

National Guidelines on Immunization Safety Surveillance:

Surveillance of Adverse Events Following Immunization



**Epidemiology Unit,
Ministry of Health
2012**



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Safety Surveillance:**

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FOREWARD

National Immunization Programme, Sri Lanka is one of the best performing public health programmes in the region and in the world too. Vaccine Preventable Diseases are well controlled in the country and coverage of all infant and early childhood vaccination is near 100%. The Governments' strong commitment based on policy to provide free health care service, dedicated staff from national to field level and well literate public is the key to its success.

The Adverse Events Following Immunization (AEFI) Surveillance System in the country has come a long way since its inception in 1996. Intensive efforts are being made by the Ministry of Health to strengthen surveillance of AEFI in the country. Ensuring the quality and safety of vaccines are essential and of paramount importance. Therefore, it is evident that surveillance of AEFI is a challenging task, nonetheless essential.

This guideline will enable the health system to effectively respond to vaccine safety challenges by clear instruction and defining the roles and responsibilities of health staff. It provides a tool for both public health staff and hospital health staff to enable them to respond the adverse events in a timely manner as well as help to prevent AEFIs due to immunization related errors.

This document would further strengthen the AEFI surveillance and response system in the country and would help build public confidence in the national immunization programme. It reinforces the commitment of the Government of Sri Lanka to provide quality and safe immunization services in the country.

Dr. Ajith Mendis

Director General of Health Services

PREFACE

The goal of national immunization programme is to protect the individual and the public from vaccine Preventable Diseases. Vaccines used in the national immunization programme are very safe and effective; however no vaccine is entirely free from adverse reactions as for other medicines. The adverse events following immunization are largely not due to the vaccine or not related to the vaccination and in fact, it is largely due to other reasons related to immunization or may be coincidental. However, to maintain public confidence, it is necessary to strengthen the surveillance of all adverse events following immunization (AEFI); detect, report, investigate and carryout remedial corrective actions.

Strict regulatory procedures in vaccine registration, procurement, close monitoring and supervision of divisional, district and national level immunization related activities, continued training of staff are in place to ensure quality and safety of the national immunization programme.

Ministry of Health has been making efforts to ensure Immunization safety of National Immunization Programme through strengthening the Adverse Events Following Immunization (AEFI) Surveillance System in the country. This guideline for surveillance of AEFI enable the health system to detect, report, investigate and monitor the adverse events in a timely manner as well as help to prevent AEFIs due to immunization related errors.

I am thankful to all experts who contributed in the development of this guideline. It is my fervent hope that this document will guide the health staff at all levels to further strengthen the AEFI surveillance in the country and thereby improve the quality of national immunization programme in the country.

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Table of Contents

Glossary.....	09	4.2.2 How should an investigation take place.....	53
Abbreviations.....	12	4.2.3 Stages of the investigation.....	54
1 Introduction.....	13	4.2.3.1 Initial Step.....	
1.1 Vision.....	15	4.2.3.2 Second Stage.....	
1.2 General Objective.....		4.2.3.3 Collection of Specimens.....	55
1.2.1. Specific objectives.....		4.2.4 Investigation of Deaths.....	56
1.3. Key elements of an effective AEFI surveillance system.....	16	4.2.5 Basis of AEFI Investigation.....	58
2 Adverse Events Following Immunizations.....	17	4.2.5.1 Events not related to the Vaccine/Vaccination.....	59
2.1. Vaccine Reaction.....	19	4.2.5.2 Events related to vaccination.....	
2.1.1. Common, minor vaccine reactions.....		4.2.5.3 Events related to the vaccine.....	60
2.1.1.1. Fever.....	20	4.2.6 Investigation of AEFI cluster.....	62
2.1.1.2 Local reactions.....		5 Analysis of AEFI Data.....	64
2.1.1.3 Systemic reactions.....		5.1 Who should analyse the data?.....	
2.1.2 Rare serious vaccine reactions.....	21	5.2 How should analyse the data?.....	65
2.1.3. Prevention of vaccine reactions.....	24	5.3 How should a cause be determined?.....	66
2.2 Immunization error–related reaction.....	25	6 Causality Assessment of AEFI.....	68
2.3 Coincidental Events.....	29	6.1 Levels of causality assessment.....	
2.4 Immunization anxiety-related reactions.....	30	6.2 Criteria for establishing causality.....	70
2.5. Special Issues.....	32	6.3 Causality Assessment Method.....	
2.5.1 Serious Events.....		7 Follow -up Action.....	73
2.5.2 Cluster of AEFI.....		7.1 Treatment.....	
2.5.3 Signals.....		7.2 Corrective actions.....	
3 AEFI Surveillance System in Sri Lanka.....	34	7.3 Training & awareness.....	75
3.1 Roles and Responsibilities of Key Players.....	37	7.4 Management of crisis situations.....	
3.1.1 Responsibilities of Public Health Midwives (PHM).....	38	7.5 Sharing AEFI information with stakeholders.....	76
3.1.2 Responsibilities of Public Health Inspector (PHI).....		7.6 Communication.....	79
3.1.3 Responsibilities of Senior Public Health In (SPHI).....	39	8 Evaluating Immunization Safety surveillance system.....	81
3.1.4 Responsibilities of Public Health Nursing Sister (PHNS).....		Websites on immunization safety.....	
3.1.5 Responsibilities of Medical Officer of Health (MOH).....	40		
3.1.6 Hospitals: Responsibilities of Medical Officers in Hospitals.....	42		
3.1.7 District Level: Responsibilities of Regional Epidemiologist.....			
3.1.8 National Level: Responsibilities of the Epidemiology Unit.....	43		
3.1.9 National Level: National Regulatory Authority (NRA).....	44		
3.1.10 National Control Laboratory (NCL).....	46		
3.2. TOR of the Expert Committee at the Epidemiology Unit.....			
3.2.1. TOR of the National Expert Committee on AEFI.....	47		
4 Reporting and Investigating of AEFI.....	49		
4.1 Reporting events.....			
4.1.1 Mass Immunization / Special immunization Programme.....			
4.1.2 Private sector reporting.....	50		
4.1.3 How can reporting be encouraged?.....	51		
4.2 AEFI case investigation.....			
4.2.1 What adverse events to investigate and when?.....	52		

A LIST OF TABLES & FIGURES

Table 1	Classification of adverse events following immunization (1996)
Table 2	Cause specific categorization of AEFIs (2012)
Table 3	Frequency of common minor adverse reactions.
Table 4	Rare vaccine reactions, onset interval, and rates.
Table 5	Immunization errors leading to adverse events.
Table 6	Guide to specimen samples obtained following selected AEFIs.
Table 7	Adverse events rates by selected antigen in Sri Lanka -2010.
Table 8	Adverse events rates by selected antigen in a defined area.
Table 9	Follow-up action to be taken after investigating AEFI.
Figure 1	AEFI surveillance system in Sri Lanka.
Figure 2	Identifying cause of AEFI cluster.

