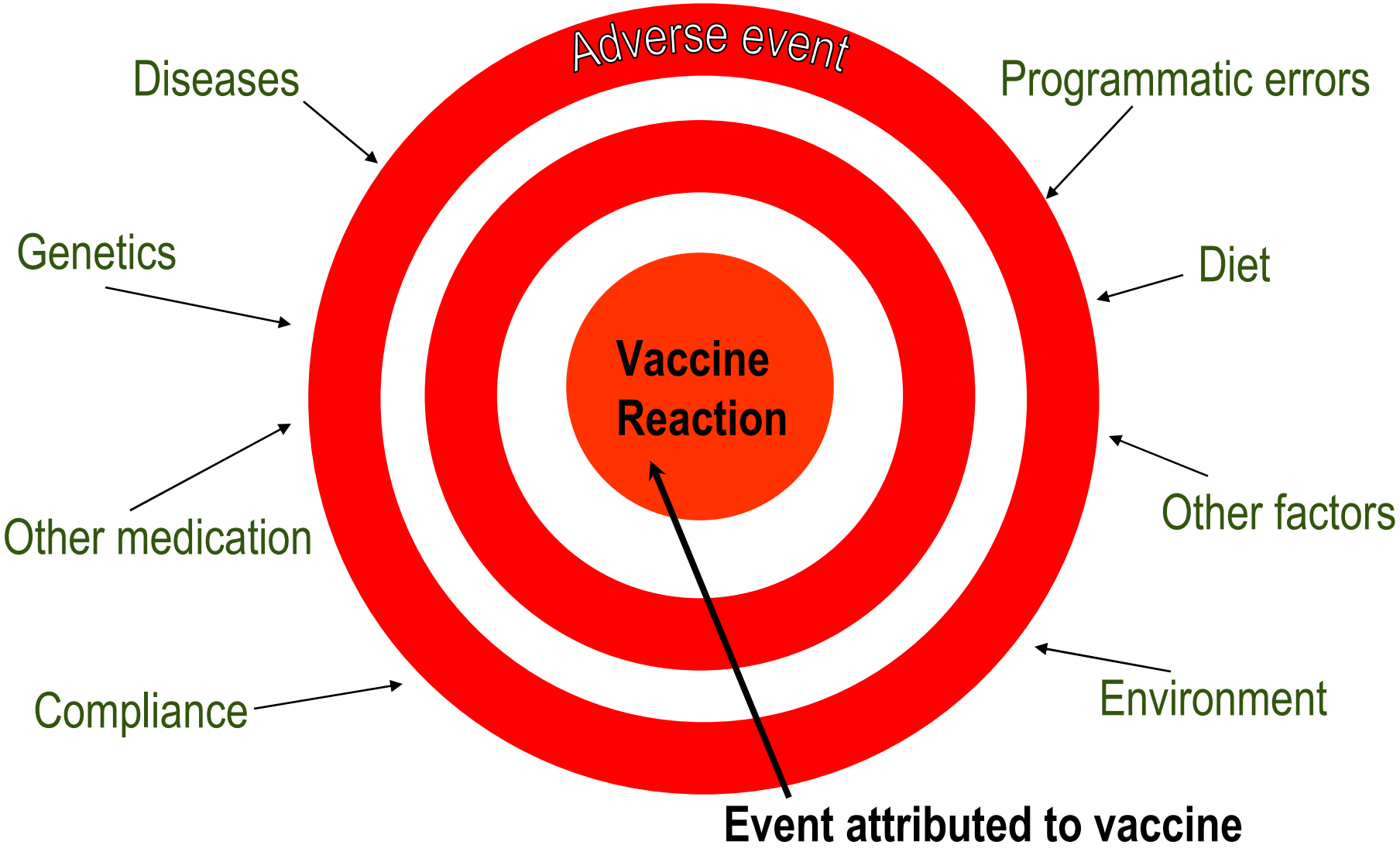


WHAT IS AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI)?

A medical incident that takes place after an immunization, causes concern, and is believed to be caused by immunization

- **Vaccine reaction** - caused by vaccine's inherent properties
- **Programme error** - caused by error in vaccine preparation, handling, or administration
- **Coincidental** - happens after immunization but not caused by the vaccine or vaccination process (a chance association)
- **Injection reaction** - anxiety about or pain caused by the injection not vaccine/vaccination
- **Unknown** - cause cannot be determined

Adverse reaction vs. adverse event



Objectives of monitoring AEFIs

- Identify urgent problems for investigation and action
- Detect signals for potential follow-up and research
- Estimate rates for serious AEFIs
  - for comparison between products
  - to determine risks and benefits of immunization
  - to validate pre-licensure data
- Identify programmatic errors and batch problems
- Create awareness of risks among health professionals

Frequency of Adverse Reactions

Very common*	**≥ 1/10**	**≥ 10%**
Common (frequent)	**≥ 1/100 and < 1/10**	**≥ 1% and < 10%**
Uncommon (infrequent)	**≥ 1/1,000 and < 1/100**	**≥ 0.1% and < 1 %**
Rare	**≥ 1/10,000 and < 1/1,000**	**≥ 0.01% and < 0.1%**
Very rare*	**< 1/10,000**	**< 0.01%**

* Optional categories

Source: Council for International Organizations of Medical Sciences (CIOMS), 1995

VACCINE REACTIONS

- Common, minor reactions
  - Part of immune response to vaccine
  - Settle on their own
  - Warn parents and advise how to manage
  - e.g. fever, malaise etc.

