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IMMUNIZATION SAFETY SURVEILLANCE:

GUIDELINES FOR MANAGERS OF IMMUNIZATION PROGRAMMES ON REPORTING AND INVESTIGATING ADVERSE EVENTS FOLLOWING IMMUNIZATION

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An electronic version of this document is available on the WPRO website: www.who.org.ph. The contents of this document are also available as a PowerPoint presentation, on request from the Immunization Focus, World Health Organization, Western Pacific Regional Office (WPRO).

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GLOSSARY

Adverse event following immunization (AEFI)	A medical incident that takes place after an immunization, causes concern, and is believed to be caused by immunization (Table 1, p. 7 has classification of AEFIs).
Cluster	Two or more cases of the same or similar event related in time, geography, and/or vaccine administered. National programme managers may decide upon a more precise definition.
Injection safety	The public health practices and policies dealing with various aspects of the correct administration of injections (including waste disposal) so that the risk of transmission of bloodborne pathogens is minimized. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).
Immunization/ vaccination/ vaccine safety	The public health practices and policies dealing with the various aspects of the correct administration of vaccines, focusing on minimizing the risk of transmission of disease with the injection and maximizing the effectiveness of the vaccine. The term encompasses the spectrum of events from proper manufacture to correct administration. *The term usually includes both injection safety (programmatic errors compromising injection safety) and vaccine safety (faults in the vaccine itself compromising vaccine safety).*
Immunization safety surveillance	A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFIs.
Safe injection practice	Those public health practices and policies which ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected. *This is the preferred generic term for this subject.*
Surveillance	The continuing, systematic collection of health data that is analysed and disseminated to enable public health decision-making and action to protect the health of populations.
Vaccine	[1]Biological substance that is administered to individuals to elicit immunity (protection) against a specific disease. [2]Combination vaccines (e.g. DTP) protect against more than one disease. [3]Live viral vaccines (e.g. poliomyelitis, measles) contain attenuated (weakened) version of the disease-causing virus. The vaccine virus causes a mild infection, usually with no or minimal symptoms, that creates immunity against that virus.

ABBREVIATIONS

BCG	Bacillus Calmette-Guerin - vaccine for tuberculosis (TB)
DT	diphtheria-tetanus vaccine
DTP	diphtheria-tetanus-pertussis (whole-cell) vaccine
EPI	Expanded Programme on Immunization
Hib	*Haemophilus influenzae* type b vaccine
MMR	measles-mumps-rubella vaccine
MR	measles-rubella vaccine
OPV	oral poliomyelitis vaccine
Td	Adult tetanus-diphtheria vaccine
WHO	World Health Organization

1. PURPOSE

This document provides a guideline for managers of immunization programmes (and others responsible for vaccine safety) on adverse event following immunization (AEFI) surveillance. As vaccine preventable diseases become less visible through effective immunization programmes, more attention will be given to AEFIs.

A good example of this is poliomyelitis. When there are many cases of poliomyelitis in the community, the very rare risk (about 1 in 3 million) of vaccine associated paralytic poliomyelitis (VAPP) is unlikely to cause major concern. In countries where there is no longer wild poliovirus, VAPP becomes much more visible. In some countries, VAPP has become of sufficient concern that they have changed from oral to injectable poliomyelitis vaccine.

An increase in vaccine use (e.g., mass immunization campaigns) will lead to more vaccine reactions as well as more coincidental events. Programme errors may also increase. Reporting and investigating AEFIs can be used to identify and correct programme errors and may help to distinguish a coincidental event from a true AEFI. Surveillance of AEFIs is an effective means of monitoring immunization safety and contributes to the credibility of the immunization programme. It allows for proper management of AEFIs and avoids inappropriate responses to reports of AEFIs that can create a sense of crisis in the absence of immunization safety surveillance.

The purpose of this document is to help managers establish an immunization safety surveillance system. It provides:

- a classification for AEFIs and the objectives of immunization safety surveillance
- the expected rates of vaccine reactions
- descriptions of AEFI reporting, investigating, and responding processes
- a communication strategy on immunization safety for the public and the media.

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2. ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFIS)

Vaccines used in national immunization programmes are extremely safe and effective. But, no vaccine is perfectly safe and adverse events can occur following immunization. In addition to the vaccines themselves, the process of immunization is a potential source of adverse events.

An adverse event following immunization (AEFI) is any adverse event that follows immunization that is believed to be caused by the immunization. Reported adverse events can either be true adverse events, i.e. really a result of the vaccine or immunization process, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization. For the purpose of these guidelines AEFIs are classified into five categories (see Table 1 below). Immunization can cause adverse events from the inherent properties of the vaccine (**vaccine reaction**), or some error in the immunization process (**programme error**). The event may be unrelated to the immunization, but have a temporal association (**coincidental event**). Anxiety-related reactions can arise from the fear or pain of the **injection** rather than the vaccine. In some cases the cause of the AEFI remains **unknown**.

Table 1. Classification of adverse events following immunization (AEFIs)

Vaccine reaction:	event caused or precipitated by the vaccine when given correctly, caused by the inherent properties of the vaccine.
Programme error:	event caused by an error in vaccine preparation, handling, or administration.
Coincidental:	event that happens *after* immunization but **not** caused by the vaccine - a chance association.
Injection reaction:	event from anxiety about, or pain from, the injection itself rather than the vaccine
Unknown:	event's cause cannot be determined.

2.1 Vaccine reactions

Vaccine reactions may be classified into common, minor reactions or rare, more serious reactions. **Most vaccine reactions are minor and settle on their own.** More serious reactions are very rare and in general do not result in long-term problems.

2.1.1 Common, minor vaccine reactions

The purpose of a vaccine is to induce immunity by causing the recipient's immune system to react to the vaccine. Local reaction, fever and systemic symptoms can result as part of the immune response. In addition, some of the vaccine's components (e.g. aluminium adjuvant, stabilizers or preservatives) can lead to reactions. **A successful vaccine reduces these reactions to a minimum while producing the best possible immunity.** The proportion of reaction occurrences likely to be observed with the most commonly used vaccines, and their treatments, are listed in Table 2.

These reactions occur within a day or two of immunization (except for measles/MMR - 6 to 12 days after immunization) and they only last one to a few days.

Table 2. Common, minor vaccine reactions and treatment

Vaccine	Local reaction (pain, swelling, redness)	Fever >38°C	Irritability, malaise and systemic symptoms
BCG	90-95%	-	-
Hib	5-15%	2-10%	-
Hepatitis B	adults ~15% children ~ 5%	1-6%	-
Measles / MMR /MR	~10%	5-15%%	5% (rash)
Oral poliomyelitis (OPV)	-	<1%	<1%#
Tetanus / DT / Td	~10%&	~10%	~25%
Pertussis (DTP – whole cell)	up to 50%	up to 50%	up to 55%
Treatment	• Cold cloth at injection site • paracetamol*	• give extra fluids • wear cool clothing • tepid sponge or bath • paracetamol*	• give extra fluids • paracetamol*

\# Symptoms include diarrhoea, headache, and/or muscle pains

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

* Paracetamol dose: up to 15mg/kg every 4 hours, maximum of 4 doses in 24 hours

Local reactions include pain, swelling and/or redness at the injection site and can be expected in about 10% of vaccinees, except for those injected with DTP (whole cell), or tetanus boosters, where up to half can be affected. BCG causes a specific local reaction that starts as a papule (lump) two or more weeks after immunization that then becomes ulcerated and heals after several months, leaving a scar. Keloid (thickened scar tissue) from the BCG lesion is more common among Asian and African populations.

Systemic reactions include fever and occur in about 10% or less of vaccinees, except for DTP where it is again about half. Other common systemic reactions (e.g., irritability, malaise, 'off-colour', loss of appetite) can also occur after DTP. For measles/MMR and OPV the systemic reactions arise from vaccine virus infection. Measles' vaccine causes fever, rash and/or conjunctivitis, and affects 5-15% of vaccinees. It is very mild compared to 'wild' measles, but for severely immunocompromised individuals, it can be severe, even fatal. Vaccine reactions for mumps (swollen parotid gland) and rubella (joint pains and swollen lymph nodes) affect less than 1% of children. Rubella vaccine causes symptoms more often in adults, with 15% suffering from joint pains. Systemic reactions from OPV affect less than 1% of vaccinees with diarrhoea, headache and/or muscle pain.

2.1.2 Rare, more serious vaccine reactions

Table 3 details the rare vaccine reactions; case definitions are in Annex A. Most of the rare and more serious vaccine reactions (e.g., seizures, thrombocytopaenia, hypotonic hyporesponsive episodes, persistent inconsolable screaming) do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects. Although encephalopathy is included as a rare reaction to measles or DTP vaccine, it is not certain that these vaccines in fact cause encephalopathy (brain damage).

Although other serious events have been reported following immunization, it is likely that there other events are coincidental, rather than true reactions.

Table 3. Rare vaccine reactions, onset interval, and rates

Vaccine	Reaction	Onset interval	Number of doses per reaction	Reactions per million doses
BCG	Suppurative lymphadenitis	2-6 months	1 in 1-10 000	100- 1000
	BCG osteitis	1-12 months	1 in 3 000 to 1 in 100 million	0.01 - 300
	Disseminated BCG infection	1-12 months	~1 in 1 million	0.19-1.56
Hib	None known			
Hepatitis B	Anaphylaxis	0-1 hour	1 in 6-900 000	1-2
Measles/MMR/MR[#]	Febrile seizures	6-12 days	1 in 3000	330
	Thrombocytopaenia (low platelets)	15-35 days	1 in 30 000	30
	Anaphylactoid (severe allergic) reaction	0-2 hours	~1 in 100 000	~10
	Anaphylaxis	0-1 hour	~1 in 1 000 000	~1
	Encephalopathy	6-12 days	<1 in 1 000 000	<1
Oral poliomyelitis	Vaccine associated paralytic poliomyelitis	4-30 days	1 in 2.4-3 million	~0.4[!]
Tetanus	Brachial neuritis	2-28 days	0.5-1 in 100 000	5-10
	Anaphylaxis	0-1 hour	1 in 100 000 to 1 in 2 500 000	0.4-10
Tetanus – diphtheria	None extra to tetanus reactions			
Pertussis (DTP– whole cell))	Persistent (> 3 hours) inconsolable screaming	0-24 hours	1 in 15 to 1 in 1000	(0.1-6%) 1 000-60 000
	Seizures	0-2 days	1 in 1750 to 1 in 12 500	80-570[@]
	Hypotonic, hyporesponsive episode (HHE)	0-24 hours	1 in 1000-33 000	30 - 990
	Anaphylaxis	0-1 hour	1 in 50 000	20
	Encephalopathy (*note*: risk may be zero)	0-2 days	0-1 in 1 million	0-1

[#] Reactions (except anaphylaxis) do not occur if already immune (~90% of those receiving a second dose); children over six years unlikely to have febrile seizures.

[@] Seizures mostly febrile and risk depends on age, with much lower risk in infants under the age of 4 months.

[!] VAPP Risk higher for first dose (1 in 750,000 compared to 1 in 5.1 million for subsequent doses), and for adults and immunocompromised.

The information in Tables 2 and 3 can be used to:

- anticipate the expected rate and type of reactions for a specific immunization programme
- identify events that are probably unrelated to immunization (e.g. outside the time window or not clinically compatible)
- compare reported with expected rates of reactions (the efficiency of reporting)

- trigger an investigation if the reported rate is greater than the expected rate for minor reactions, or if a major reaction is reported.

2.1.3 Prevention and treatment of vaccine reactions

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, vaccines are contraindicated if there is serious allergy to the vaccine or its components. Live vaccines should not be given to immune-deficient children.