List of Annexures

1. List of working definitions to be used in AEFI surveillance
2. Guideline for initial management of anaphylaxis at field setting
3. List of AEFI to be Reported and investigated
4. Notification form for Adverse Events Following Immunization (AEFI Form 1)
5. Monthly Surveillance Report on Adverse Events Following Immunization (AEFI Form 2)
6. Regional Epidemiologist's Monthly Consolidated Return of AEFI
7. Adverse Events Following Immunization Case Investigation Form (AEFI Form 3)
8. Format for Investigation of Sudden Unexpected Deaths following immunization
9. Format for Investigation of Anaphylactic reaction following immunization
10. Clinic AEFI Register
11. MOH Office AEFI register
12. Child Health Development Record
13. Guidelines for paediatric autopsies on deaths following Immunization

GLOSSARY

Adverse event following immunization (AEFI)	Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
Causal association/link	An AEFI which is caused by administration of a particular vaccine. Causally associated events are also temporally associated (i.e. they occur within a limited time period after vaccine administration), but events which are temporally associated may not necessarily be causally associated.
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.
Coincidental adverse events	A medical event that occurs after immunization, but is not caused by the vaccine. It would have occurred whether or not the individual had received an immunization prior to the event. And this is due to a chance temporal association
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, Administration and 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 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.
Minor AEFI	An event that is not 'serious' and poses no potential risk to the health of recipient
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.
Serious AEFI	An event that is causing a potential risk to the health/life of recipient leading to hospitalization, disability/incapacity, congenital abnormalities/birth defects or death
Surveillance	The continuing, systematic collection of data that is analysed and disseminated to enable decision-making and action to protect the health of populations.
Temporal association/link	If the presumed event occurs close in time to vaccine administration which precedes the onset of the suspected adverse events then they are temporally associated. Temporal association is independent of causal association and an event which is temporally associated with vaccine administration may or may not be shown to be caused by the vaccine.

ABBREVIATIONS

Trigger event	A medical incident following immunization that stimulates a response, usually a case investigation
Vaccine	Biological substance that is administered to individuals to elicit immunity (protection) against a specific disease.
Vaccine Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFIs and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer). This is due to inherent properties of the vaccine
Vaccination failure	Vaccination failure may be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Primary failure (for example, lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to 1) vaccine failure or 2) failure to vaccinate, i.e. that an indicated vaccine was not administered appropriately for any reason.

AEFI	Adverse Event Following Immunization
BCG	Bacillus Calmette-Guerin - vaccine for tuberculosis (TB)
CIOMS	Council for International Organizations of Medical Sciences
CHDR	Child Health Development Record
DT	Diphtheria-tetanus vaccine
DTaP	Diphtheria-tetanus-pertussis (acellular) vaccine
DTwP	Diphtheria-tetanus-pertussis (whole-cell) vaccine
EPI	Expanded Programme on Immunization
Hib	<i>Haemophilus influenzae</i> type b vaccine
IPV	Injectable polio vaccine
MMR	Measles-mumps-rubella vaccine
MOH	Medical Officer of Health
MR	Measles-rubella vaccine
NRA	National Regulatory Authority
OPV	Oral poliomyelitis vaccine
PHI	Public Health Inspector
PHM	Public Health Midwife
PHNS	Public Health Nursing Sister
PMS	Post Marketing Surveillance
PvV	Pentavalent (DTP-HepB-Hib) vaccine
RDHS	Regional Director of Health Services
RE	Regional Epidemiologist
Td	Adult tetanus-diphtheria vaccine
VAPP	Vaccine associated paralytic poliomyelitis
VPD	Vaccine Preventable disease
WHO	World Health Organization

1. INTRODUCTION

The goal of immunization is to protect the individual and the public from vaccine preventable diseases. Although modern vaccines are safe, no vaccine is entirely without risk. Some people experience adverse events following immunization (AEFI) ranging from mild side effects to life-threatening but rare, illnesses. In the majority of cases these events are merely coincidences; in others they are caused by vaccine or by an error in the administration of vaccine or sometimes, there is no causal relationship at all.

The technology continues to improve with time, as do the quality, efficacy (level of protection) and effectiveness (disease reduction) of the vaccines utilized. New vaccines are adding into the programme and the schedule becomes more tight and congested. Also with emerging diseases demand for new vaccine has increased. An increase in vaccine use (e.g., mass immunization campaigns) will lead to more AEFIs. 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.

Public alert on vaccine safety has increased through awareness and increased access to the information such as through internet. Also, the vigilance of health care providers on vaccine safety has increased. The goal of immunization is to protect the individual and the public from vaccine preventable diseases. Although modern vaccines are safe, no vaccine is entirely without risk. Some people experience adverse events following immunization (AEFI) ranging from mild side effects to life-threatening but rare, illnesses. In the majority of cases these events

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Public alert on vaccine safety has increased through awareness and increased access to the information such as through internet. Also, the vigilance of health care providers on vaccine safety has increased too, due to strengthening AEFI surveillance. As a result, more and more concerns on quality and safety of vaccine are highlighted and demanded by both service providers and public. With this complexity, to rule out or rule in causality of true or possible vaccine link and prove coincidence need more detailed investigations, i.e causality assessment. Causality assessment is an evidence based approach with more scientific analysis of data, often requires a wide ranges of expert's opinions, even further research studies.