- Rare, more severe reactions
  - Usually require clinical management

  Examples
  - Severe allergic reaction (e.g. anaphylaxis) including exaggerated response to vaccine/ component
  - Vaccine specific reactions (e.g. BCG osteitis)

COMMON, MINOR REACTIONS

Vaccine	Local reaction (pain, swelling, redness)	Fever >38°C	Irritability, malaise & systemic symptoms
BCG	90-95%	-	-
Hib	5-15%	2-10%	-
HepB	Adults: 15%; Children: 5%		1-6%
Measles/ MMR	~10%	5-15%	5% rash
Polio (OPV)	-	<1%	<1%**
Tetanus	~10%*	~10%	~25%
DTP (pertussis)	Up to 50%	Up to 50%	Up to 55%

* Rate of local reactions likely to increase with booster doses, up to 50-85%

** Symptoms include diarrhoea, headache, and/or muscle pains

RARE, MORE SEVERE REACTIONS

Vaccine	Reaction	Onset interval	Rate per million doses
BCG	Suppurative lymphadenitis BCG osteitis Disseminated BCG	2-6 months 1-12 months 1-12 months	100-1000 1-700 2
Hib	Nil known		
Hep B	Anaphylaxis Guillain Barré syndrome	0-1 hour 1-6 weeks	1-2 5
Measles /MMR	Febrile seizures Thrombocytopaenia Anaphylaxis	5-12 days 15-35 days 0-1 hour	333 33 1-50
OPV	Vaccine-associated paralytic poliomyelitis (VAPP) **Risk is higher for first dose, adults, and immunocompromised**	4-30 days	0.76-1.3 (1st dose) 0.17 (subsequent doses) 0.15 (contacts)

RARE, MORE SEVERE REACTIONS (2)

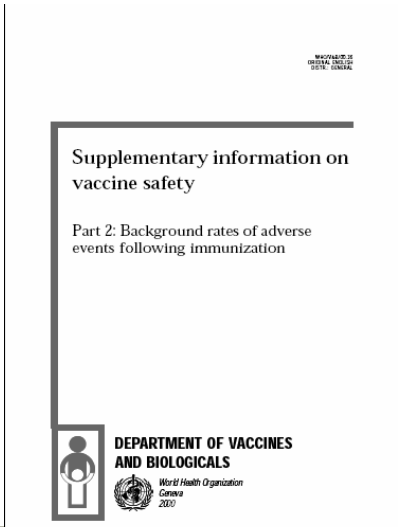
Vaccine	Reaction	Onset interval	Rate per million doses
Tetanus	Brachial neuritis Anaphylaxis Sterile abscess	2-28 days 0-1 hour 1-6 weeks	5-10 1-6 6-10
Tetanus-diphtheria	Nil extra to tetanus reactions		
DTP	Persistent (>3 hrs) inconsolable screaming Seizures Hypotonic, hyporesponsive episode (HHE) Anaphylaxis/shock Encephalopathy	0-24 hours 0-3 days 0-24 hours 0-1 hour 0-3 days	1000-60 000 570 570 20 0-1

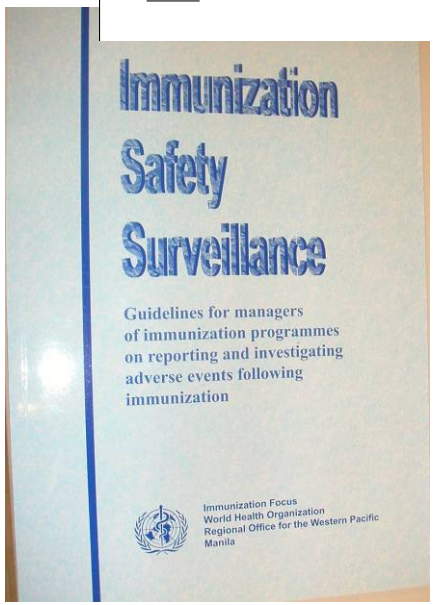
RARE, MORE SEVERE REACTIONS (3)

Vaccine	Reaction	Onset interval	Rate per million doses
Japanese encephalitis	Serious allergic reaction Neurological event		10-1000 1-2.3
Yellow fever	Post-vaccination Encephalitis Allergic reaction/anaphylaxis Viscerotropic disease (multiple-organ failure)	7-21 days 0-1 hours	500-4000 in infants<6 months 5-20 1/10,000,000 Brazil

Practical value of Rates of Rare Reactions

- Can be used to assess extent of underreporting
- Used to identify trends of concern (e.g. higher than expected rates reported in system)
  - Consider product quality
  - Special risks in local population
- Time to onset of events useful for case investigation and verifying case validity





MEASLES SIA CONDUCTED IN 1,526,530 CHILDREN

ESTIMATED AEFI

Common, minor AEFI (not reportable)

- 152,653 cases of local reaction, pain swelling redness
- 76,327 cases of fever
- 76,327 cases of irritability, malaise, non-specific symptoms

Rare, more severe AEFI (reportable?)

- 508 cases of febrile seizures
- 50 cases of thrombocytopenia
- between 1 and 76 cases of anaphylaxis

ACTUAL AEFI

- 6 non-serious

EXAMPLES OF REAL SAFETY ISSUES

- Rare "disasters" due to faulty production; risk drastically reduced by better production controls and better science
    - Lubeck incident (1929-30): occurrence of TB following vaccination
    - Cutter (inactivated) polio incident (1955)

- True vaccine reactions
    - Vaccine-associated paralytic polio
    - Mumps vaccine-associated aseptic meningitis
    - Rotavirus and intussusception
    - Bell's palsy following intranasal flu
    - Influenza vaccine and oculorespiratory syndrome

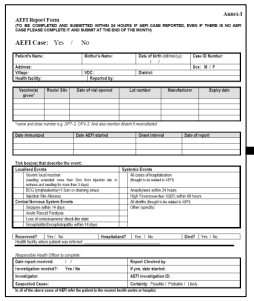
EXAMPLES OF UNPROVEN ASSOCIATIONS AND PUBLIC CONCERNS

- Influenza vaccine and Guillain Barré Syndrome
- MMR and autism, Crohn's disease
- Polio and HIV
- Hepatitis B and multiple sclerosis
- DTP and permanent brain damage
- DTP and increased risk of mortality
- Aluminium and macrophagic myofasciitis
- Bovine spongiform encephalopathy (BSE)
- Thimerosal and autism, neurodevelopmental problems
- Multiple vaccines given simultaneously

PRACTICAL POINTS

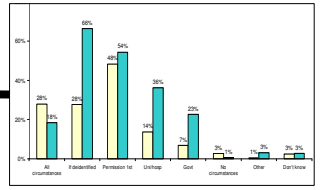
- Vaccination should only be conducted by trained and appropriately equipped staff
- Provide training to health staff on what common reactions to expect and what to advise parents accordingly
- Contraindications and precautions should be known and followed by all vaccinators
- Health staff need to know how to diagnose and manage vaccine reactions and differentiate them from other events
- Maintain knowledge on expected rates of severe events – useful in case investigation and causality assessment.