Advice on managing the common reactions should be given to parents, as well as instructions to return if there are more serious symptoms. This will help to reassure parents about immunization and prepare them for these common reactions.

Paracetamol, at a dose of up to 15mg/kg every four hours with a maximum of four doses in 24 hours, is useful for the common minor reactions. It eases pain and reduces fever. Paracetamol can also be used at the time of DTP immunization to prevent fever.

A feverish child can be cooled with a tepid sponge or bath, and by wearing cool clothing. Extra fluids need to be given to feverish children. For a local reaction, a cold cloth applied to the site may ease the pain.

More details on treatment of vaccine reactions are in Annex A and for anaphylaxis Annex B.

2.2 Programme errors

Programme errors result from errors and accidents in vaccine preparation, handling, or administration (see Table 4 below). They are preventable and detract from the overall benefit of the immunization programme. The identification and correction of these errors are of great importance.

A programme error may lead to a cluster of events associated with immunization. These clusters are usually associated with a particular provider, or health facility, or even a single vial of vaccine that has been inappropriately prepared or contaminated. Programme errors can also affect many vials (e.g. by freezing vaccine during transport leading to an increase in local reactions).

Table 4. Programme errors leading to adverse events

Programme errors	Adverse event
Non-sterile injection: • reuse of disposable syringe or needle • improperly sterilized syringe or needle • contaminated vaccine or diluent • reuse of *reconstituted* vaccine at subsequent session	⇒ Infection (e.g. local suppuration at injection site, abscess, cellulitis, systemic infection, sepsis, toxic shock syndrome, transmission of blood borne virus (HIV, hepatitis B or hepatitis C)).
Vaccine prepared incorrectly: • vaccine reconstituted with incorrect diluent • drugs substituted for vaccine or diluent.	⇒ Local reaction or abscess from inadequate shaking. ⇒ Effect of drug (e.g. muscle relaxant, insulin).
Immunization injected in wrong site: • subcutaneous instead of intradermal for BCG • too superficial for toxoid vaccine (DPT, DT, TT) • buttocks.	⇒ Local reaction or injection site abscess. ⇒ Sciatic nerve damage (+ ineffective vaccine-hepatitis B).
Vaccine transported/stored incorrectly.	⇒ Increased local reaction from frozen vaccine (and ineffective vaccine).
Contraindications ignored.	⇒ Avoidable severe vaccine reaction.

The most common programme error is an infection (including bloodborne virus) as a result of non-sterile injection. The infection can manifest as a local reaction (e.g. suppuration, abscess), systemic effect (e.g. sepsis or toxic shock syndrome), or bloodborne virus infection (e.g. HIV, hepatitis B or hepatitis C).

The symptoms arising from a programme error may help to identify the likely cause. For example, children immunized with contaminated vaccine (usually the bacterium *Staphylococcus aureus*) become sick within a few hours; local tenderness and tissue infiltration, vomiting, diarrhoea, cyanosis and high temperature are the most frequent symptoms. Bacteriological examination of the vial, if still available, can confirm the source of the infection.

Sterile abscesses are rare (~1 per 100 000 doses) local reactions from aluminium containing vaccines, especially DTP. Inadequate shaking of the vaccine before use, superficial injection, and use of frozen vaccine increase the risk of sterile abscess and of local reactions. Contamination of vaccine or injection equipment can also lead to a **bacterial abscess**. For BCG vaccine, injection abscess can arise from improper injection (subcutaneous rather than intradermal injection).

When a drug is used instead of a vaccine or diluent, the effect will depend on the drug used.

Case studies

In 1997 in country A, four separate AEFI clusters of "collapse" occurred up to five minutes following immunization with measles vaccine. All 14 cases presented with hypotonia; 11 became pale; seven cases had cyanosis, dyspnoea and increased saliva secretion; three patients had depressed respiration and one patient died; others recovered in less than one hour. In two of the clinics vials that contained muscle relaxants were found stored with vials containing diluent, and of the same size and shape; labels on a number of vials recovered could not be read. Infrared spectrophotometry of the urine of one of the cases and thin layer chromatographic analysis of vaccine from one of the implicated vials showed the presence of muscle relaxant.

Cause: Use of muscle relaxant instead of diluent.

In one hospital in 1992 in country B, five neonates collapsed a few minutes following immunization with BCG and OPV. Four were resuscitated and one died. Muscle relaxant drugs were found in the refrigerator in which vaccines were also kept.

Cause: *Use of muscle relaxant instead of diluent.*

In 1997 in country C, 21 infants died out of 70 infants supposedly given DTP vaccine. Insulin was stored in similar vials and in the same refrigerator as DTP vaccine.

Cause: *Use of insulin instead of DTP.*

Three infants died, in 1995 in country D, after administration of measles vaccine. Symptoms, developing within five hours post immunization, were fever, rash, vomiting, and diarrhoea, described by the attending health worker as "toxic shock syndrome." Reconstituted vaccine was routinely kept until it was used, and syringes were never sterilized, but washed with ordinary water and wiped with cotton wool. No testing could be done.

Cause: *Non-sterile injection (contaminated reconstituted vaccine).*

In 1996 in country E, four children died and a fifth was hospitalized after receiving measles vaccine from the same vial. Vaccine was not refrigerated, and was transported house to house for immunization. Reactions began four to five hours after vaccination, with vomiting, unconsciousness, and meningeal irritation. *S. aureus* was cultivated from the incriminated vial.

Cause: Non-sterile injection (contaminated reconstituted vaccine).

To avoid programme errors [VSQ 1996]:

- vaccines must only be reconstituted with the diluent supplied by the manufacturer
- **reconstituted vaccines must be discarded at the end of each immunization session and never retained**
- no other drugs or substances should be stored in the refrigerator of the immunization centre
- immunization workers must be adequately trained and closely supervised to ensure that proper procedures are being followed
- careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.

2.3 Coincidental events

An event may occur coincidentally with immunization and at times may be falsely attributed to be a result of the vaccine. In other words a chance temporal association (ie,

event happens *after* immunization) is falsely considered to be *caused* by immunization. These purely temporal associations are inevitable given the large number of vaccine doses administered, especially in a mass campaign.

Vaccines are normally scheduled early in life, when infections and other illnesses are common, including manifestations of an underlying congenital or neurological condition. It is therefore possible for many events, including deaths, to be falsely attributed to vaccine through chance association.

For example, Sudden Infant Death Syndrome (SIDS or cot death) incidence peaks around the age of early childhood immunization. So, many SIDS cases will be in children who have been recently immunized. However, controlled studies have shown that the association of SIDS and immunization is purely coincidental and not causal [Howson et al, 1991].

Case study

In response to a severe diphtheria outbreak in country F in 1996, DT was delivered to children in a mass campaign. The death of a seven-year-old girl, two to three days following immunization was reported. The symptoms reported included convulsions that might have been attributable to a vaccine reaction. Upon investigation, it was found that the girl had a history of convulsions and neurological symptoms unrelated to immunization.

Cause: Coincidental event.

Coincidental adverse events are predictable. The number of events to be expected depends upon the size of the population and the incidence of disease or death in the community. Knowledge of these background rates of disease and deaths allows estimation of the expected numbers of coincidental events.

For example, assume that one million children aged 1-15 years are immunized in a mass campaign and the background mortality rate for this population is 3 per 1000 per year. Then, 250 deaths can be expected in the month after immunization and 8 deaths on the day of the immunization, simply by coincidence. These deaths will be temporally associated with, even though entirely unrelated to, immunization.

A similar calculation is shown in Table 5 for infant (aged under one-year) deaths in selected Western Pacific countries for the number of deaths temporally associated with routine DTP immunization. There will be many coincidental deaths in the day, week and month after immunization, which are only temporally related to immunization. The actual number of coincidental deaths depends on the population size, infant mortality rate, the number of immunization episodes and the immunization coverage.

When comparing expected versus actual events, it is possible to do statistical analysis to ensure that differences are not simply the result of chance. Note that the expected number of death calculations presented here may be inflated as it assumes that children who are near to death will still be immunized.

Table 5. Coincidental deaths temporally linked to DPT immunization

	Infant mortality Per 1000 live births	Number of births per year	Number of infant deaths during one year in: month after immunization	week after immunization	day after immunization
Calculation	=IMR*1,000	N	=(IMR*N/12)* (nv*ppv /12) *12	=(IMR*N/52)* (nv*ppv /52)*52	=(IMR*N/365)* (nv*ppv/365)*365
Australia	5.7	257 874	331	76	11
Cambodia	89.6	406 676	8199	1892	270
China	36.4	20 781 652	170 202	39 277	5596
Japan	4.3	1 193 269	1154	266	38
Laos	104.0	189 195	4427	1022	146
New Zealand	6.68	57 587	86	20	3
Philippines	48.9	1 981 529	21 802	5031	717

NOTE: Assumes uniform distribution of deaths and children who are near to death will still be immunized.
Infant mortality and births from 1998 Western Pacific Region Health Data Bank.

IMR= Infant mortality rate per live birth (can substitute for rate of any event).
N = Number in population (births used as proxy for numbers aged under one year).
nv = number of immunization doses: assumed here to be three visits.
ppv= proportion of population vaccinated: assumed here to be 90% for each dose.
Note: in calculation of deaths the first line of equation shows number of total deaths in period, second line adjusts for exposure to vaccine within that period, multiplied by the number of periods in the year.

In general, coincidental events are clearly unrelated and do not require any investigation (e.g. pneumonia). However, certain serious events may be blamed on the vaccine by the parents or community because of the close temporal association with immunization, especially if the child was previously healthy. Such cases need to be investigated, to allay public fear and maintain credibility. Responding to a community's concerns about immunization safety is important in maintaining confidence in the immunization programme. Calculation of the expected coincidental rate of that event may be helpful in the investigation of an AEFI.

If the same or similar event also affected others in the same age group around the same time, but they did not receive the suspect vaccine(s), then a coincidental event is more likely. There may also be evidence showing that the event is not related to immunization.

Case study

Following a National Immunization Day (NID) in 1996, cases of paralysis were reported after they had received OPV. On laboratory analysis, the wild virus was found, showing that the children had been infected by wild poliovirus before immunization. The cases of poliomyelitis were coincidental, and not caused by vaccine. There were no more poliomyelitis cases after the second NID.

Example of a known vaccine reaction which on investigation proved to be coincidental.

2.4 Injection reactions

Individuals and groups can react in anticipation to and as a result of an injection of any kind. This reaction is unrelated to the content of the vaccine. Fainting is relatively common, but usually only affects children aged over five years. Fainting does not require any management beyond placing the patient in a recumbent position.

The likelihood of faints can be anticipated when immunizing older children, and reduced by minimizing stress in those awaiting injection, through short waiting times, comfortable room temperatures, preparation of vaccine out of recipient's view, and privacy during the procedure. Avoiding injury from the fall is important, and those at risk should be immunized while seated. However, the faint can occur many minutes after the immunization.

Hyperventilation as a result of anxiety about the immunization leads to specific symptoms (light-headedness, dizziness, tingling around the mouth and in the hands).

Younger children tend to react in a different way, with vomiting a common anxiety symptom. Breath-holding may occur, which can end in a brief period of unconsciousness, during which breathing resumes. They may also scream to prevent the injection or run away.

An anxiety reaction to injection can include convulsions in some case. These children do not need to be investigated but should be reassured.

These reactions are not related to the vaccine, but to the injection. Some individuals may be needle-phobic, aggravating such reactions. In a group situation, mass hysteria is possible, especially if a vaccinee is seen to faint or have some other reaction. Clear explanations about the immunization and calm, confident delivery will decrease the level of anxiety about the injections, and thus reduce the likelihood of an occurrence.