Irrespective of the cause, when adverse events following immunization (AEFI) occur, confusion is created among people to the extent that they may refuse further immunizations for their children leaving them susceptible to vaccine preventable diseases which are more disabling and life threatening. Surveillance of AEFI i.e. systematic collection of data on events following immunization therefore provide information to help plan on regaining public confidence on immunization.

To increase acceptance of immunization and improve quality of services, AEFI surveillance must become an integral part of the immunization programmes.

Thus, a field guide for immunization programme managers at all levels (Regional Directors of Health Services /Regional Epidemiologists at district level, Medical Officer of Health at divisional level) will facilitate achievement of the objectives of AEFI surveillance.

Benefits of immunization against diseases such as measles, neonatal tetanus and polio is far outweigh the adverse events caused by immunization. Monitoring AEFI will enable programme managers to reduce those risks even further.

In order to maintain or further improve confidence of public in immunization programme, health staff at all levels, from the field level up to the national level, should be familiarized with all aspects of immunization. Furthermore, they should be equipped to respond to any concerns of the public about immunization safety, including vaccine safety concerns. Timely response to public concerns about safety of vaccines as well as prompt communication will protect the public and preserve the integrity of the immunization programme as well.

1.1 Vision:

To protect the individual and the public from vaccine preventable diseases (VPD) through ensuring immunization safety

1.2 General Objective :

To improve efficiency of surveillance activities of adverse events following immunization and to improve the quality of immunization services at all levels and immunization and to improve the quality of immunization services at all levels and thereby ensure immunization safety of all recipients leading to achievement of goals and objectives of the national immunization programme in the country.

1.2.1. Specific objectives :

- ♦ To detect and timely identify problems with vaccines, which could be attributed to their inherent properties

- ♦ To detect, correct and prevent immunization related errors (programme-errors)
- ♦ To identify clustering or unusually high rates of AEFI even if they are considered as mild
- ♦ To identify signals of unknown AEFI
- ♦ To ensure and facilitate causality assessment of all serious AEFI and events with public concern ;coincidental, serious and unexpected/unusual AEFIs
- ♦ To estimate AEFI rates in the population
- ♦ To maintain the confidence of the community and health staff in the immunization programme by appropriately and timely responding to their concerns about immunization safety
- ♦ To effectively communicate with parents, community, media and other stakeholders, to create awareness on AEFIs without jeopardizing the immunization programme.

1.3. Key elements of an effective AEFI surveillance system include:

1. Early detection and notification of AEFI
2. Timely and effective analysis/ evaluation of data/information received
3. Conducting timely and comprehensive investigation and causality assessment
4. Dissemination of investigation and causality assessment findings to other responsible persons/units/institutions
5. Timely and effective response/ follow up actions based on investigation and causality assessment findings
6. Evaluation of the activities of service providers involved and to train and re-train when it is justified
7. Defining responsibility and avoid duplication of efforts
8. Effective communication

2. ADVERSE EVENTS FOLLOWING IMMUNIZATION

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 untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine**. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease. 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.

Table 1: Classification of adverse events following immunization (1996)

Type of AEFI	Definition
Vaccine reaction	An event caused or precipitated by the active component or ingredient or one of the other components of the vaccine. This is due to the inherent properties of the vaccine. This can be either due to product defect or without any quality defect.
Programme Errors (<i>Programmatic error, programme operation errors</i>)	An event caused by an error in vaccine preparation, handling or administration.
Coincidental	An event that occurs after immunization but is <u>not</u> caused by the vaccine. It is due to a chance association.
Injection Reaction	Event from anxiety due to fear of pain from the injection itself rather than the vaccine.
Unknown	Event's cause cannot be determined.

Earlier AEFIs were classified into five categories (Table 1). Immunization can cause adverse events from the inherent properties of the vaccine (**vaccine reaction**), or some error in the immunization process (**programme error** or *programmatic error* or *Programme operation 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**.

In 2012, Council for International Organizations of Medical Sciences (CIOMS) / WHO revised this classification concerning particularly cause-specific categorization of AEFIs and a **new categorization** has been introduced. (Table 2)

Table 2: Cause –specific categorization of adverse events following immunization (CIOMS/WHO, 2012)

Cause –specific Type of AEFI	Definition
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.
Immunization error-related reaction	Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Coincidental event	An AEFI caused by something other than the vaccine product, immunization error or immunization anxiety
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.

Note: “Immunization” as used in these definitions means the usage of a vaccine for the purpose of immunizing individuals. “Usage” includes all processes that occur after a vaccine product has left the manufacturing/ packaging site, i.e. handling, prescribing and administration of the vaccine.

2.1. Vaccine Reaction

A vaccine reaction is an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. The new cause-specific categorization is important for decision making on a vaccine product, as it clearly differentiates the two types of possible vaccine reactions.

- (i) **Vaccine product related reaction;** a vaccine reaction is an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly and
- (ii) **Vaccine quality defect-related reaction;** which is important to note that vaccine quality defect during manufacturing process has an impact on individuals response and there by increased risk of adverse vaccine reactions. *(Details are available on the "Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012).*

Vaccine reactions may be classified into common, minor reactions and 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. **A quality and safe vaccine reduces these reactions to a minimum while producing the best possible immunity.** The proportion of reaction occurrences likely to be expected and observed with the most commonly used vaccines. (Refer Table 3) In addition, some of the vaccine components, excipients (e.g. aluminium adjuvant, stabilizers or preservatives) can also lead to the vaccine reactions.

2.1.1.1. Fever

Can result as part of the immune response. Fever shall be anticipated in nearly 10% of vaccinees, except with DPT which produce fever in nearly 50% of those vaccinated. Fever is a systemic reaction usually occur within 24-48 hours of immunization except for those produced by measles, mumps and rubella vaccines which may occurs 6 to 12 days after immunization. However, it continues only for 24 – 48 hours.