Key elements of an effective AEFI surveillance system



Rapid notification of basic information

Rapid & effective evaluation of information

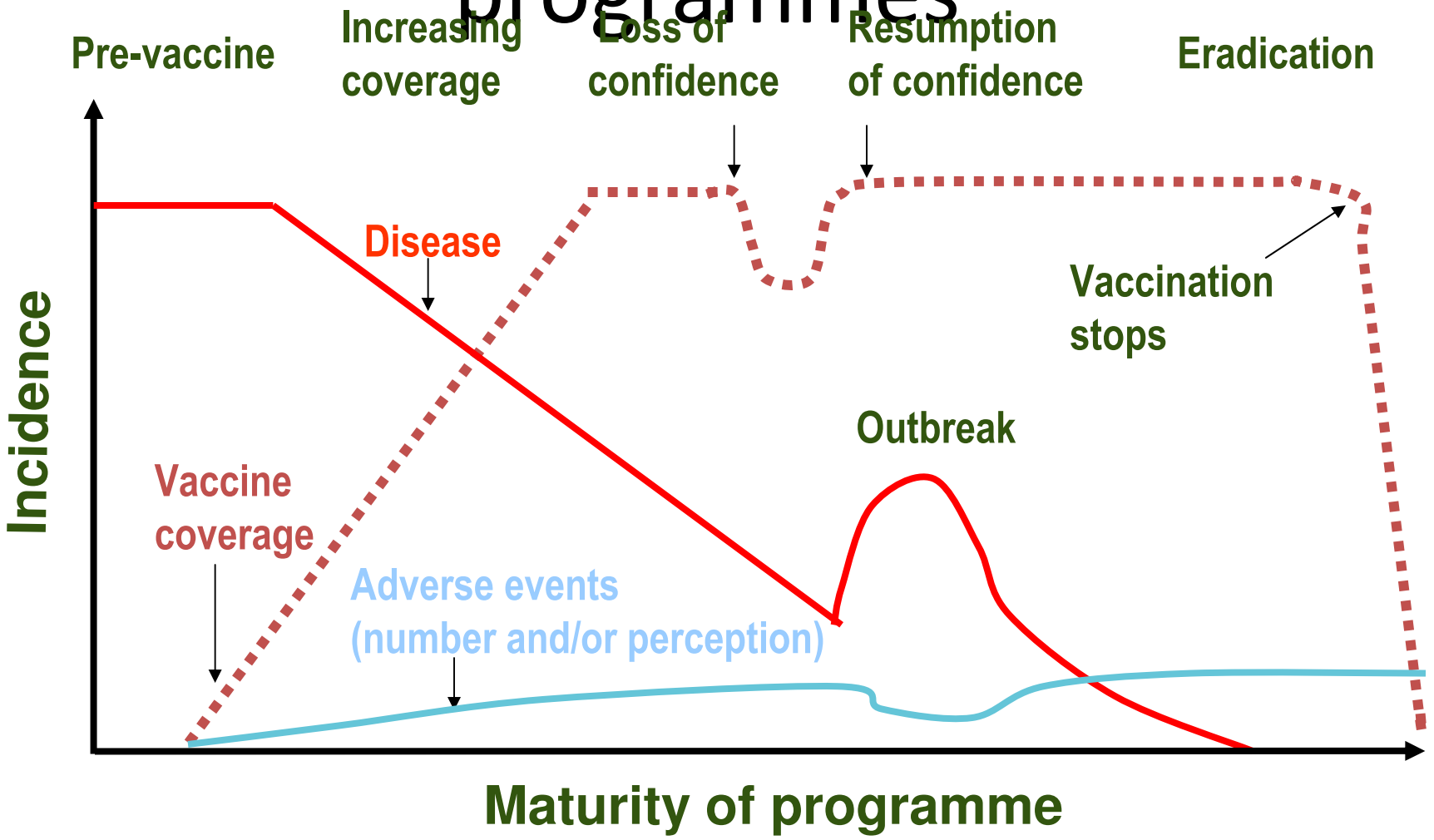


Rapid and effective response/action

Ensure appropriate outcome of action/response

Adequate education and training of role players

Evolution of immunization programmes

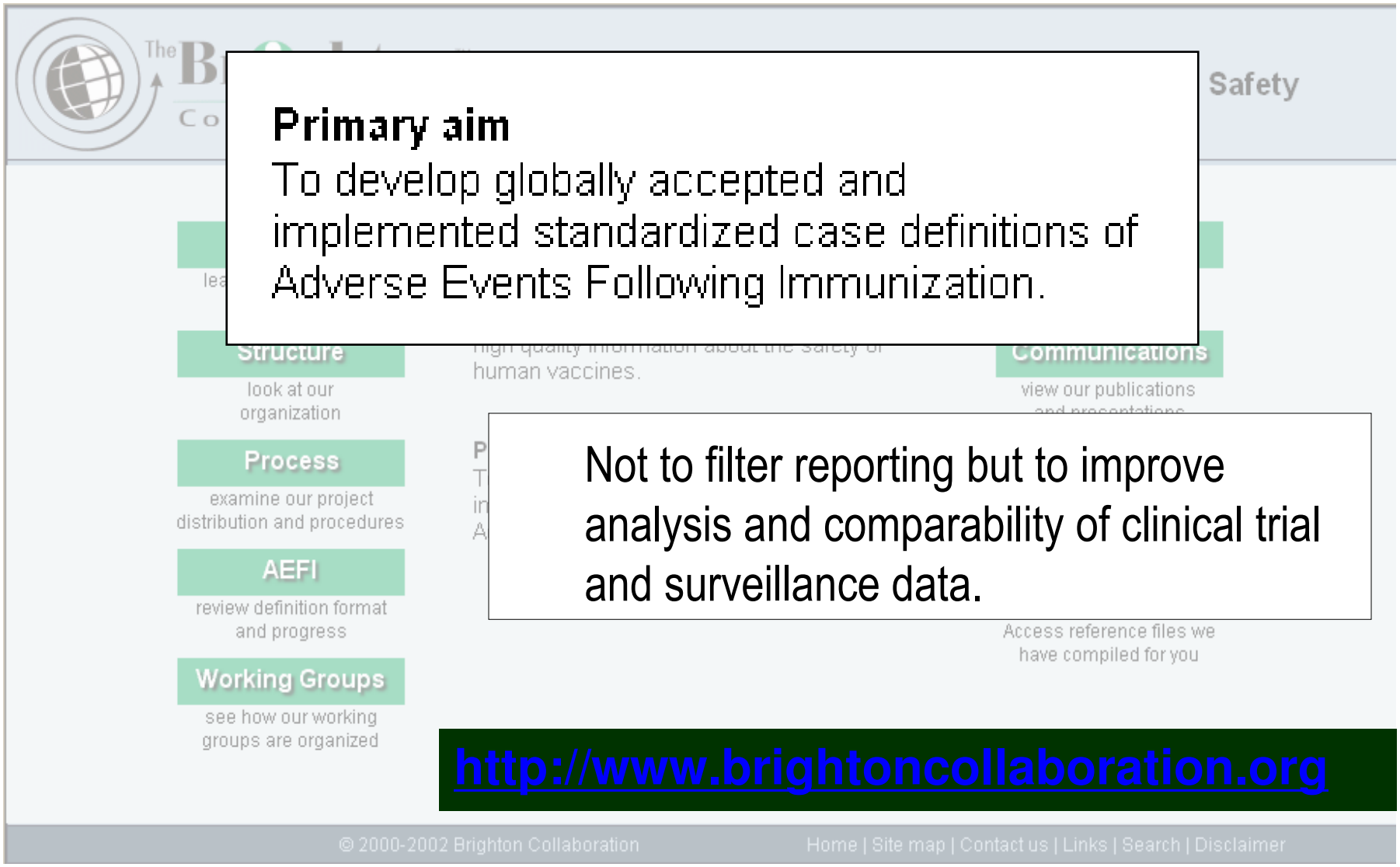


Adapted from: Chen RT et al, *Vaccine* 1994;12:542-50

Global initiatives

- Global Advisory Committee on Vaccines Safety (GACVS)
- WHO International Drug Monitoring Program (Uppsala Monitoring Centre)
- Vaccine Safety Net
- Brighton Collaboration
- Global Training Network (GTN)

The Brighton Collaboration



The Brighton Collaboration

- FEVER
  - what does it mean for WHO
  - what does it mean in different countries
  - what does it mean in clinical trials
  - what does it mean for manufacturers
  - what does it mean for YOU?