Case study

In 1998, a mass measles immunization campaign was piloted in an area. AEFI reporting and investigation was instituted for the programme. Of the 30 reports of AEFIs, nearly half were anxiety reactions, and of the other 16 events that were investigated a further 11 events were found to also be anxiety reactions.

Apparently serious events may in fact be simple injection (anxiety) reactions upon investigation

2.5 AEFIs during immunization campaigns

A campaign involves a **large number of doses** given over a **short period of time** leading to more vaccine reactions and coincidental events. The **rate** of events remains **unchanged**, but the **increased number** of events tend to be noticed by both staff and the public, particularly when injectable vaccines are used and at a time of intensive social mobilization.

Common events in campaigns:

- a **real increase in programme errors** is possible with staff who are unfamiliar with a given vaccine or situation and under pressure from a lot of children needing vaccine quickly; staff may not observe normal safe injection practice
- a wider age group (usually older) is immunized than routinely and staff have less experience in dealing with adverse events to be expected in this older group (e.g. fainting)
- antagonism from some sectors, for a variety of reasons, that will add fuel to any concerns about AEFI during the campaign to justify criticism of the campaign
- rumours spread rapidly and damage the campaign before there is a chance to counter them.

A campaign is an opportunity to strengthen or establish immunization safety surveillance. Proper planning to reduce programme errors, and monitor and respond to AEFI can minimize adverse events and their effects during a campaign. This will limit the potential for negative publicity from an AEFI.

2.6 Differences between surveillance of AEFIs and of adverse events to drugs

Vaccines are administered to healthy people for the prevention of disease while most drugs are used to treat or control disease in sick people. Thus, a much higher level of risk is acceptable for a drug compared to a vaccine. An involuntary risk is perceived as greater than a voluntarily taken risk. This further reduces tolerance of AEFI if there is any element of compulsion in the immunization programme. Also, unlike drugs, vaccines are administered not only for the benefit of the individual, but also for the benefit of the community. Hence, AEFI may be perceived as being the responsibility of the community, as compared to drug reactions.

These differences do not preclude a monitoring system for adverse drug events being used to monitor AEFI. But the system must be sensitive to the specificity of vaccines. Furthermore, in many countries with a single monitoring system, surveillance of AEFI is often overlooked. Different reporting pathways and responses to AEFI need to be built into the existing system of adverse drug event surveillance.

The reporting pathways for the immunization programme may not be part of the usual reporting scheme for drugs and that the most efficient way to collect adverse event reports may be different for vaccines and drugs. The investigation and assessment of causality cannot be done in the same manner for vaccines and drugs. This investigation requires a very different type of expertise and an understanding of immunization programmes. The priority for immunization safety surveillance is to identify and correct programme errors.

The implication of an adverse event is quite different in scale for a vaccine, which is given to an entire cohort of the population compared with a drug, which is only used in a relatively small number of individuals. Hence, the response and communication about AEFI is likely to be both more important to the health of the population, of greater interest, and more of a challenge. The wide use of vaccines also leads to the reporting of many coincidental events, which are only temporally related to immunization.

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3. ESTABLISHING IMMUNIZATION SAFETY SURVEILLANCE

Immunization safety surveillance needs to be a collaborative venture between the immunization programme and, when it exists, the national regulatory authority (NRA), as both parties are responsible for the safety of vaccines. However, the overall administration of the immunization safety surveillance system may be delegated to another organization (e.g. university department), as long as the links with the NRA and the national immunization programme are maintained.

Effective immunization safety surveillance needs to involve the following people:

- **peripheral health workers** - detect and report event (to district office)
- **district level supervisor** - completes an AEFI report, if adverse event meets criteria
- **province level AEFI investigator** - assesses AEFI report and investigates AEFI if it meets criteria; produces regular line listing of reports received, and the conclusion of the investigation if conducted
- **regional/national assessor** - a person (with a deputy for periods of absence) with designated responsibility for immunization safety at regional/national level; reviews information on provincial AEFI returns; conducts regular analysis of AEFI and feeds results back down the system; provides support to provincial investigator; spokesperson for immunization safety
- **regional/national Immunization Safety Committee** - composed of NRA representative, EPI manager, paediatrician, infectious disease physician, neurologist, immunologist, epidemiologist, and possibly a pharmacologist/toxicologist,- reviews overall pattern of reports and investigations; provides the causality assessment on investigations which have not reached conclusions; provides quality control on system (can be part of national immunization advisory group)

In addition, the system needs defined procedures; case definitions; clear guidelines and standard forms for reporting and investigating; forms for line listings; and AEFI database for comprehensive analysis (from lowest practicable level in system up to national level).

The system should build on and mutually strengthen any existing system of reporting information (e.g. immunization coverage reports, disease incidence reports, and adverse drug reaction reports). The best reporting system is that which achieves the highest compliance and takes appropriate action in response to reports.

3.1 Objectives

There are several potential objectives for establishing immunization safety surveillance. Clarifying the most important objective(s) of the system will assist in design and implementation. The relative importance of the objectives will depend on the state of the immunization programme and local circumstances. The objectives may also change over time.

The major goal of immunization safety surveillance is early detection and appropriate and quick response to adverse events in order to lessen the negative impact on the health of the individuals and on the immunization programme. It is an indicator of programme quality. It will also enhance programme credibility and can provide actual country data on vaccine risks.

Potential objectives of immunization safety surveillance include:

- detecting, correcting, and preventing programme errors
- identifying unusually high rates of AEFI with specific vaccine lots or brand
- ensuring that coincidental events are not falsely blamed on immunization
- maintaining confidence in the immunization programme and properly responding to parent/community concerns about immunization safety while increasing awareness (public and professional) about vaccine risks
- generating new hypotheses about vaccine reactions that are specific to the population
- estimating AEFI rates in the population compared with trial and international data.

In establishing immunization safety surveillance, the objectives should be clearly articulated and engender the support of health workers to encourage reporting. If resources are limited, prioritizing the objectives is recommended. One option is to have a minimum level of surveillance conducted on national level to detect programme errors with a few hospitals/facilities conducting more intensive and detailed AEFI surveillance.

It is critical for any information obtained through immunization safety surveillance to be immediately assessed and analysed to identify and respond to problems. Response is a critical aspect of immunization safety surveillance.

3.2 Responsibility for immunization safety surveillance

WHO considers that in all vaccine-producing countries and in all other countries where a national regulatory authority (NRA) exists, the NRA must be involved in immunization safety surveillance.

Roles and responsibility of the NRA should include:

- licensing vaccines according to published requirements
- evaluating clinical performance of the vaccine
- controlling and releasing each batch or lot of vaccine individually, including recall if necessary
- performing laboratory testing
- monitoring vaccine performance (including safety)
- inspecting manufacturing facilities and processes regularly.

Furthermore, WHO recommends that all countries which do not actually produce vaccines must still define minimum specifications for the vaccines they use. There should also be a system of post-marketing surveillance to detect if there are problems of vaccine performance in the field. Certain adverse events following vaccination should be monitored, investigated, and reported.

Immunization safety surveillance should include structured systematic and permanent data collection on the impact of licensed vaccines. In addition, surveillance should include epidemiological analysis of data as well as dissemination to advise manufacturers, national authorities, health care providers and the population itself.

The NRA may have limited knowledge about the immunization programme. It is therefore essential that the immunization programme manager be involved in immunization safety surveillance. The respective role of the two key parties needs to be established.

The immunization programme also provides the denominator on vaccine use that helps to interpret AEFI reports. The number of reports cannot be interpreted without accurate date on the use of that vaccine or specific lot, and its distribution to different areas. Therefore, collection of vaccine distribution data is needed for immunization safety surveillance.

3.3 Learning and training

Immunization safety surveillance needs to include training that will enable appropriate response at all levels in the system. It is also important to learn more about the process and the outcomes in relation to immunization safety from past experience.

The person responsible for immunization safety surveillance needs to keep informed about the latest developments in safety monitoring, and current concerns regarding immunization. This person also needs to be aware of any allegations that may be circulating. This involves keeping abreast of scientific literature and debates on vaccine safety. The information that is gathered needs to be disseminated with a response, as appropriate. The Websites of WHO and the US National Immunization Programme (NIP) provide useful resources on their Web pages (see References).

3.4 Steps for establishing a system

In summary, when developing an immunization safety surveillance system, the following steps must receive strong consideration.

Steps for developing an immunization safety surveillance system:

1. Clarify respective roles of the national regulatory authority and EPI, and agree on the objectives for the system.
2. Identify the resources available and needed and establish political commitment to immunization safety surveillance.
3. Appoint or designate regional/national assessors for immunization safety.
4. Establish an expert regional/national Immunization Safety Committee.
5. Develop and disseminate a list of events to be reported and their case definitions; a standard investigation procedure; and AEFI report and investigation forms.
6. Designate and train staff to prepare reports (peripheral health worker), complete report forms (district level) and investigate AEFI (province level).
7. Inform all health workers/clinicians of the need to report an AEFI immediately, and clarify which ones should be reported.
8. Consider establishment of a compensation scheme for specified AEFIs.

4. REPORTING AEFIS

4.1 What events should be reported?

A list of suggested reportable events with case definitions is listed in Table 6 and Annex A. Reportable AEFIs must include any deaths or serious events believed by the public or health workers to be caused by immunization. Some events (abscess, toxic shock syndrome, sepsis, and BCG lymphadenitis) are indicators of programme error, and need to be monitored at a minimum to identify and correct programme errors.

Reportable events listed in Table 6 only indicate those events that could be considered for inclusion in the AEFI surveillance system. Each country should decide individually which events are appropriate for inclusion in its system.

Table 6. List of reportable AEFIs

Occurring within 24 hours of immunization	• Anaphylactoid reaction (acute hypersensitivity reaction) • Anaphylaxis • Persistent (more than 3 hours) inconsolable screaming • Hypotonic hyporesponsive episode (HHE) • Toxic shock syndrome (TSS) #
Occurring within 5 days of immunization	• Severe local reaction # • Sepsis # • Injection site abscess (bacterial/sterile) #
Occurring within 15 days of immunization	• Seizures, including febrile seizures (6-12 days for measles/MMR; 0-2 days for DTP) • Encephalopathy (6-12 days for measles/MMR; 0-2 days for DTP)
Occurring within 3 months of immunization	• Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact) • Brachial neuritis (2-28 days after tetanus containing vaccine) • Thrombocytopaenia (15-35 days after measles/MMR)
Occurring between 1 and 12 months after BCG immunization	• Lymphadenitis # • Disseminated BCG infection • Osteitis/Osteomyelitis
No time limit	**Any death, hospitalization, or other severe and unusual events that are thought by health workers or the public to be related to immunization #**

 # limit reporting to these events, if only limited reporting capacity

There is no point in reporting common minor reactions such as local reactions, fever, and self-limiting systemic symptoms. These are expected to occur and if reported, the volume of reports would overwhelm the system while contributing information of limited value. It is therefore **important for health workers to advise the parent/patient at the time of immunization that these reactions are expected, and advise them how to manage these common minor reactions** (e.g. paracetamol to treat fever). For more serious problems, the parent/patient should be advised to return or seek medical attention to allow detection of an AEFI. More importantly, they should be advised not to delay treatment of a coincidental illness falsely attributed as a vaccine reaction.