2.1.1.2. Local reactions:

Include pain, swelling and/or redness at the injection site and can be expected in about 10% of vaccinees. BCG causes a specific local reaction which starts as a papule (lump) 2-4 weeks after immunization and may get ulcerated and healed after several months, leaving a scar. Keloid (thickened scar tissue) from the BCG lesion is more common among Asian and African populations.

2.1.1.3. Systemic reactions:

Common systemic reactions are irritability, malaise and loss of appetite. These systemic reactions are relatively common following DPwT vaccination. For measles/MMR and OPV vaccines, systemic reactions arise from vaccine virus infection. Measles vaccine may cause fever, rash, and/or conjunctivitis. It is very mild compared to "wild" measles virus, but for severely immuno--compromised individuals, it can be severe, and may be even fatal. Vaccine reactions for Mumps (parotitis ; swollen parotid gland) and Rubella (joint pains and swollen cervical lymph nodes) minimally affect the vaccinees.

Table 3: Frequency of common minor adverse reactions

Vaccine	Local Effects(pain, swelling, redness) ¹	Fever (> 38°C)	Irritability, malaise and systemic symptoms
BCG	Common 90%-95%		
Hepatitis B	Adults up to 30% Children up to 5%	1 – 6%	
Hib	5%-15%	2%-10%	
Pertussis (DTP– whole cell) ²	up to 50%	up to 50%	up to 55%
Measles/MR/MMR	~10%	5%-15%	5% (Rash)
Tetanus/DT/aTd	~ 10% ³	~ 10%	~ 25%
OPV	None	Less than 1%	Less than 1% ⁴

¹Local reactogenicity varies from one vaccine brand to another, depending on the strain and the number of viable antigen in the vaccine.

²When compared with whole cell pertussis vaccine, acellular pertussis vaccine rates are lower.

³Rate of local reactions are likely to increase with booster doses, up to 50-85%.

⁴Diarrhoea, Headache and/or muscle pains

Note: Although local and systemic reactogenicity are more commonly associated with wholecell pertussis (Pw)-containing vaccines, both acellular (Pa) and Pw vaccines have excellent safety records: (For details: <http://www.who.int/wer> : No 40, 2010, 85. 385-400)

2.1.2 Rare serious vaccine reactions

It is important to note that there is a difference between the terms "serious" and "severe" adverse events or reactions. "Serious" and 'severe' are often used as interch-

-angeable terms but they are not. A serious adverse event or reaction is a regulatory term. "Severe" is used to describe the intensity of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance. (e.g Fever is a common relatively minor medical event, but according to its severity it can be graded as mild fever or moderate fever. Anaphylaxis is a always serious event and life threatening.)

As defined by the Uppsala Monitoring Centre (UMC), a serious adverse event or reaction is any untoward medical occurrence following any dose of vaccine that

- ◆ Results in death
- ◆ Requires hospitalization or prolongation of hospital stay
- ◆ Results in persistent or significant disability/incapacity is life-threatening

Most of the rare and more serious vaccine reactions [e.g seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE), persistent inconsolable screaming] do not lead to long term problems. Anaphylaxis, while potentially fatal, is treatable without having any long term effects. Although encephalopathy is included as a rare reaction to measles or DPT vaccine, it is not certain whether these vaccines in fact cause encephalopathy. Case definitions for these reactions are given in annexure 1.

To determine the exact cause of serious AEFIs, such suspected vaccine adverse events should be reported and investigated

The information in tables 3 and 4 can be used to:

- ◆ Anticipate the expected rate and type of reactions
- ◆ Identify events that are probably unrelated to immunization (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.

Table 4: Rare vaccine reactions, onset interval and rates

Vaccine	Reaction	Onset Interval	Doses per reaction
BCG	Suppurative lymphadenitis	2-6 months	1 in 1-10,000
	BCG osteitis	1-12 months	1 in 3000 to
	Disseminated BCG infection	1-12 months	1 in 100 million
Hib	None known		
Measles/MMR /MR ¹	Febrile seizures	6-12 days	1 in 3000
	Thrombocytopenia (low platelets)	15-35 days	1 in 30 000
	Anaphylactic (severe allergic reaction)	0-2 hours	~1 in 100, 000
	Anaphylaxis	0-1 hour	~1 in 1, 000, 000
	Encephalopathy	6-12 days	< 1 in 1, 000, 000
Oral poliomyelitis	Vaccine associated paralytic poliomyelitis	4-30 days	1 in 2.4 - 3 million ¹
Tetanus Toxoid	Brachial neuritis	2-28 days	5-1 in 100, 000
	Anaphylaxis	0-1 hour	1 in 100, 000 to 1 in 2,500,000

Tetanus diphtheria	None extra than tetanus reactions		
Pertussis (DTP-whole cell)	Persistent (>3 hours) inconsolable screaming	0-24 hours	1 in 15 to 1 in 1000
	Seizures	0-3 days	1 in 600 ²
	Hypotonic Hypo-responsive episode(HHE)	0-48 hours	1 in 1000-33 000
	Anaphylaxis	0-1 hour	1 in 50 000
	Encephalopathy	0-2 days	0-1 in 1 million

Notes :

1. VAPP Risk is higher following the first dose (1 in 750,000 compared to 1 in 5.1 million for subsequent doses), and for adults and immunocompromised
2. Seizures are mostly febrile and the risk depends on age, with much lower risk in infants under the age of 4 months. Children over six years are unlikely to have febrile seizures

2.1.3. Prevention 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;

1. Serious allergy to the vaccine (anaphylaxis) or its components (excipients)
2. Progressive neurological illness
3. Immunodeficiency (in the case of live vaccines)

Use of vaccines in pregnancy is limited or mostly not recommended. Vaccines which are recommended in pregnancy would benefit and protect both mother and the newborn. However, limited use of vaccine in pregnancy is largely due to the potential risk and harm to the foetus. Risk is mostly theoretical and limited to live attenuated vaccines which have demonstrated evidence of potential risk and harm. Risk or harm caused by killed or conjugated vaccines are either not proven or limited to case reports. Vaccine manufacturers highlight pregnancy as a contraindication not only due to lack of evidence in safety studies and but also as a precautionary measure against litigation.