Clinical Infectious Diseases 2004; 39:389–94 INVITED ARTICLE VACCINES
Bruce Gellin and John F. Modlin, Section Editors

Fever after Immunization: Current Concepts and Improved Future Scientific Understanding

Katrin S. Kohl,[1] S. Michael Marcy,[2,3] Michael Blum,[6] Marcy Connell Jones,[5] Ron Dagan,[9] John Hansen,[4] David Nalin,[7,a] Edward Rothstein,[8] and the Brighton Collaboration Fever Working Group[b]

- **Lower limit**
  - ≥37.1°C to ≥ 38.5°C
- **Site of measurement**
  - rectum, oral, axillary, tympanic, umbilical, inguinal, great-toe, forehead, abdominal skin
- **Instrument for measurement**
  - mercury-in-glass, electronic, infrared, and thermophototropic liquid crystal thermometers

Available online at www.sciencedirect.com
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Vaccine 22 (2004) 551–556
Vaccine
www.elsevier.com/locate/vaccine

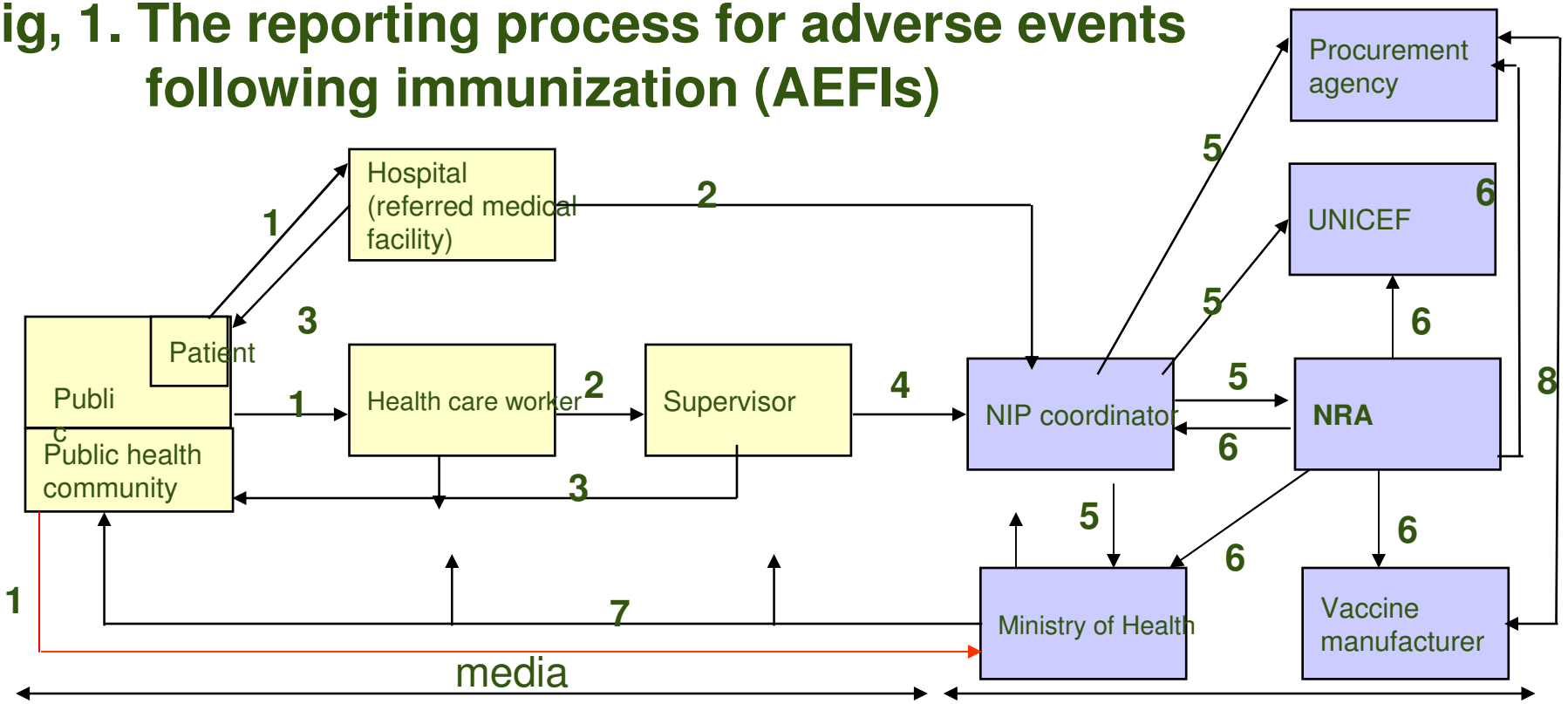
Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation

S. Michael Marcy[a], Katrin S. Kohl[b,*], Ron Dagan[c], David Nalin[d], Michael Blum[e], Marcy Connell Jones[f], John Hansen[g], Jerry Labadie[h], Lucia Lee[i], Bryan L. Martin[j], Katherine O'Brien[k], Edward Rothstein[l], Patricia Vermeer[m], The Brighton Collaboration Fever Working Group[n, o, 1]

ELEMENTS OF AEFI SURVEILLANCE SYSTEM

- Detection
- Reporting
- Investigation
- Analysis
- Corrective action
- Communication/feedback

Fig, 1. The reporting process for adverse events following immunization (AEFIs)



Functions	Loop 1		
Health care worker	**Supervisor**	**NIP coordinator**	**NRA**
Recognizes AEFIs Reports AEFIs Treats patient/ refers patient for treatment	Stimulates reports Investigates Filters Provides feedback Manages data Proposes classification	Receives reports Transmits reports Triages Works with environment Manages data Ensures response	Receives reports Transmits reports Shares database Evaluates reports Takes action Checks product Notifies

NIP: national immunization programme; NRA: national regulatory authority

Loop 2

1 Initial report
2 Report to action level
3 Investigation
4 Send on reports meeting criteria
5 Report for consultation/ action
6 Decision communication (regulatory, public health)
7 Public statement/feedback
8 Contract information

Discussion on Case Investigation

Learning from

The Mangaldan Affair!!

WHO Aide Memoire: AEFI Investigation

A Useful Investigation and training Tool!

WORLD HEALTH ORGANIZATION

AEFI Investigation

AIDE MEMOIRE

An adverse event following immunization (AEFIs) is a medical incident that takes place after an immunization, causes concern and is believed to be caused by the immunization. Programmes providing immunization services should include a system for AEFI detection and reporting, investigation and management, data analysis, corrective action, relevant communication and evaluation of the system.

The ultimate goal of an investigation is to determine whether the vaccine or immunization process is responsible for the reported event(s) or to find another and correct it if possible, and reassure the public.

There are 4 possible causes of AEFI:

Vaccine reaction: event caused by some component of the vaccine – the active component of the vaccine itself, the preservative, the stabilizer or other. The majority of vaccine reactions are "common" and expected, mild, settle without treatment and have no long-term consequences. More serious reactions are very rare – usually of a fairly predictable (albeit extremely low) frequency;

Programme error: event caused by error in vaccine preparation, handling or administration;

Coincidence: event where something happens after the immunization but is not caused by the vaccine or the programme; and

Injection reaction: event arising from anxiety about the injection (needle).

The purposes of investigating AEFI cases are:

1) to confirm a reported diagnosis of AEFI and clarify the details and outcome;
2) to determine whether unimmunized persons are experiencing the same medical event(s);
3) to investigate the link between the vaccine given and the AEFI ;
4) to determine the contribution of operational aspects of the programme to the reported AEFI;
5) to determine whether a reported event was isolated or part of a cluster;
6) to determine the cause of the AEFI so as to provide the best intervention/medical care and take any further action deemed necessary.

In most cases, a preliminary investigation of an AEFI can be made by the health worker who detected the case, e.g. a health centre staff member or a nurse or physician in a hospital.

Serious AEFI cases or AEFI clusters should be investigated immediately with involvement from central levels including epidemiological and/or clinical expertise. A cluster of AEFIs can be defined as two or more cases of the same adverse event related in time, place or vaccine administered.

Inadequate planning or response may lead to a crisis with loss of confidence in the vaccination service. It is essential that programme managers:

1) anticipate the crisis and be prepared to deal with it when it occurs;
2) verify the facts of any event before making any public statement;
3) are familiar with a plan for reacting to any crisis should it happen. If no plan exists programme managers should develop one;
4) be well informed so that appropriate national and regional managers can be rapidly briefed to take charge and deal with political and media enquiries.

☑ Checklist

1. Be prepared

- ☐ Read the resource documents on reporting, management and investigation of AEFIs.
- ☐ Develop standards: case definitions for reportable AEFIs, use of reporting forms and investigation procedures.
- ☐ Designate and train staff to conduct an AEFI investigation using the investigation form.
- ☐ Train staff on how to collect specimens.
- ☐ Establish procedure, criteria and designated person for notifying WHO and UNICEF (if UN- supplied vaccine) or other relevant party depending on procurement mechanism
- ☐ Establish a National Technical Advisory Committee with representation from major medical organizations
- ☐ Identify a spokesperson for public communications.