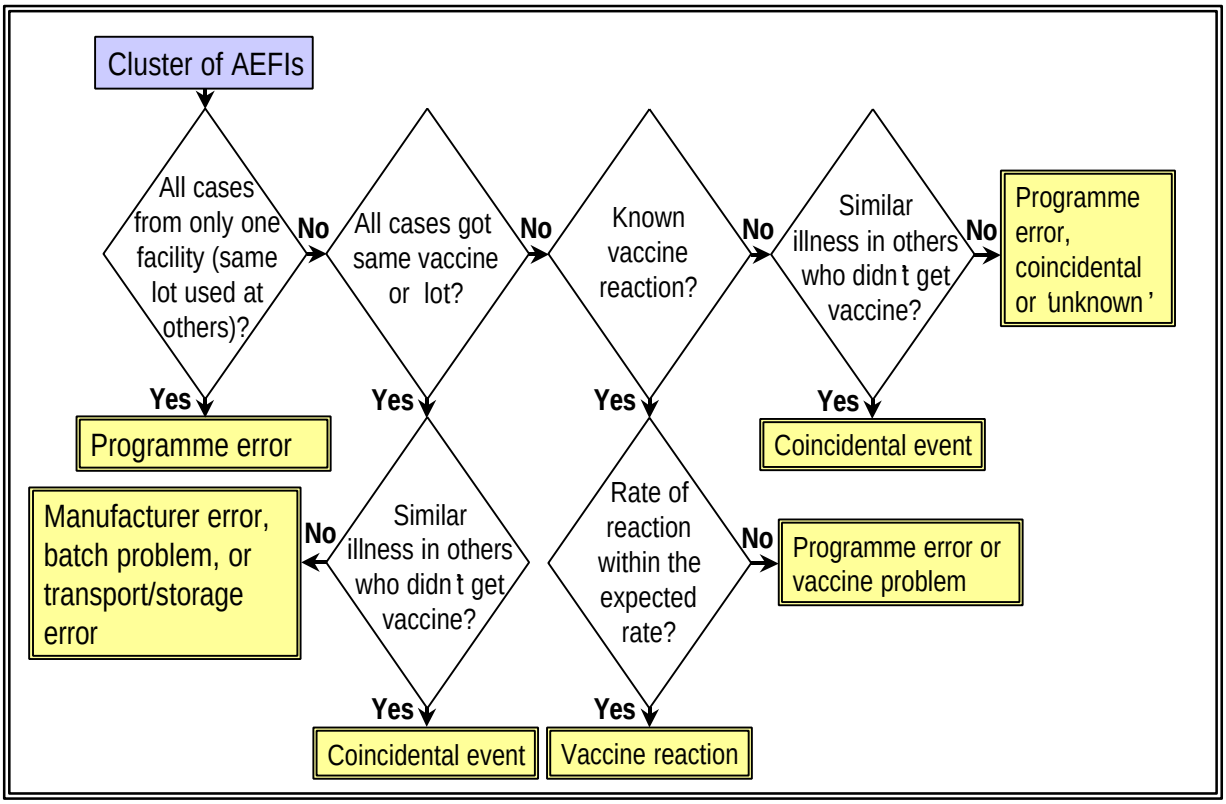
Severe local reactions (e.g. swelling beyond the nearest joint; pain, redness, and swelling of more than 3 days duration; or requiring hospitalization), especially if occurring in clusters, should be reported. Local reactions occurring at increased frequency, even if not severe, should also be reported. They can be markers for programme errors or for problems with specific vaccine lots

Investigation of a cluster requires:

- establishing a case definition for the event (if not one of the AEFI defined events)
- identifying all the people in the area who have an illness that meets the case definition
- obtaining immunization histories (when, where and which vaccines were given)
- identifying any common exposures among the cases.

If all cases received vaccines from the same health worker/facility and there are no other cases, programme error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine is likely. If the event is a known vaccine reaction but occurring at an increased rate, a programme error or a vaccine problem are likely causes. Finally, if cases include people from the same area in the same age group who were not immunized, then the adverse event was probably coincidental (Figure 2).

Figure 2. Identifying cause of AEFI cluster



4.3 When to report?

Immediately. A report always needs to be made as quickly as possible so that an immediate decision on the need for action and investigation can be made. In incidents with many cases or a high level of community concern, an urgent phone call/fax to the province should be made.

4.4 How to report?

Reports should be made on a standard AEFI Report Form (Annex D). A phone call to a more central office where trained staff can complete the form may sometimes be a more practical option. The report needs to be kept simple to ensure that health workers will complete all essential information.

At a minimum, the report needs to include:

- description of the event
- timing of the event in relation to immunization
- vaccine(s) given
- patient's identifying details.

Additional items, such as patient information (age, ethnicity, gender), vaccine information (manufacturer, lot number) and administration information (site and route of injection, outcome) should also be recorded.

4.5 Barriers to reporting

Peripheral health workers may not report AEFI for one or more of these reasons:

- **not considering** the event as related to immunization
- **not knowing** about the reporting system and process
- **lethargy** - procrastination, lack of interest or time, inability to find the report form
- **fear** that the report will lead to personal consequences
- **guilt** about having caused harm and being responsible for the event
- **diffidence** about reporting an event when not confident about the diagnosis.

These barriers to reporting can be over come by:

- increasing awareness of the importance of reporting, and the system for reporting, and making it easy to report, especially in situations of uncertainty
- emphasizing that investigations are about finding problems with the system and not blaming individuals
- giving positive feedback for reporting.

It is worth emphasizing that, unless health workers appropriately process reports, an adequate immunization safety surveillance system will not exist. Health workers must be encouraged to **report** adverse events **without fear of penalty** . The aim is to **improve systems or provide further training** and **not to blame individuals** .

Positive feedback to health workers for making reports is essential. At a minimum, a personal acknowledgement to the health worker with a 'thank-you' for the report, even if the report is incomplete, should be required. The feedback should also include future management of the child especially concerning the need for additional doses of the vaccine(s) and the outcome of the report.

There must be an adequate supply of forms to support reporting. Pre-addressed and postage-paid forms may improve reporting in some countries, especially for private physicians.

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5. INVESTIGATING AEFIS

5.1 Which reports should be investigated?

Once the report has been received, an assessment should be conducted to determine whether or not an investigation is needed.

The reported AEFI must be investigated if it:

- may have been caused by programme error
- is on the list of events defined for AEFI surveillance
- is a serious event of unexplained cause
- is causing significant parental or community concern.

Certain events (toxic shock syndrome, sepsis, abscess, and BCG lymphadenitis) are likely to arise from programme errors and must always be investigated.

The number of vaccine reactions will naturally increase with increased vaccine use, so it is essential to calculate reaction reporting rate based on estimated vaccine use. In considering concerns with specific lots, it is important to have as accurate a denominator of vaccine use as possible, as **it is always the *rate* and not the number of reports that needs evaluation** .

Improved reporting can lead to more AEFI reports without a real increase in reaction rate. The investigator needs to determine if there is a real increase in reaction rate as well as to identify the cause of the increase. For example, a change in vaccine manufacturer or in vaccine lot can lead to a change in reaction rate.

In general, the provincial level will decide which reports need to be investigated. Criteria should be established to define the type of AEFI that requires investigation. The regional/national assessor needs to ensure that all reports requiring investigation have been adequately investigated.

5.2 Who should investigate?

The provincial level should provide an investigator with adequate training and should also identify resources for the investigation. In some cases, the regional assessor or other expert person from the region will need to direct the investigation. The provincial investigator should generally advise the regional assessor when embarking on an investigation, and update him/her through the investigation. This is necessary, as the regional assessor should usually be the spokesperson about the investigation.

5.3 When to investigate?

The urgency of the investigation will depend on the situation. However, if is it determined that an investigation is needed, it should be initiated as soon as practicable. It may be useful to include a timeliness criterion in the evaluation of the system , (e.g. investigation should commence within two working days for urgent investigations and five working days for less urgent ones). The criteria that make an investigation urgent

(e.g. continuing problem, high community concern) should be specified in advance.

5.4 How to investigate?

It is important to investigate suspected adverse events promptly and completely. The investigator will need to look directly at the suspected reaction as well as gather information from the patient/parent, health workers and supervisors, and community members. The information collected (and conclusions) should be recorded on an AEFI Investigation Form (Annex E).

The investigator should seek to identify system problems rather than find individuals to blame. While an individual may have been at fault, it is more effective to concentrate on changing the system/procedures to avoid such errors than to blame or punish any individuals. Such an approach is essential to ensure that AEFI reports are encouraged. It is also much more likely to improve system performance. Errors provide opportunity for learning, and creating a system that encourages hiding errors will cause more errors.

Programme errors are the most likely causes of adverse events. Therefore, the investigator should suspect programme error as the cause and examine the evidence for any errors in the storage, handling, or administration of vaccines. Attention can then focus on finding out more about the particular error and taking the necessary corrective action.

The probability that the AEFI was caused by a programme error will be even higher if symptoms are suggestive of a non-sterile injection or a drug effect. Even known vaccine reactions may in fact, upon investigation, turn out to be programme errors. Programme errors may also be identified during the investigation, even when not the primary cause of the AEFI.

Case studies

In 1983 in country G, an outbreak of lymphadenitis three months after BCG immunization was traced to a switch to a different strain of vaccine. The investigation also highlighted a number of programme errors (vaccines not properly reconstituted, and injections not given intradermally). Changing brands of vaccine and correcting the programme errors strengthened the immunization programme.

Cause: Vaccine reaction (related to manufacturer) compounded by programme errors.

In 1994 in country H, a one-year-old child died within 12 hours of receiving measles vaccine. It was reported as anaphylaxis because of its rapid onset. However, the investigation found that the vaccine used was likely to have been reconstituted some days prior to this particular use. Although the vial was not available for bacteriological examination, the likelihood of contamination was very high.

Cause: Non-sterile injection (contaminated reconstituted vaccine).

5.4.1 Investigating AEFI clusters

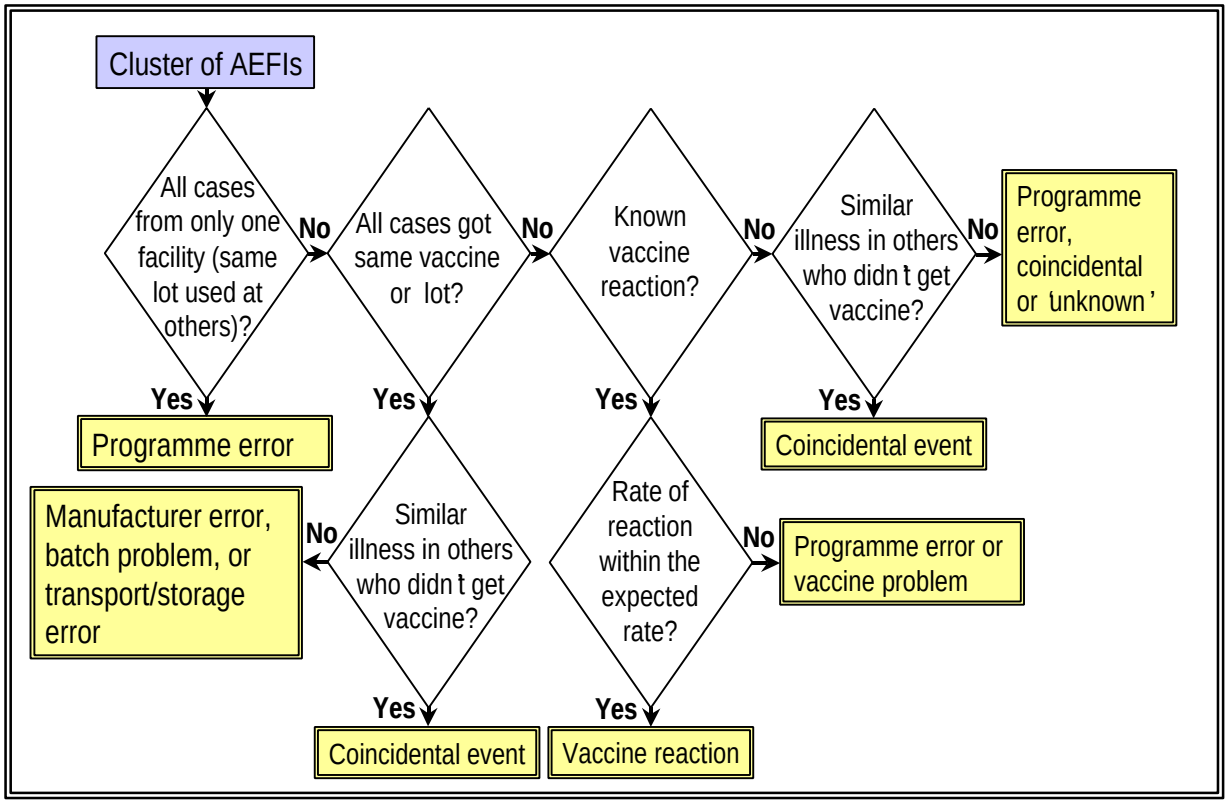
A cluster of similar adverse events is likely to arise from programme errors. If the event also occurred in unimmunized people, it may be coincidental. It is therefore important to identify if unimmunized people also developed similar symptoms around the same time.