2.2 Immunization error–related reactions

“Immunization” as used here means the usage of a vaccine for the purpose of immunizing individuals. “Usage” includes all processes that occur after a vaccine product has left the manufacturing/ packaging site, i.e. handling, prescribing and administration of the vaccine.

Earlier, this AEFI type was categorised as “Programme errors” (*Syn; Programmatic error or Programme operation errors*) result from errors and mistakes in vaccine preparation, handling, or administration (Table 1).

Immunization errors (previously classified as Programme errors) are preventable and controlled. They reduce the overall benefit of the immunization programme. Identification and correction of these errors are of great importance.

An immunization error (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. Immunization errors (Programme errors) can also affect a stock of vaccines (e.g. by freezing vaccines during transport leading to an increase in local reactions in recipients).

Table 5: Immunization Errors (Programme Errors) leading Adverse Events Following Immunization

Immunization Error	Adverse Event
Non sterile injections: <ul style="list-style-type: none"> - Contaminated vaccine or diluents - Reuse of reconstituted vaccine at a subsequent session 	Infection[e.g.local suppuration at injection site abscess, cellulitis, systemic infection, sepsis, toxic shock syndrome, transmission of blood borne viruses (HIV, Hepatitis B or Hepatitis C)]
Vaccine prepared incorrectly: <ul style="list-style-type: none"> - Vaccine reconstituted with incorrect diluents - Drugs substituted for vaccine or diluents 	Local reaction or abscess due to inadequate shaking of vaccine vial Effect of other drugs (e.g. Insulin, muscle relaxant), used by mistake, instead of vaccine or diluents
Vaccine injected at wrong site/route: <ul style="list-style-type: none"> - Use of subcutaneous route instead of intradermal for BCG - Use of subcutaneous route instead of intramuscular for toxoid vaccines (DPT, DT, TT) - Injecting into buttocks 	Local reaction or injection site abscess Ineffective vaccination Sciatic nerve damage
Vaccine transported or stored incorrectly	Increased local reactions from frozen vaccine Ineffective vaccination
Contraindications ignored	Avoidable serious vaccine reactions

The most common Immunization errors (Programme errors) reported in Sri Lanka are sterile abscesses and nodules due to incorrect technique used in vaccine administration. Infection resulting in non sterile injections was dominant before introducing Auto disable (AD) syringes in many parts of the world. Infection can manifest as a local reaction (e.g. suppuration, abscess), systemic effect (e.g. sepsis or toxic shock syndrome) or blood borne virus infection (e.g. HIV, Hepatitis B, or Hepatitis C). Immunization errors may also result in AEFIs when another chemical or drug, other than the intended vaccine or diluent, is inadvertently used in the reconstitution of freeze dried vaccines (e.g. muscle relaxant given instead of relevant diluent for measles vaccine) or administered directly in place of liquid vaccines. Immunization error can occur if wrong vaccine is administered to a person or a vaccine was given where it was not indicated (e.g. JE vaccine given instead of DPT vaccine). These also occur if the contraindications were ignored.

Also, need a clear understanding of contraindications and precautions. Precautions are not contraindications, but decision on vaccination requires a case base assessment. Use of vaccines in pregnancy is limited or mostly not recommended. The vaccines which are recommended in pregnancy would benefit and protect both mother and the newborn. However, the limited use of vaccine in pregnancy is largely due to the potential risk and harm to the foetus. The risk is mostly theoretical and limited to live attenuated vaccines which have demonstrated evidence of potential risk and harm, particularly in animal models. Vaccine manufacturers instruct pregnancy as a contraindication not due to proven evidence, but as a precautionary measure against litigation.

An Immunization 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. Immunization errors can also affect many vials (e.g. by freezing vaccines during transport leading to an increase in local reactions)

Programme errors can usually be prevented through properly organized immunization clinic practices, by training of health workers, maintaining regular supervision and by providing an adequate supply of equipment for safe injections

Immunization errors (Programme errors) can be avoided by adhering to following guidance:

- ◆ Vaccine must only be reconstituted with the diluent supplied by the manufacturer.
- ◆ Reconstituted vaccine should not be used for more than six hours after reconstitution.
- ◆ Reconstituted vaccine must be discarded at the end of each immunization session and never retained.
- ◆ No other drugs or substances should be stored in the same refrigerator where vaccines are stored.
- ◆ Immunization staff must be adequately trained and closely supervised to ensure that proper procedures are being followed.
- ◆ Careful epidemiological investigation of an AEFI is needed to ascertain the cause and to correct the wrong immunization practices

2.3 Coincidental Events

Children are usually given vaccines at an age when they are susceptible to many diseases. Thus, situations may arise when an adverse medical event is falsely attributed to the vaccine. In other words a chance temporal association (ie, an event occurs after immunization) is falsely considered to be caused by immunization. These are purely temporal associations which are inevitable when large number of vaccine doses administered, especially in mass campaigns.

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. Many SIDS cases will be in children who have been recently immunized. Controlled studies have shown that the association of SIDS and immunization is purely coincidental and not causal. Knowledge of Infant mortality rates and, rates of SIDS are helpful when investigating and in causality assessment to make valid conclusions and to rule out vaccine reactions.

Coincidental adverse events are clearly unrelated to vaccination. However, certain serious events may be blamed on the vaccine by parents or community because of its close temporal association with immunization, especially if the vaccinated individual was previously healthy. Therefore, these 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. If the same event also affected others in the same age group around the same time, who did not receive the suspect vaccine(s), then a coincidental event is more likely. There may also be other evidence showing that th-

-e event is not related to immunization.

Coincidental adverse events may be 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, particularly *age specific disease incidence rates* allows estimation of the expected numbers of coincidental events.

With increasing awareness of AEFI surveillance, even health staff may report more coincidental events. Also, with introduction of new vaccines, there is a trend of reporting many AEFI including coincidental events. It is crucial to differentiate these reported coincidental events from potential 'signals' [e.g. Hypotonic Hyporesponsive Episodes (HHE) following introduction of DTP-HepB-Hib Pentavalent (PvV) vaccine in 2008 in Sri Lanka]. Knowledge on background rates of reported coincidental events are also important and helps to determine possible 'signals' and to correctly categorize them as coincidental events. (*Refer: "signals" is described in section 3.3*)

2.4 Immunization anxiety-related reactions

Individuals and groups can react in anticipation to an injection of any kind. This reaction may mimic an AEFI but is unrelated to the content of the vaccine.