2. Receiving a report

- ☐ Ensure immediate reporting of most serious events and rapid attention to reports received
- ☐ Verify the information in the report and classify and assess the AEFI using established case definitions. Decide whether it needs further investigating.
- ☐ If investigation is warranted, travel to the location of the AEFI, or delegate responsibility to another trained person

3. Investigate and collect data

- ☐ Ask about the patient
- ☐ Ask about the vaccine and other drugs potentially received
- ☐ Ask about other vaccinees
- ☐ Ask about immunization services
- ☐ Observe the service in action
- ☐ Ask about cases in unvaccinated persons
- ☐ Establish a more specific case definition if needed
- ☐ Formulate a hypothesis as to what caused the AEFI

Collect specimens if appropriate:

- ☐ from the patient
- ☐ the vaccine (and diluent if applicable)
- ☐ the syringes and needles

4. Dispatch specimens to appropriate testing facility (laboratory, regulatory authority, etc.)

5. Analyze the data

- ☐ Review epidemiological,clinical, and laboratory findings
- ☐ Summarize and report findings

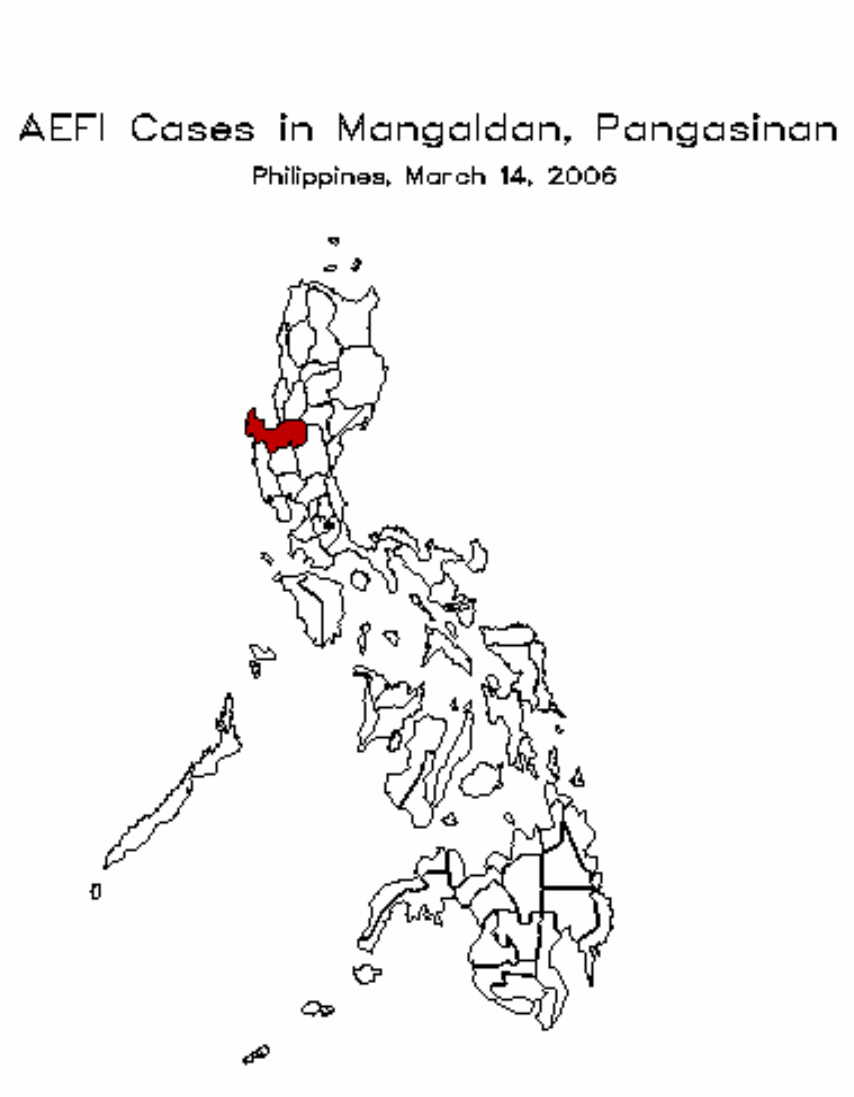
6. Take action

- ☐ Communicate with health staff
- ☐ Communicate findings and action to the parents and public
- ☐ Correct problem (based on the cause) by improving training, supervision, and/or distribution of vaccines/injection equipment
- ☐ Replace vaccines if indicated