Investigation of a cluster requires:

- establishing a case definition for the event (if not one of the AEFI defined events)
- identifying all the people in the area who have an illness that meets the case definition
- obtaining immunization histories (when, where and which vaccines were given)
- identifying any common exposures among the cases.

If all cases received vaccines from the same health worker/facility and there are no other cases, programme error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine is likely. If the event is a known vaccine reaction but occurring at an increased rate, a programme error or a vaccine problem are likely causes. Finally, if cases include people from the same area in the same age group who were not immunized, then the adverse event was probably coincidental (Figure 2).

Figure 2. Identifying cause of AEFI cluster



5.5 Outline of an investigation

An AEFI investigation follows standard epidemiological investigation principles. In addition, investigation of the vaccine(s), immunization techniques and procedures, and service in action needs to be conducted (Table 7).

Table 7. Steps in an AEFI investigation

Step	Actions
1) Confirm information in report	• Obtain patient's medical file (or other clinical record) • Check details about patient and event from medical file and document information. • Obtain any details missing from AEFI Report Form. • Identify any other cases that need to be included in the investigation.
2) Investigate and collect data: About the **patient:**	• Immunization history • Previous medical history, including prior history of similar reaction or other allergies • Family history of similar events.
About the **event:**	· History, clinical description, any relevant laboratory results about the AEFI and diagnosis of the event • Treatment, whether hospitalized, and outcome.
About the **suspected vaccine(s):**	• Conditions under which the vaccine was shipped, its present storage condition, state of vaccine vial monitor, and temperature record of refrigerator • Storage of vaccine before it arrived at health facility, where it has come from higher up the cold chain, vaccine monitor card.
About **other people:**	• Whether others received the same vaccine and developed illness • Whether others had similar illness (may need case definition); if so exposure of cases to suspect vaccine(s) • Investigate the local immunization service
3) Assess the **service** by: **asking** about:	• Vaccine storage (including open vials), distribution, and disposal • Diluent storage and distribution • Reconstitution(process and time kept) • Use and sterilization of syringes and needles • Details of training in immunization practice, supervision and vaccinator(s) • Number of immunizations greater than normal?
Observing the service in action:	• Refrigerator – what else is stored (note if similar containers stored next to vaccine vials which could be confused); which vaccines/diluents stored with other drugs; whether any vials have lost their label • Immunization procedures (reconstitution, drawing up vaccine, injection technique, safety of needles and syringes; disposal of opened vials) • Do any open vials look contaminated?
4) Formulate a working hypothesis:	• On the likely/possible cause(s) of the event.
5) Test working hypothesis	• Does case distribution match working hypothesis? • Occasionally, laboratory tests may help (see text).
6) Conclude investigation	• Reach a conclusion on the cause. • Complete AEFI Investigation Form (Annex E). • **Take corrective action, and recommend further action** (see section 6).

A series of cases without comparison of disease and exposure among controls is not likely to reveal the cause of the AEFI, except in the case of programme errors. Clear case definitions, from the guidelines on reporting or defined during the investigation, are essential. The investigation needs to identify all cases in the community and find out the outcomes for all those who received the suspect vaccine. The risk of disease should be compared for those who received the vaccine versus those who did not.

A working hypothesis should be established as soon as there is sufficient information. The working hypothesis may change during the course of the investigation. The focus of the investigation should then be to seek to confirm the working hypothesis. No action should be taken based on the hypothesis, until it is confirmed with reasonable certainty.

An AEFI investigation summary form (Annex E) should be completed at the end of the investigation.

Laboratory testing may sometimes confirm or rule out the suspected cause: the vaccine may be tested for sterility and adjuvant (e.g. aluminium content); the diluent for sterility and chemical composition; and the needles and syringe for sterility. **Testing should be requested on a *clear suspicion* and not as routine, and *never* before the working hypothesis has been formulated.** Determining which samples to send, if any, depends on the working hypothesis for the cause of the event(s) (Table 8). If the used vial of suspect vaccine is available, it should be sent with unused vials of the same lot.

Table 8. Laboratory testing to investigate AEFIs by working hypothesis

Working hypothesis – *Programme error is suspected:*	**Specimens to send**	**Laboratory test**
Vaccine transportation or storage	Vaccine vial	Composition (for frozen vaccine)
Reconstitution error	Vaccine vial and/or diluent	Sterility or composition (chemical)
Non-sterile injection	Needle, syringe, vaccine vial and diluent	Sterility
Vaccine problem	Vaccine vial	Composition

5.6 Causality assessment

The investigation needs to include an assessment on the cause of the AEFI. The WHO classification for adverse drug reactions has six categories:

(1) very-likely/certain
(2) probable
(3) possible
(4) unlikely
(5) unrelated
(6) unclassifiable.

For AEFI, the first three categories are used when a vaccine reaction or programme error is suspected, with varying levels of confidence (certain, probable, or possible). Categories 4 and 5 would be used for coincidental events, depending on level of confidence, and category 6 for AEFI where insufficient evidence is provided to make an assessment.

To arrive at an assessment of causality, it may help to go through a set of questions:

- What is the frequency of occurrence for this event (common/rare/not previously reported)?
- Are similar events known to occur with other disease?
- Is the event known to be related to this vaccine?
- Is the event explainable by the biological properties of the vaccine?
- Is the vaccine-event interval compatible with expected?
- Has the patient had similar symptoms in the past?
- Was the patient on any concomitant or preceding drug therapy?
- Did the patient have any concomitant or preceding condition?
- Were there any other contributing factors?

The Immunization Safety Committee plays a critical role in confirming the causality assessments of selected investigations and in determining causality when not established with confidence by the investigator.

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6. RESPONDING TO AEFIS

Health workers need to know how to recognize, treat, and report AEFI – immediately, if serious. The treatment of AEFI is similar to other illnesses and is outlined in Table 2 and Annex A. The treatment for anaphylaxis is in Annex B.

Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. **It is never appropriate to discontinue the immunization programme while awaiting the completion of the investigation** .

Case study

In Japan in 1975, pertussis immunization was discontinued during the investigation of two deaths that closely followed DTP vaccine. The investigation exonerated the vaccine, but as a result of the subsequent drop in immunization coverage there were 113 pertussis deaths in the four years after 1975 compared to 10 pertussis deaths in the four years before.

Trust is a key component of the exchange of information at every level, and overconfidence about risk estimates that are later shown to be incorrect contributes to a breakdown of trust among people involved. **Admit uncertainty, investigate fully, and keep the community informed** . Avoid making a premature statement about the cause of the event before the investigation is complete. If the cause is identified as programme error, it is vital not to lay personal blame on anyone, but to focus on system-related problems which resulted in the programme error(s) and steps being taken to correct the problem.

In communicating with the community, it is useful to develop links with community leaders and the peripheral health workers so that information can be rapidly disseminated. Maintaining lines of communication with the community is important throughout the investigation.

When there is a high level of concern about a vaccine, communication with the community (and the media, if appropriate) can emphasize:

- the known benefits of immunization in preventing serious disease compared to the uncertainty over whether the adverse event(s) are truly caused by the vaccine (presenting data on disease risks versus risks of vaccine reactions and vaccine effectiveness may be useful)
- a remediable programme error or coincidental illness are much more likely since serious vaccine reactions are very rare
- that appropriate action is being taken to safeguard the public (Table 9).

Upon completion of the investigation, the cause of the event(s) needs to be communicated to the community. This must include information about the steps being taken to remedy the situation and to prevent a recurrence, if such steps are needed (Table 10).

Table 9. Actions to safeguard the public during an investigation

Stage of investigation	Actions
Incident detected	• Assess and investigate with appropriate degree of urgency • Possibly quarantine suspect vaccines
Investigation starts	• Ensure that investigator has adequate resources, provide more if needed • Increase surveillance to identify similar cases in and out of area • Define any suspect vaccine
Investigator develops working hypothesis	• Do not communicate working hypothesis until confirmed • If programme errors are working hypothesis, correct them • If vaccine problem suspected, quarantine suspect vaccines
Investigator confirms working hypothesis	• Advise community of cause, and of planned response (Table 10)

6.1 Communicating with the media

The media (newspaper, radio, and television) play an important role in public perception. Understanding what the media want from a story will assist communication with them (see also Annex G).

In certain situations, media coverage is likely to raise public concern about immunization. In these situations, it is important to communicate with professional organizations, health professionals and workers before the media. The communication should include preparation on how to deal with the public concern on this issue, to minimize the potential harm. It is also useful to have other groups and individuals that have public respect and authority to make public comments to endorse and strengthen key messages.

Designating the spokesperson(s) to communicate with the media limits the possibility of conflicting messages coming from different sources. The spokesperson should have some training on media relations, and be designated and trained **before** any vaccine safety issues arise, so that the spokesperson can develop a relation with key reporters.

6.1.1 Understanding the media perspective

The media are most interested in stories that will attract attention and boost their sales/audience. One technique is to dramatize and personalize events. If you give them inappropriate material, the media can present the health service or officials responsible for immunization as being uncaring, impersonal, incompetent, or even dangerous.

The media can also be helpful allies in communicating public health messages. They can be helpful allies in reminding the public of the importance of immunization and the risks of diseases. Building a personal relationship with key health reporters will help them to understand the public health perspective.

It is easy for media stories to create a sense of panic and outrage about events which are either unrelated to immunization (coincidental) or a localized programme error. In addition, the media tend to report on numbers of events, ignoring the context of the very

small rate of occurrence. An event of unknown cause, which is being linked to immunization, also has a high potential fear factor.

The response of the health service to the concern about immunization safety must be seen to be compassionate, with careful and expert investigation of the problem. Off-hand and disparaging remarks should be avoided, and the very great and proven benefits of immunization should always be emphasized. Where possible use the term ' immunization safety' or 'vaccine safety' rather than 'adverse event', as the focus is on safety.

6.1.2 Holding a media conference

A media conference, media statements and dissemination of information through a range of channels are all useful tools for responding to public concern. A media conference gives all the reporters the same access to the information (i.e. no exclusive coverage). Thus, they may be less likely to ' sensationalize' the events.

Private professional organizations and other interested parties may have greater credibility than the government. A conference provides an opportunity for them to voice their support for immunization and the approach being taken to investigate the problem. They must show a unified face in public, and have a full and robust debate in private.