Fainting is relatively common, but usually affects children aged over five years. Fainting does not require any management beyond placing the patient in a recumbent position. The likelihood of fainting can be anticipated when immunizing older children and can be reduced by minimizing stress in those awaiting injection through short waiting times, comfortable room temperatures, preparation of vaccine

out of recipient view and privacy during the procedure. Avoiding injury from the fall is important and those at risk should be immunized while seated. However, fainting may also occur sometime after immunization.

Hyperventilation as a result of anxiety about 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. 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 has fainted or has had some other reaction following vaccination. Clear explanations regarding the immunization and calm, confident delivery will decrease the level of anxiety about the injection procedure and thus reduce the likelihood of occurrence.

It is important to note, faintish attack (syncope) can be misdiagnosed as anaphylaxis. Health worker need to be differentiating these two statuses and details are given in (Annex 2: General Circular No: 01-20/2011- Guidelines for initial management of anaphylaxis in field setting). Very careful observation and clinical judgment is necessary. However, by mistake health care worker may administer a single dose of Adrenaline (intramuscularly) to a vaccinee with just syncope, but it does not make a harm to the vaccinee. To avoid such unnecessary medical emergency interventions, continued training and awareness for health staff is necessary.

2.5. Special Issues

2.5.1 Serious Events: Serious AEFIs are defined as those that are life threatening and those that result in hospitalization (or prolonged hospitalization), disability (or have the potential to result in disability) or death.

In addition, it is recommended that certain types of AEFI should be considered serious enough to warrant special attention in order to ensure immediate reporting when they are detected and there by rapid and prompt response is initiated, including investigation and proper case management. These include AEFIs that may have been caused by immunization errors and occurring in cluster (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome, HHE), serious events of unexplained aetiology occurring within 30 days after a vaccination and events causing significant parental or community concern.

2.5.2 Cluster of AEFI

A cluster is defined as two or more cases of the same or similar event, which are related in time and have occurred within the same geographical unit or associated with the same vaccine, same batch number administered or same vaccinator or which had occurred during the same clinic session. For example, two or more cases of abscess occurring following one immunization session in a village; repeated cases of abscess following immunization by same vaccinator or same batch of the vaccine will be considered as clusters.

2.5.3 Signals

Signals are defined as possible causal relationship of a reaction/event following a vaccine to which had been previously unknown or incompletely documented. Only

3 AEFI SURVEILLANCE SYSTEM IN SRI LANKA

a systematic causality assessment based on information/data collected through research methods can detect signals and establish causal relationships. This is important with new vaccines, particularly if introduced in a mass vaccination approach.

E.g.; Narcolepsy following Pandemic H1NI influenza vaccine (*Pandemrix*) reported in Finland (*Ref:*

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109182.pdf)

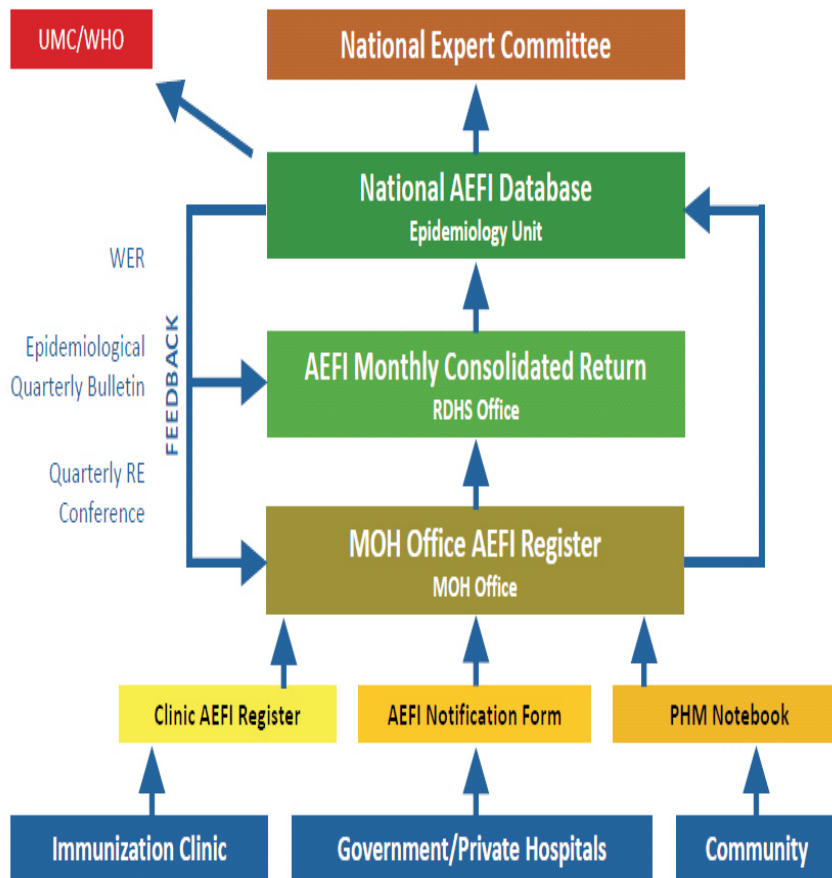
Surveillance of AEFI in Sri Lanka commenced in 1996. All serious and non serious AEFI are required to be reported. List of AEFIs to be reported and investigated are given in Annexure 3. Presently, the programme has been expanded by developing a more detailed reporting form namely, Notification Form for Adverse Events Following Immunization (AEFI Form 1) (Annexure 4), Monthly Surveillance of Adverse Events Following Immunization (AEFI Form 2) (Annexure 5), AEFI Consolidated Return from Regional Epidemiologist (AEFI Form 4) (Annexure 6) and Adverse Events Following Immunization Case Investigation Form (AEFI Form 3) (Annexure 7). Investigation of deaths and anaphylactic reactions following immunization needs to be carried out using separate investigation forms given in Annexure 8 and 9 respectively. If information was obtained during the clinic session these should be entered in the Clinic AEFI Register (Annexure 10), which is kept in the immunization clinic. Information coming from any other source should be documented in the 'MOHAEFI Register' (Annexure 11), which is kept in the MOH office.