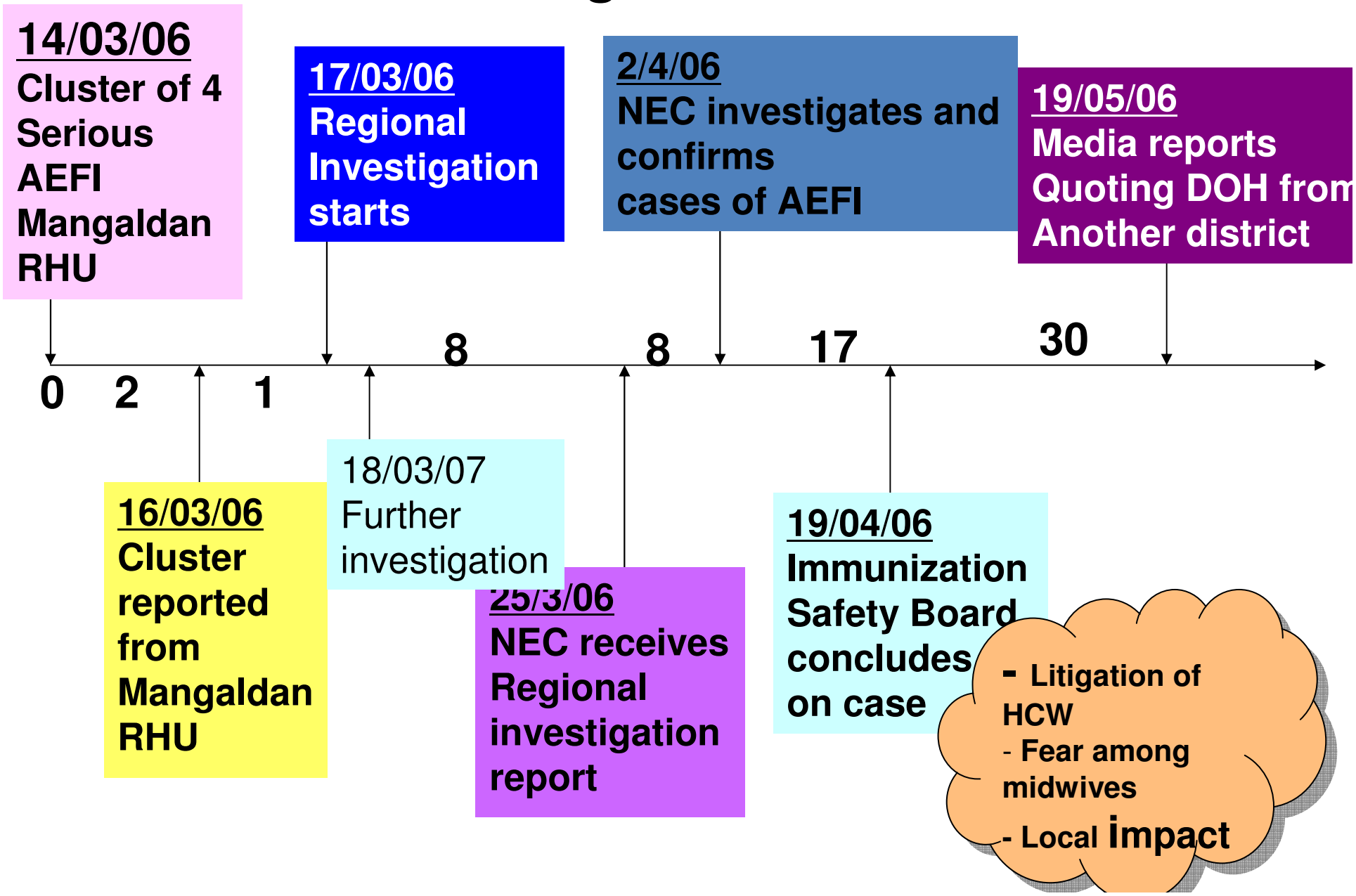
March 14, 2006

4 hours following Measles vaccination, 4 cases of apparent signs and symptoms of fever, vomiting, generalized redness manifested

Mangaldan, Pangasinan
- First class municipality
- Barangays 30
- Total Population 92,881
- Target population (FIC) 2,786



The Mangaldan Cluster…



Timelines

- Detection
- Reporting
- Investigation
- Response
- Communication/Feedback

What are the challenges we faec in achieving efficient timelines?

Investigation Procedure

1. Ask about the patient
2. Ask about vaccine and other drugs
3. Ask about other vaccines
4. Ask about immunization services
5. Observe the services in action
6. Ask about cases in unvaccinated?
7. Establish a more specific case definition
8. Formulate hypothesis on cause
9. Collect specimens
   - Patient, vaccine, syringes

Refer to the Aide Memoire on Case Investigation!

1) Ask about the patients

- These were the only 4 immunized at that time
- Diagnosis/Outcome
  - Child #1: “Hypersensivity Reaction”—not admitted
  - Child #2: “Toxic Shock Syndrome”—Admitted ICU
  - Child #3: “Systemic Viral Illness” — Admitted ICU
  - Child #4: “Septic Shock Syndrome—Admitted ICU and Died. Autopsy revealed: Cause of Death was cerebral edema, severe, secondary to acute disseminated meningoencephalitis, probably viral in etiology
- Siblings were not ill

Any other information?

2) Ask about vaccine and other drugs

Morning (Brgy Guilig, Mangaldan)

- 15 children given DPT vaccine
- 14 children given OPV vaccine
- 5 children given BCG vaccine

- 4 children given Measles vaccine
  - All 4 children received measles vaccine from the *same vial* at the *same site*; 2:45-3:30 PM, *same lot number and expiry date*.

Any other information?

3) Ask about other vaccines…

Other vaccines given at the same time?

4) Ask about immunization services & 5) Observe services in action…

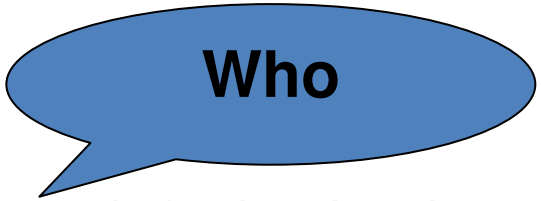
- Medical records and EPI documents reviewed
- Immunization Process assessed
- Ocular Inspection & vaccine storage audited
- Interview with health worker revealed use of aspirating needle and leaving it pierced on the vial and placing back the vial in multicooler while waiting for the next child
- Use of ADS not practiced
- Vaccinator did not follow prescribed guidelines in the administration of vaccines (use of plastic iced water instead of cold dogs)

6) Ask about cases in unvaccinated…

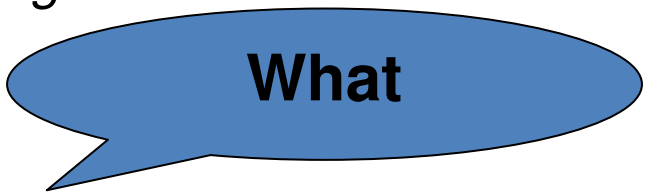
- RITM identified 3 other regions allocated same vaccine lot numbers ; No reported similar event from time of receipt of AMV.
  - No other reported AEFI within the region.

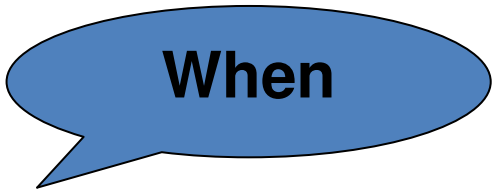
Any other information?
Would this information be adequate in your country?