Media conferences need to be used judiciously, as there are also dangers, especially if inadequately prepared and facing a hostile pack. Press conferences are hard work, and require careful preparation management, especially if different stakeholders will be present. Prepare:

- the key messages to be communicated
- the spokesperson(s) (identify one, if not already identified)
- a media kit for all reporters and other community leaders that includes:
    - a concise press release with all the essential information
    - supplementary background information (e.g. on the benefits of immunization)
    - 'questions and answers' that includes questions that have been or are likely to be asked by concerned members of the public.

Media interest is usually greatest initially when relatively little is known. In this environment rumours can flourish, and the potential for harm is huge. It is wise to call a media conference early, even if there is only very limited information to give. This will prevent the circulation of rumours and build a relationship with the reporters. At the end of the press conference, advise that a further conference will be held within a day or so, at which time full details of the event and the investigation will be provided. Regular contact with the media about the progress of the investigation, and at the end on the conclusion of the investigation is advisable.

6.1.3 Preparing a press statement

All the information to be conveyed in a media conference should be prepared in advance and included in a press statement.

The press statement needs to include:

- a complete account of events (in terms that will be understood by people not familiar with health services or immunization) framed in their appropriate context (i.e. an isolated event, a coincidental event) so that it limits the concern of spreading the event to the immunization programme, in general
- whether the event is ongoing or not - it is unlikely that there will be an ongoing incidence of new cases linked to immunization
- an outline of actions taken or planned (depending on the stage, this will range from a **plan of action** to a completed **investigation**)
- the cause of the event (when identified with reasonable certainty)
- the corrective action that has been or will be taken.

6.2 Fixing the problem

The remedy for the adverse event will depend on the cause, and whether it was identified. In all cases, the investigation needs to be clearly documented. It is worth disseminating the results of the investigation so that others can also learn from the experience. The investigation can also make a useful teaching resource in training investigators in the future.

Programme errors will need to be corrected, and there should be a checking mechanism to ensure that they don't happen again. A problem with a specific vaccine may lead to the withdrawal of a lot or a change in the vaccine supplier. For coincidental events, the main task is communication to avoid false attribution of blame. Table 10 outlines these responses.

Decisions to suspend use of, or recall, a vaccine or specific lot needs to be made as swiftly as possible, but should be very carefully thought out. The impact on the immunization programme, alternate sources of vaccine, and the reliability of the evidence on which the decision is based, needs careful scrutiny. In particular, there needs to be consideration concerning the possibility of biased reporting resulting from an alert about a possible problem with a vaccine or lot. Consultation with the vaccine manufacture and WHO is advisable before making the decision.

Table 10. Actions to be taken upon completion of the investigation

Vaccine reaction:	If a higher reaction rate than expected from a specific vaccine or lot then obtain information from the manufacturer and consult with WHO to consider: • withdrawing that lot • changing manufacturing specifications or quality control • obtaining vaccine from a different manufacturer.
Programme error:	Correcting the cause of the error. This may mean one or more of the following: • change in logistics for supplying vaccine • change in procedures at the health facility • training of health workers • intensified supervision. Whatever action is taken, it is important to review at a later date to check that the programme errors have been corrected.
Coincidental:	Main task is communication to ensure that people are persuaded that the link is just coincidental. This communication can be challenging when there is widespread belief that the event was caused by immunization. Sometimes, it may be useful to enlist further expert investigation to convince/ensure that the event truly was coincidental. The potential for coincidental events to harm the immunization programme through false attribution is immense.
Unknown:	Depending on the nature of the event, its extent and whether it is ongoing, a further investigation by an expert may be needed. However, it must be accepted that in some cases the relationship to immunization is not clear.

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7. EVALUATION OF THE IMMUNIZATION SAFETY SURVEILLANCE SYSTEM

The immunization safety surveillance system should be evaluated regularly to determine its effectiveness. This evaluation should be based on criteria that are already defined.

Criteria should include:

- **timeliness, completeness and accuracy of AEFI reporting** (by monitoring information from reports and site visits - comparing reports with the facility's patient register, talking to health workers and observing their work - see WHO/EPI manual *Training for Mid-level Managers: Disease Surveillance*)
- **timeliness and completeness of investigation** (check reports to ensure that those meeting the investigation criteria were investigated; that investigation was begun within the defined time criteria (say 48 hours of report receipt); confirm the adequacy of the investigation and the soundness of the conclusion reached, and corrective action recommended)
- **audit of corrective action** (review by regional/national assessor to check that corrective action recommended has been checked, and adequacy of change in practice to prevent future programme error).

The progress in immunization safety surveillance can also be monitored from the annual data reported to national level.

Annual data reports should include:

- number of AEFI reports, categorized by type of reaction and vaccine(s) and causality assessment (with denominator data on number of doses of vaccine given)
- rate of each adverse event by vaccine (and lot number) nationally and by region
- unusual or unusually severe events or large clusters
- summary of other important/unusual investigations.

Making the annual report available to health workers encourages and provides positive feedback for their reporting. Publication of the data also allows international comparisons to be made.

An expert Immunization Safety Committee plays an important role in ongoing evaluation of the system, and provides useful comments for the outputs above. In addition, the committee can confirm, or determine (if not identified), the causality assessment of investigations [Pless, 1996].

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United States of America:	www.cdc.gov/nip/vacsafe
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South Australia:	www.health.sa.gov.au/pehs

ANNEX A: AEFIS TO REPORT, CASE DEFINITIONS AND TREATMENTS

Events that should be reported after immunization

Occurring within 24 hours of immunization	• Anaphylactoid reaction (acute hypersensitivity reaction) • Anaphylaxis • Persistent (more than 3 hours) inconsolable screaming • Hypotonic hyporesponsive episode (HHE) • Toxic shock syndrome (TSS) #
Occurring within 5 days of immunization	• Severe local reaction # • Sepsis # • Injection site abscess (bacterial/sterile) #
Occurring within 15 days of immunization	• Seizures, including febrile seizures (6-12 days for measles/MMR; 0-2 days for DTP) • Encephalopathy (6-12 days for measles/MMR; 0-2 days for DTP)
Occurring within 3 months of immunization	• Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact) • Brachial neuritis (2-28 days after tetanus containing vaccine) • Thrombocytopaenia (15-35 days after measles/MMR)
Occurring between 1 and 12 months after BCG immunization	• Lymphadenitis # • Disseminated BCG infection • Osteitis/Osteomyelitis
No time limit	**Any death, hospitalization, or other severe and unusual events that are thought by health workers or the public to be related to immunization #**

 # limit reporting to these events, if only limited reporting capacity

Case definitions and treatments for AEFI

Adverse event	Case definition	Treatment	Vaccines
Acute flaccid paralysis (Vaccine associated paralytic poliomyelitis)	Acute onset of flaccid paralysis within 4 to 30 days of receipt of oral poliovirus vaccine (OPV), or within 4 to 75 days after contact with a vaccine recipient **and** neurological deficits remaining 60 days after onset, or death.	No specific treatment available; supportive care.	OPV
Anaphylactoid reaction (acute hypersensitivity reaction)	Exaggerated acute allergic reaction, occurring within 2 hours after immunization, characterized by one or more of the following: • wheezing and shortness of breath due to bronchospasm • laryngospasm/laryngeal oedema • one or more skin manifestations, e.g. hives, facial oedema, or generalized oedema. **Less severe allergic reactions do not need to be reported.**	Self-limiting; anti-es may be helpful.	All
Anaphylaxis	Severe immediate (within 1 hour) allergic reaction leading to circulatory failure with or without bronchospasm and/or laryngospasm/laryngeal oedema (See Annex B).	Adrenaline injection (See Annex B)	All
Arthralgia	Joint pain usually including the small peripheral joints. **Persistent** if lasting longer than 10 days, **transient:** if lasting up to 10 days.	Self-limiting; analgesics	Rubella, MMR

Brachial neuritis	Dysfunction of nerves supplying the arm/shoulder without other involvement of nervous system. A deep steady, often severe aching pain in the shoulder and upper arm followed in days or weakness by weakness and wasting in arm/shoulder muscles. Sensory loss may be present, but is less prominent. May present on the same or the opposite side to the injection and sometimes affects both arms.	Symptomatic only; analgesics.	Tetanus
Disseminated BCG infections	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of *Mycobacterium bovis* BCG strain. Usually in immunocompromised individuals.	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.	BCG
Encephalopathy	Acute onset of major illness characterized by any two of the following three conditions: • seizures • severe alteration in level of consciousness lasting for one day or more • distinct change in behaviour lasting one day or more. Needs to occur within 48 hours of DTP vaccine or from 7 to 12 days after measles or MMR vaccine, to be related to immunization.	No specific treatment available; supportive care.	Measles, Pertussis
Fever	The fever can be classified (based on rectal temperature) as mild (38 to 38.9^{o}C), high (39 to 40.4^{o}C) and extreme (40.5^{o}C or higher). Fever on its own does not need to be reported.	Symptomatic; paracetamol.	All
Hypotonic, hyporesponsive episode (HHE or shock-collapse)	Event of sudden onset occurring within 48 [usually less than 12] hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. **All** of the following must be present: • limpness (hypotonic) • reduced responsiveness (hyporesponsive) • pallor or cyanosis – or failure to observe/ recall	The episode is transient and self-limiting, and does not require specific treatment. It is **not** a contraindication to further doses of the vaccine.	Mainly DTP, rarely others
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. **Bacterial** if evidence of infection (e.g. purulent, inflammatory signs, fever, culture), **sterile** abscess if not.	Incise and drain; antibiotics if bacterial.	All
Lymphadenitis (includes suppurative lymphadenitis)	**Either** at least one lymph nodes enlarged to >1.5 cm in size (one adult finger width) **or** a draining sinus over a lymph node. Almost exclusively caused by BCG and then occurring within 2 to 6 months after receipt of BCG vaccine, on the same side as inoculation (mostly axillary).	Heals spontaneously (over months) and best not to treat unless lesion is sticking to skin. If so, or already draining, surgical drainage and local instillation of anti-tuberculous drug. Systemic treatment with anti-tuberculous drugs is ineffective	BCG
Osteitis/ Osteomyelitis	Inflammation of the bone with isolation of *Mycobacterium bovis* BCG strain.	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.	BCG

Persistent inconsolable screaming	Inconsolable continuous crying lasting 3 hours or longer accompanied by high-pitched screaming.	Settles within a day or so; analgesics may help.	DTP, Pertussis
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. **Febrile seizures**: if temperature elevated >38°C (rectal) **Afebrile seizures**: if temperature normal	Self-limiting; supportive care; paracetamol and cooling if febrile; rarely anticonvulsants.	All, especially Pertussis, Measles
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture. Needs to be reported as possible indicator of programme error.	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids.	All
Severe local reaction	Redness and/or swelling centred at the site of injection and one or more of the following: • swelling beyond the nearest joint • pain, redness, and swelling of more than 3 days duration • requires hospitalization. **Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported.**	Settles spontaneously within a few days to a week. Symptomatic treatment with analgesics. Antibiotics are inappropriate.	All
Thrombocytopaenia	Serum platelet count of less than 50,000/ml leading to bruising and/or bleeding	Usually mild and self-limiting; occasionally may need steroid or platelets.	MMR
Toxic shock syndrome (TSS)	Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization. Often leading to death within 24 to 48 hours. Needs to be reported as possible indicator of programme error.	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids.	All

ANNEX B: RECOGNITION AND TREATMENT OF ANAPHYLAXIS

Anaphylaxis is a very rare, unexpected, and occasionally fatal allergic reaction. It is reported even more rarely from developing countries. In addition, misdiagnosis of faints and other common causes of collapse as anaphylaxis, can lead to inappropriate use of adrenaline. Vaccinators should be able to distinguish anaphylaxis from fainting (vasovagal syncope), anxiety and breath-holding spells, which are common benign reactions.