Screening all children for AEFI following previous immunization is mandatory and a separate column for this is available in the immunization record of the CHDR (Annexure 12). In this format the last column is specifically to record any adverse events which occurred following a previous immunization. For example, when a mother brings her infant for the first dose of PvV/OPV the midwife the health care worker conducting the immunization must specifically inquire about any adverse events following BCG vaccination. If no AEFI are reported a "0" must be marked in the relevant column against the particular vaccine.

When a supervising officer inspects the CHDR when a six month old infant is brought to the immunization clinic for the third dose of PvV/OPV and notices that the AEFI column is blank against previous vaccinations, it indicates that the health care worker has not screened the child regarding AEFI during clinic immunization visits.

In addition to the above, some AEFI may be detected in medical institutions when affected patients seek treatment for the said AEFI. Out Patients' Department (OPD) in these institutions, paediatric wards, and surgical wards are potential places where AEFI could be detected. Therefore it is important that relevant health workers in hospitals are made aware of AEFI and AEFI surveillance. When a patient is detected as having an AEFI in a health institution, the case should be notified in the prescribed format (AEFI Form 1/Annexure 4) to the MOH of the area where the patient resides. This form is available as a carbonized copy book and each page contains 3 copies. The white coloured copy should be sent to the MOH and the pink coloured copy to the Regional Epidemiologist and the yellow coloured copy should be kept filed as the office (institution) copy.

Figure 1: AEFI surveillance system in Sri Lanka



At the monthly conference in the MOH office, these AEFI notifications must be cross checked with the AEFI registers of each field clinic (which the PHM in charge of the field clinic should bring with her to the monthly conference) to avoid duplicating of cases and should be entered in the MOH Office AEFI Register. AEFI reported during the month must be consolidated in the prescribed format (AEFI Form 2 -Monthly Surveillance Report on AEFI/ Annexure 5). This is a printed book in a carbonized triplicate copy; one copy must be sent to the Epidemiology Unit (white colour) and another to the Regional Epidemiologist (pink colour). Office copy (yellow colour) should be kept in the printed book as an institutional record for any follow up references. With this report, completed investigation form for each case that was investigated should be attached and sent to the Epidemiology Unit. The list of AEFI that needs to be investigated is given in both AEFI form 1 and 2.

AEFI that are required to be reported and their case definitions are given on the reverse side of the AEFI notification form (Annexure 4) and the monthly AEFI return (Annexure 5).

3.1 Roles and Responsibilities of Key Players:

An effective immunization safety surveillance system involves health workers at all levels in the immunization programme and other health service providers. This section identifies the key role players at different levels of the surveillance system and also outline their roles and responsibilities in carrying out these surveillance activities. Details of methods of reporting and flow of information are provided.

AEFI surveillance system has three different starting points at the community level; field immunization clinics, hospitals and community (reporting by parents/guardians).

3.1.1 Responsibilities of Public Health Midwife (PHM):

Detection and Reporting of AEFIs –

- ◆ Inquiries should be made from each receipt or parent/guardian of the recipient regarding any AEFIs experienced after previous vaccination at immunization clinics and record same in the Child Health Development Record (CHDR- Annexure 12) and Clinic AEFI Register (Annexure 10).
- ◆ Inquiries should be made regarding any AEFIs in recipients during the PHMM field visit and if found they should be recorded in the pocket note book of the PHM. All information in the pocket note book should be entered in the MOH Office AEFI Register (Annexure 11) on monthly conference day or another selected day by the MOH.
- ◆ PHMM should bring the Clinic AEFI Register to MOH Office on monthly conference day or a selected day by the MOH.
- ◆ PHM should inform SPHM, PHNS, MOH immediately regarding serious adverse events, unusual AEFIs and deaths.
- ◆ If treatment is necessary for a particular condition the recipient having AEFIs should be referred to the MOH or to the nearest hospital.
- ◆ Whenever an opportunity is available, make aware and educate the community regarding AEFIs.

3.1.2 Responsibilities of Public Health Inspector (PHI):

- ◆ Any adverse event identified during vaccination of students at schools during School Medical Inspection (SMI), should be recorded in the pocket note book and the data should be transferred to the “MOH Office AEFI Register” (Annexure 11) at the MOH Office.
- ◆ If there is a necessity, students with AEFI should be referred to the MOH or to the hospital.
- ◆ SPHI and MOH should be informed immediately regarding serious

adverse events, unusual AEFIs and deaths.

- ◆ Whenever the PHI finds a recipient with AEFIs during field visits, the information should be recorded in the pocket note book and transferred to the MOH Office AEFI Register in the MOH Office.

3.1.3 Responsibilities of Senior Public Health Inspector (SPHI):

- ◆ Whenever an opportunity is available during the clinic session parents/community should be educated and made aware on AEFIs.
- ◆ Should motivate PHI for timely reporting of AEFIs and conduct follow up.
- ◆ Should encourage the PHI to detect and report AEFIs.
- ◆ Should inform MOH immediately regarding serious adverse events, unusual AEFIs and deaths.
- ◆ If assigned by MOH, minor AEFIs should be investigated.

3.1.4 Responsibilities of Public Health Nursing Sister (PHNS):

- ◆ Should inquire all vaccine recipients of any AEFIs experienced by them following previous vaccination during the screening for subsequent immunization.
- ◆ Should monitor and supervise PHM regarding immunization procedure, and detection and reporting of AEFIs. Any error in these should be identified and immediately corrected at the clinic session itself.
- ◆ Whenever an opportunity is available during the clinic session, parents/community should be educated and made aware on AEFIs.
- ◆ Should motivate PHMM to detect timely report AEFIs and conduct follow up.
- ◆ Should prepare the Monthly Surveillance report of AEFI (AEFI Form 2) timely and accurately and forward to the MOH for inspection and certification if the work has been delegated by the MOH.