7) Establish a more specific case definition



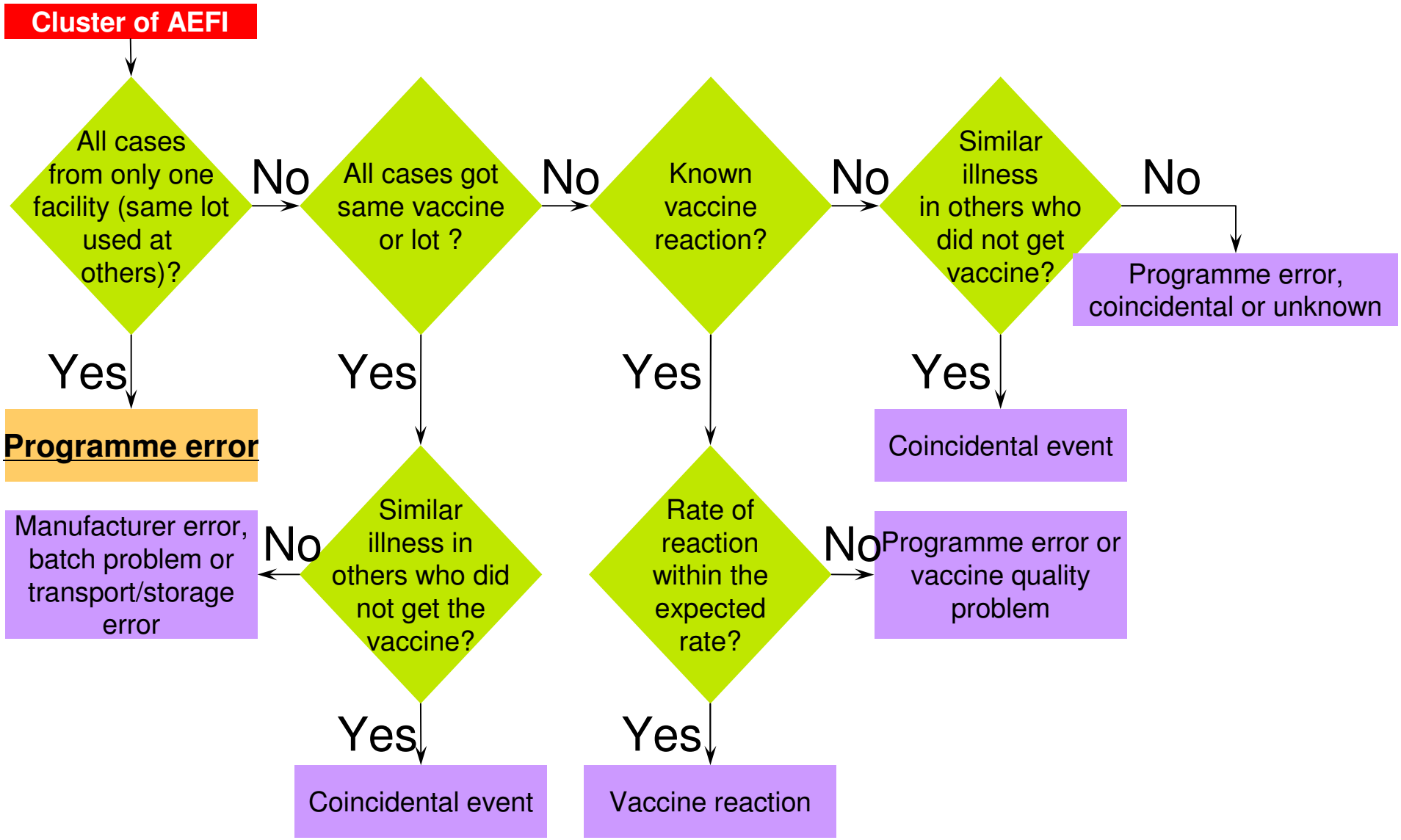
- ***Case definition:*** *Child (9 -13 months) who developed 3 or more of the following:*
  - *fever,*
  - *vomiting,*
  - *diarrhea,*
  - *seizure,*
  - *redness,*
  - *change of behavior,*
  - *swelling on vaccine site,*
  - *cyanosis*

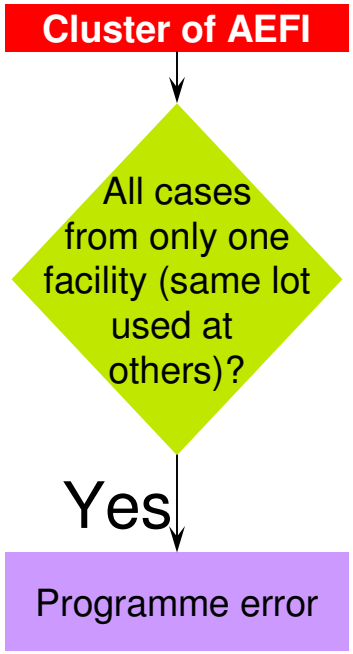




Within the first 24 hours of measles vaccination
on March 14, 2006
in Bgy. Guilig, Mangaldan, Pangasinan

8) Formulate hypothesis on cause





- Lot distributed to other sites, but not yet in use?
- Coincidental?
  Ability to identify other common factors
- Unknown

9) Collect specimens and dispatch: Patient, vaccine, syringes

- Region tested 3 AMV vials & 1 diluent in RITM
  - 1 opened vial: (+) Staph aureus
  - 1 diluent positive Bacillus spp.
  - 2 Unopened vials
    - 1 No growth on primary media; but positive Bacillus spp. on BHIB
    - 1 no growth on any media
- Used vial was (+) Staphylococcus aureus
- Recovery of Baccillus spp in 1 unopened MV vials & diluent
  - According to BFAD specialized collection techniques are needed. Most likely a contaminant.

Would you like any additional laboratory information or tests?
Should the vaccine or diluent have been tested?
Any issues on specimen collection, testing and validity of results?

Analyze Data & Summarise Findings

ISB Conclusion

AEFI were caused by programme error most probably due to non-sterile injection from contaminated vial

- **Clustering of AEFI**
- **No reported AEFI cases in other health facilities using the same lot of AMV**
- **Diagnoses of Infection (Abscess, TSS)**
- **Use of aspirating needle, leaving it pierced on vial & placing back vial in the mini-cooler while waiting for next child**
- **Used vial was (+) for Staph. aureaus**
- **Vaccinator did not follow prescribed guidelines in the administration of the vaccines (e.g. used of iced water in plastic instead of cold dogs)**

Practical Issues when Developing your Investigation Procedures

- Decide WHAT should be investigated
  - (develop reporting system around these events)
- Decide WHO should conduct investigation and in what TIMEFRAME
- Design Investigation procedure and forms to collect all relevant information for determining cause and assessing causality
  - (see Aide Memoire on Case Investigation)
- Have system in place to conduct post mortems and lab testing (e.g. blood samples etc)
- Decide which events require high level versus lower level investigation