During fainting, the individual suddenly becomes pale, loses consciousness and collapses to the ground. Fainting is sometimes accompanied by brief clonic seizure activity (ie, rhythmic jerking of the limbs), but this requires no specific treatment or investigation. Fainting is relatively common after immunization of adults and adolescents, but very rare in young children. It is managed by simply placing the patient in a recumbent position. Recovery of consciousness occurs within a minute or two, but patients may take some more time to recover fully.

An anxiety spell can lead to pale, fearful appearance and symptoms of hyperventilation (light-headed, dizziness, tingling in the hands and around the mouth). Breath holding occurs in young children and will lead to facial flushing and cyanosis. It can end in unconsciousness, during which breathing resumes.

Anaphylaxis develops over several minutes and usually involves multiple body systems. Unconsciousness is rarely the sole manifestation of anaphylaxis - it only occurs as a late event in severe cases. A strong central pulse (e.g. carotid) is maintained during a faint, but not in anaphylaxis.

Distinguishing anaphylaxis from a faint (vasovagal reaction)

	Faint	**Anaphylaxis**
Onset	Usually at the time or soon after the injection	Usually some delay between 5-30 minutes after injection
System		
Skin	Pale, sweaty, cold and clammy	Red, raised, and itchy rash; swollen eyes, face; generalized rash
Respiratory	Normal to deep breaths	Noisy breathing from airways obstruction (wheeze or stridor)
Cardiovascular	Bradycardia Transient hypotension	Tachycardia Hypotension
Gastrointestinal	Nausea/Vomiting	Abdominal cramps
Neurological	Transient LOC, good response once prone	LOC, little response once prone

LOC= loss of consciousness

Before immunization, check for contraindications to immunization by asking about known allergies and previous adverse reactions to vaccines. In cases of possible serious allergies, check with a specialist before giving the vaccine.

Recognition

Anaphylaxis is a severe reaction of rapid onset, characterized by circulatory collapse. The early signs of anaphylaxis are generalized erythema and urticaria with upper and/or lower respiratory tract obstruction. In more severe cases, limpness, pallor, loss of consciousness and hypotension become evident in addition. Vaccinators should be able to recognize the following signs and symptoms of anaphylaxis:

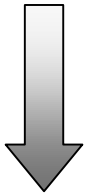
Skin: A generalized red, raised and itchy rash (urticaria); swelling of the face and body (angioedema).

Respiratory: Dry persistent cough; noisy breathing (wheeze or, stridor); hoarse voice; difficulty talking or swallowing; struggling for breath (respiratory distress); blue tongue and lips (cyanosis).

Gastrointestinal: Cramps (abdominal pain) ; urge to pass stool.

Cardiovascular: Fast pulse (tachycardia); limb pulses not felt (hypotension).

Neurological: Collapse (loss of consciousness - LOC)

Time Scale	Signs and symptoms of anaphylaxis	Severity
Early Warning Signs	Dizziness, perineal burning, warmth, pruritus	***Mild***
	Flushing, urticaria, nasal congestion, sneezing, lacrimation, angioedema	***Mild to moderate***
	Hoarseness, nausea, vomiting, sub-sternal pressure	***Moderate to severe***
	Laryngeal oedema, dyspnoea, abdominal pain	***Moderate to severe***
Late, life-threatening symptoms	Bronchospasm, stridor, collapse, hypotension, dysrhythmias	***Severe***

In general, the more severe the reaction, the more rapid the onset. Most life-threatening reactions begin within 10 minutes of immunization. **Keep the recipient under observation for at least 20 minutes after the injection.**

Symptoms limited to only one system can occur, leading to delay in diagnosis. Biphasic reactions where symptoms recur 8 to 12 hours after onset of the original attack and prolonged attacks lasting up to 48 hours have been described.

Treatment

Adrenaline stimulates the heart and reverses the spasm in the blood vessels and the lung passages, reduces oedema and urticaria, thus countering the anaphylaxis. But this very potent agent can cause irregular heartbeat, heart failure, severe hypertension, and tissue necrosis if used in inappropriate doses, but not in anaphylaxis.

Each vaccinator must have an emergency kit with adrenaline, and be familiar with its dosage and administration. The expiry date of the adrenaline should be written on the outside of the emergency kit and the whole kit should be checked three or four times a year. Adrenaline that has a brown tinge must be discarded.

Events happen without warning. Emergency equipment must be immediately at hand whenever immunizations are given. All vaccinators must be familiar with the practical steps necessary to save life following anaphylaxis.

Initial Management

a) Place the unconscious recipient in the recovery position and ensure the airway is clear.

b) Assess breathing and pulse (if strong carotid pulse, is not anaphylaxis).

c) If appropriate begin cardiopulmonary resuscitation.

d) Give adrenaline (see below for dosage) by deep intramuscular injection.

e) If the recipient is conscious after the adrenaline is given, place the head lower than the feet and keep the recipient warm.

f) Give oxygen by facemask, if available.

g) Send for professional assistance but never leave the recipient alo ne. Call an ambulance, and medical practitioner if necessary, after the first injection of adrenaline, or sooner if there are sufficient people present.

h) If there is no improvement in the recipient's condition within 5 minutes, repeat the dose of adrenaline up to a maximum of three doses. Recovery from an anaphylactic shock is usually rapid after adrenaline.

Hydrocortisone and an anti-histamine may be used as adjunctive medication. Nebulized salbutamol is helpful for bronchospasm and nebulized adrenaline for laryngeal oedema.

Adrenaline dosage for 1:1000 formulation is 0.01ml/kg up to a maximum of 0.5 ml. If weight unknown:

Less than 2 years	0.0625 ml (1/16)
2-5 years	0.125 ml (1/8)
6-11 years	0.25 ml (1/4)
Over 11 years	0.5 ml (1/2)

Note: Anaphylaxis may be caused by agents other than vaccines (e.g. drugs) and there may be country-specific protocols for treatment of anaphylaxis.

ANNEX C: DISEASE RISKS TO COMPARE WITH VACCINE RISKS

Diphtheria

Largely eliminated from the region through immunization - has re-emerged, and potential remains:

Disease complication	Risk
Damage to heart	10 - 25%
Damage to nerve (2 to 8 weeks after)	20%
Death	2 - 10%

Haemophilus influenzae type b (Hib)

Pre-immunization risk was about 1 in 200 to 1 in 400 for the first five years of life in industrialized countries. Risk peaks in the second six months of life, then decreasing to become very rare after the fifth birthday.

Hib infection may manifest in a variety of systems leading most often to meningitis, pneumonia, epiglottitis. Also causes septicaemia, cellulitis (often facial), septic arthritis, osteomyelitis.

Meningitis complication	Risk
Death	5% (with early treatment)
Neurological impairment	15 – 30%

Hepatitis B

Lifetime risk of infection up to 50% (or even higher) in some countries of Western Pacific compared to about 5% in Europeans.

	Risk for population:		
Disease complication	**Infancy**	**Childhood**	**Adult**
Acute hepatitis	Rare	6%	33-45%
Chronic carrier state	68% (up to 90% for neonate)	6-23%	2-5%

1. *Case fatality is usually less than 1% for acute hepatitis B*
2. *Consequences of carrier state*
   Chronic active hepatitis/cirrhosis* 5% (death 2%)
   Hepatocellular carcinoma (HCC)* 5% (female); 10% (male)
   *Risks doubled with delta infection

Measles

Universal prior to immunization. Risks from disease from industrialized countries - complications higher developing countries with case fatality of 5-15%.

Disease complication	Risk
Otitis media	7-9%
Pneumonia	1-6%
Diarrhoea	6%
Encephalitis	0.5-1 per 1000 (of these 15% die and 25% subsequently brain damaged)
Subacute sclerosing panencephalitis (SSPE)	1 in 100 000
Death	0.1-1 per 1000

Mumps

Usually a disease affecting primary school and pre-school children and 85% of adults have evidence of past infection. Of these 15-20% are asymptomatic, and 40-50% with non-specific or respiratory symptoms.

Disease complication	Risk
Aseptic meningitis (most cases very mild)	10%
Pancreatitis (usually mild)	4%
Orchitis in postpubertal males	Up to 38% (little evidence that this leads to sterility)
Oophoritis in postpubertal females	5%
Unilateral sensorineural deafness	1 in 15,000
Encephalitis	1 in 300 to 1 in 6,000
Death	2 per 10 000 (USA)

Also neuritis, arthritis, mastitis, nephritis, thyroiditis and pericarditis.

Pertussis

Nearly universal without immunization. Up to 90% of susceptible household contacts and 50-80% of susceptible school contacts acquire the disease.

Disease complication	Description of Disease complication
Minor pressure effects	Nosebleeds and small bleeds in the white of the eye
Respiratory	Pulmonary complications in almost all (atelectasis and bronchopneumonia). Does not appear to cause permanent lung damage.
CNS	Convulsions (1 to 3%); Encephalitis and coma following anoxia. Paralysis, deafness, blindness, mental retardation and epilepsy are permanent sequelae (0.1 to 0.3%)
Death	1 in 200 chance of death if hospitalized younger than 1 year of age

Note: Figures relate to industrialized countries - may be higher in developing countries.

Poliomyelitis

Although the global eradication programme is rapidly clearing poliomyelitis from many parts of the world, the threat of reintroduction remains. Most infections were asymptomatic or non-specific febrile illness.

Disease complication	Risk
Aseptic meningitis	About 1%
Paralytic illness	0.1 to 1% (incidence increases with age of infection)

Case fatality for paralytic case between 2 and 10%, increasing with age.

Rubella

Generally mild illness but can rarely cause more serious illness, similar to measles with encephalitis. If infected in first eight weeks of pregnancy up to 85% of infants will be affected with one or more defects, including deafness, blindness, brain damage and heart problems

Risks (per case) from the 1964 USA rubella epidemic that had 12.5million cases.

Disease complication	Risk
Encephalitis	1.7 per 10 000
Neonatal deaths	1.7 per 10 000
Other deaths	0.05 per 10 000
Fetal loss	5 per 10 000
Congenital Rubella Syndrome (CRS):	
Deaf children	6.4 per 10 000
Deaf-blind children	2.9 per 10 000
Mentally retarded children	1.4 per 10 000
Total CRS	16 per 10 000

Tetanus

Infection may follow even trivial wound. Infection of umbilicus leads to neonatal tetanus. Overall case fatality is 25 to 70%, but approaches 100% at older age groups. Even with modern intensive care treatment, case fatality rate is 10-20%.
Neonatal tetanus case fatality is 95% without treatment, and 25-90% with treatment, depending on intensity of supportive care.

Tuberculosis

The risk of infection is variable. 95% of those infected enter a latent phase from which there is a lifelong risk of reactivation. The other 5% progress directly to pulmonary tuberculosis or by lympho-haematogenous dissemination of bacilli to miliary, meningeal or other extrapulmonary involvement. Infants, young children, older people and the immuno-compromised are more likely to progress rapidly to severe generalized infection with a poorer outcome. Extrapulmonary manifestations occur in 15% of adults and 25% of children.

ANNEX D: AEFI REPORT FORM

Demographic details

Family name:	**First name:**	**Date of birth (dd/mm/yy):** / /	**Unique ID:**
Address:		**Sex:** Male/Female	**Ethnicity:**
District:		**Province:**	
Health facility:		**Reporter (health worker):**	

Vaccine(s) given*	Route	Site	Lot number	Manufacturer	Expiry date

**name and dose number e.g. DPT-2, OPV-2; diluent too, if reconstituted*

Date immunized	Date AEFI started	Onset interval	Date of report

Tick box(es) and describe event:

- ❑ Toxic shock syndrome
- ❑ Sepsis
- ❑ Abscess: sterile❑ or bacterial❑
- ❑ Lymphadenitis: >1.5 cm❑ or draining sinus❑)
- ❑ Severe local reaction: >3 days❑, beyond nearest joint❑, or hospitalized❑
- ❑ Vaccine reaction on list (state):
- ❑ Other AEFI (state):

Recovered: **Yes / No / ?**
Hospitalized: **Yes / No / ?**
Died: **Yes / No / ?**

Past medical history (including history of similar reaction or other allergies) and any other relevant information(e.g. other cases):

Province Level Office to complete:

Date report received: / /	**Checked by:**
Investigation needed: **Yes / No / ?**	**If yes, date started:**
Investigator:	**AEFI investigation ID:**
Causality assessment:	**Certainty:**

Annex E: AEFI Investigation Form

Complete this summary page at end of investigation; file with field report and AEFI report forms

Investigation ID:	**AEFI report ID:**	**Date investigation started:** **/ /**

Describe trigger event:

Diagnosis/ case definition of event:

Community investigation: Yes/No/? If yes, number of cases immunized with suspect vaccine in time window:

immunized:_____ not immunized:____

Clinic investigation carried out: Yes/No/? If yes, key finding(s):

Laboratory investigation(s) : Yes/No/? If yes, key result(s):

Assessment

Conclusion about cause of AEFI:
& tick categories, rank if more than one cause:

❑ **Programme error**	❑ **Vaccine reaction**	❑ **Coincidental**	❑ **Unknown**
❑ Non-sterile injection	❑ Vaccine lot problem	❑ Similar event in unimmunized	
❑ Vaccine prepared incorrectly	❑ Known vaccine reaction at expected rate	❑ Other:	
❑ Administration technique/site	❑ Other:		
❑ Vaccine transportation/ storage			
❑ Other:			

Confidence about conclusion on main cause of AEFI: ❑certain ❑probable ❑possible

Reason(s) for conclusion:

Corrective action taken: Yes/No/? If yes, specify

Further actions recommended: Yes/No/? If yes, specify

Investigator: Signature: Date: / /

ANNEX F: AEFI LINE LISTING

A line listing form may be used at province level to identify trends and clusters of AEFI and as a means of sending AEFI data to regional/national level.

Name/ID	District	Date of birth (dd/mm/yy)	Date of immunisation (dd/mm/yy)	Reaction type (code)	Outcome (**R**ecovered/**D**ied/**?**)	Suspect vaccine (name and dose, eg DPT-2)	Batch number	Onset time (**h**ours, **d**ays, **w**eeks)	Date of report (dd/mm/yy)	Investigated? (If yes, date)	Cause (code)	Confidence (code)

Establishing codes for area, reaction type, cause of AEFI, and certainty of cause will facilitate recording, data entry and analysis. Because of the potential for coding errors, the code should be double-checked.

An example of coding for cause of AEFI is shown here:

1. Programme error
A) Non-sterile injection
B) Vaccine prepared incorrectly
C) Administration technique/site
D) Vaccine transportation/ storage
E) Other:

2. Vaccine reaction
A) Vaccine manufacturer error
B) Known vaccine reaction at expected rate
C) Other:

3. Coincidental
A) Similar event in unimmunized
B) Other:

4. Unknown

Thus: Code '1A' would be for programme error [non-sterile injection]
Code '2B' would be vaccine reaction [known vaccine reaction at expected rate], etc.

Coding for confidence could be: certain = 1 probable = 2 possible = 3.

ANNEX G: COMMUNICATING WITH THE MEDIA

Risk communication is an interactive process that requires active listening and discussion. Individuals differ in their perceptions of risk depending on their life experience and knowledge. Certain risks are more acceptable to people than other risks. If possible reframe risks using that framework (e.g. emphasizing extensive international use of vaccines and known risks).

Perceptions of risk

Less Risk		Greater Risk
Voluntary	Vs.	Involuntary
Individual control	Vs.	System control
Omission	Vs.	Commission
Natural	Vs.	Manmade
Memorable	Vs.	Not memorable
Knowable	Vs.	Unknowable
Not dreaded	Vs.	Dreaded
Trustworthy	Vs.	Untrustworthy
Familiar	Vs.	Exotic

The guiding principle with dealing with the media must be one of honesty and building up trust. The effectiveness of our communication is largely determined by whether the audiences perceive us to be trustworthy and believable. Trust and credibility are difficult to achieve; if lost, they are even more difficult to regain. Public assessment of how much we can be trusted and believed is based upon four factors:

- empathy and caring
- competence and expertise
- honesty and openness
- dedication and commitment.

It is vital to **prepare** before any media contact with:

- key messages
- answers for the likely and awkward questions
- identifying which issues not to respond to (e.g. blaming an individual or speculating on the cause before the investigation is complete).

Messages need to be as simple as possible. Use simple words and short sentences. It is helpful to tell a story, when possible - create a 'word picture' to get the message across. The **key messages** should be kept to a minimum and are likely to include some of these facts:

- that benefit of immunization in preventing disease is well proven
- it is very risky not to immunize (risk of disease and complications)
- vaccine-preventable diseases caused millions of death and/or disability before the introduction of vaccines, and that situation would return without continued use of vaccines
- vaccines do cause reactions, but these are rarely serious and hardly ever cause long-term problems (use Tables 2 and 3 to outline known risks of suspect vaccine(s)

- immunization safety is of paramount importance, and any suspicion of a problem is investigated (advantage of well established immunization safety surveillance)
- the AEFI is currently being investigated, but is likely to be coincidental/due to a local problem (depending on type of event), and the immunization programme must continue to keep the population safe from disease
- action is being taken (see Table 10).

It is essential to present information to the media in a way that will generate a sense of credibility and confidence by being:

- **honest -** never lie; if you do not know, say so, but promise to find out (e.g. "We don't know at this time, but we have taken steps to answer that question"); note that a lie or cover-up can become a bigger news story than the initial event (e.g. Watergate)
- **caring** - create a strong, compassionate, competent image for yourself and the service
- **clear -** avoid jargon; use simple phrases and give examples to clarify meaning
- **serious** – jokes can disastrous and the subject is rarely amusing anyway
- **aware** of body language - it is of critical importance in perceptions
- **responsible** - don't be defensive, but accept responsibility appropriate to your position and avoid blaming someone else (e.g. "We will see if there is any truth in the report".)
- **responsive** - hold a daily press conference if that is what is needed to meet the needs of the pubic and media; regular contact helps build a trusting relationship with the media.
- **positive** - reframe the situation in positive terms; use terms such as *vaccine safety* (which has a positive connotation) rather than *adverse event*

When facing a hostile interviewer, prepare these techniques:

- **block** - respond to a negative question with a positive answer (e.g. when asked, "How many children have died from immunization?", answer: " Immunization saves lives. Since our immunization programme began X children have been immunized, and of them Y% might have died from one of these diseases. That is the context in which we must consider the tragic, but thankfully rare adverse events which follow immunization."
- **bridge** - having answered a difficult question, move quickly to something linked but positive
- **correct what is wrong** - immediately correct information from the interviewer that is wrong. Be assertive, not aggressive and state the facts simply, factually and in a friendly way

- **stay cool** - no matter how bad it gets, don't get angry or defensive; stay friendly, polite and warm
- **be assertive** - means stating what you want to say in a clear way without getting aggressive; take time to think about the response and don't be rushed or forced

Bridge technique

Question: Does vaccination cause abscesses?

Answer: (Face the element of truth) We know that vaccination can rarely cause abscesses. (here comes the first bridge….) That is why we train staff to avoid them by using a sterile needle and syringe for every child. (Now comes the second bridge) When combining this policy with purchasing only the highest quality vaccines approved by WHO and UNICEF, we are able to assure parents that we have one of the safest vaccine programmes in the world.

Examples of other "nasty" questions that could be anticipated, depending on situation .:

1. Why does the government provide inferior vaccines for children which cause bad reactions/death?
2. Why does the Ministry of Health not train vaccinators so these accidents are avoided?
3. Why are injections for vaccines and other medical procedures still dangerous in this country?
4. Why are vaccines still given which damage our children with serious side effects?
5. Why are parents not given the truth about vaccines . Is there a cover up?
6. Does vaccination spread HIV (AIDS) and hepatitis B infection?
7. Have children died after getting reconstituted measles vaccine?
8. Does OPV (oral poliomyelitis vaccine) cause paralysis?
9. Why should our children get OPV and risk paralysis when there is no poliomyelitis in the country any more?
10. Why is hepatitis B vaccine still given in our country when France has said it causes multiple sclerosis and has withdrawn it?
11. Are vaccines contaminated with other organisms (bugs) from the manufacture process?

ANNEX H: CHECKLIST FOR IMMUNIZATION SAFETY SURVEILLANCE SYSTEM

1. Be prepared

- ❑ Clarify respective roles of the national regulatory authority and EPI, and agree on the overall goal and specific objectives for the system.
- ❑ Identify the resources available and needed and establish political commitment to immunization safety surveillance.
- ❑ Appoint or designate regional/national assessors for immunization safety.
- ❑ Establish expert regional/national Immunization Safety Committee.
- ❑ Develop and disseminate a list of events to be reported and their case definition; a standard investigation procedure; and AEFI report and investigation forms.
- ❑ Designate and train staff to make reports (peripheral health worker), complete report forms (district level) and investigate AEFI (province level).
- ❑ Inform all health workers/clinicians of the need to report immediately an AEFI, and which ones should be reported.
- ❑ Consider establishment of a compensation scheme for specified AEFI.

2. Receive a report (Province level investigator)

- ❑ Decide if the report is a genuine AEFI according to your definition, and whether it needs investigating and/or advising to the public/media.
- ❑ Travel to the location of the AEFI, or delegate responsibility to another trained person or team to do this.
- ❑ Decide if need to communicate with community and/or media to alleviate concern.

3. Investigate and collect data

- ❑ Ask about the patient, the event, and the vaccine.
- ❑ Ask about immunization service and observe it in action (emphasise that aim is to find system error **not** to blame individual).
- ❑ Formulate a working hypothesis as to what was the cause of the AEFI.
- ❑ If appropriate, collect and dispatch specimens to the laboratory.

4. Analyse the data

- ❑ Review on-site investigation, clinical findings, and laboratory results (if sent).
- ❑ Review epidemiological findings e.g. clustering of cases in time or space or by vaccine manufacturer or lot.
- ❑ Summarise findings and complete Investigation Form.

5. Take action

- ❑ Communicate with health staff (e.g. treatment, information).
- ❑ Communicate findings and action to the parents and public (and media).
- ❑ Correct problem (based on the cause) by improving training, supervision, and/or distribution of vaccines/injection equipment (see Table 10).

The Immunization Focus of the WHO office of the Western Pacific Region has established the following mission statement and objective:

To eliminate sickness and death caused by vaccine-preventable diseases through the development of strong, sustainable national immunization programmes capable of delivering high quality vaccines in a safe and effective way to all children and adults who require them.

The Immunization Focus achieves this by working with national immunization programmes in all the countries and areas of the Region to achieve common goals on the prevention of disease. This is accomplished through immunization for all children against tuberculosis, poliomyelitis, pertussis, diphtheria, tetanus, measles, and hepatitis B, the protection of newborn infants against neonatal tetanus by immunizing pregnant women and women of child bearing age, and the immunization of broader age groups during disease control activities.

This document aims to assist immunization programme managers to improve programme quality by establishing an immunization safety surveillance system. It explains the types of adverse events following immunization (AEFI); provides the guidance to enable reporting, investigating and responding to AEFI, including expected rates of vaccine reactions; and advice on communicating about immunization safety for the public and the media.

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