- ◆ Should supervise or carry out transferring information from Clinic AEFI Register to MOH Office AEFI Register as delegated by the MOH.
- ◆ Should train PHM on good quality immunization practices.
- ◆ Should inform MOH immediately regarding serious adverse events, unusual AEFIs and deaths.
- ◆ If assigned by MOH minor AEFIs should be investigated.

Note: If PHNS is not available, then Senior Public Health Midwife (SPHM) should be responsible for all above mentioned functions of PHNS.

3.1.5 Responsibilities of Medical Officer of Health (MOH):

- ◆ Inquiries should be made on any AEFIs experienced by the recipient following previous vaccination during the screening for subsequent immunization.
- ◆ Should designate a responsible person for maintaining the MOH Office AEFI Register (Annexure 11) to include data from;
 - i. Pocket note books of PHII and PHMM.
 - ii. Notification from Medical Institutions
 - iii. Notification from General Practitioners (GP)
 - iv. Information from any other source
 - v. Information from clinic AEFI register (on monthly conference day).
- ◆ Should coordinate with hospitals and obtain information on AEFI from the wards and immunization clinics as well as from private hospitals/General Practitioners.
- ◆ Information in the MOH Office AEFI Register should be transferred to the Monthly Surveillance Report on AEFI (AEFI Form 2) to be sent to the Epidemiology Unit with a copy to Regional Epidemiologist on or before the 10th of the following month. This activity could be delegated to an officer

(PHNS, SPHM). However, MOH should sign the form only after checking the details included in the forms. MOH is the responsible person for forwarding accurate information in the designated form correctly completed.

- ◆ Should motivate field health staff to detect and timely report AEFIs using AEFI Form 2.
- ◆ Investigation of AEFIs (Annexure 7) should be carried out and if relevant, corrective action should be taken immediately.
- ◆ Investigation of AEFIs is a responsibility of the MOH. MOH may assign either SPHI/SPHM or PHNS for investigation of minor AEFI only.
- ◆ Investigation reports should be sent to the Epidemiology Unit with a copy to Regional Epidemiologist immediately after reporting the case.
- ◆ Monitoring and supervision of the field health staff should be carried out regularly.
- ◆ Should immediately inform regarding unusual AEFIs, serious adverse events and deaths to the Regional Epidemiologist and to the Epidemiology Unit. Investigation of these cases should commence within 24 hours after receiving the information. May seek advices and assistance from Regional Epidemiologist or Epidemiology, if necessary or event with a very serious /high public concern.
- ◆ Should provide guidance and adequate training to the field health staff on AEFI surveillance and good quality immunization practices. Whenever necessary staff should be re-trained.
- ◆ Should communicate with the staff and the community especially in an event of a serious AEFI: Public should be kept informed regarding what is being done during the investigation and once it is over, the conclusions and results should be shared with other members of the team and the community.

3.1.6 Hospitals: Responsibilities of Medical Officers in Hospitals:

- ◆ Should always inquire regarding immunization history of the child.
 - ◆ Reporting should be done immediately to MOH of the patient's residential area by the Medical Officer (MO) who is treating the patient on suspicion of AEFI using the Notification form for AEFI (AEFI Form 1).
 - ◆ Assistance from the Infection Control Nursing Officer (ICNO) should be obtained for the process of reporting. This activity could be delegated to the ICNO or other Nursing Officer as well. Further, AEFI notification book (AEFI Form 1) may be kept and maintained by the ICNO.
- i. Serious adverse events, unusual AEFIs and deaths should be notified directly to the Regional Epidemiologist and to the Epidemiology Unit.
- Special Note:** Head of the institution is the final responsible officer regarding all above activities and implementation of AEFI surveillance system in the hospital and delegation of responsibility of the reporting mechanism is his/her responsibility.
- ii. **Private medical institutions** are also recommended to maintain and follow AEFI notification practices using notification book (AEFI Form 1), as it is done by government medical institutions.

3.1.7 District Level: Responsibilities of the Regional Epidemiologist:

- ◆ Should undertake guiding and training the field staff on detection and timely reporting of AEFI and maintaining good quality immunization procedures.
- ◆ Should supervise data management; screening, compilation and analysis of AEFI data in the district.
- ◆ Should coordinate with the Epidemiology Unit and the field staff.
- ◆ Should send district data from all MOH areas on AEFIs to the Epidemiology Unit before 20th of the following month, using Monthly Consolidated Return of AEFI -

(AEFI form 4).

- ◆ District records on AEFI surveillance should be maintained.
- ◆ Regular supervisory visits should be undertaken for monitoring the routine immunization programme and detect problems in reporting or identify programme errors.
- ◆ Should keep up monitoring and supervision of field staff and ensure regular feedback to the staff regarding their AEFI activities.
- ◆ Review of MOH activities on AEFI should be carried out at least once in two months. Serious adverse events, unusual AEFIs and deaths should be immediately investigated with the MOH and immediately informed to the Epidemiology Unit. Deaths and unusual cases after immunization should be investigated within 24 hours after reporting by the district team, which include Regional Epidemiologist, Medical Officer of Health in the area, PHNS, and PHM. They should inform the Epidemiology Unit immediately on receiving the information. If necessary, Epidemiology Unit too will assist the team

3.1.8 National Level: Responsibilities of the Epidemiology Unit:

- ◆ Chief Epidemiologist will identify and assign a focal point within the unit to carry out all immunization safety activities.
- ◆ Should screen all Monthly Surveillance Reports on AEFI (form 2) when received at the Epidemiology Unit and send for data entry.
- ◆ Should identify incomplete and erroneously filled forms and return for rectification.
- ◆ Should identify unusual and serious AEFIs.
- ◆ Should monitor investigation of AEFIs and send reminders for investigation of cases.
- ◆ Should assist investigations of deaths and unusual events conducted by

district team.

- ◆ Should conduct investigation of any AEFI case which has a national significance.
- ◆ Should report deaths and unusual events to the team of experts in the AEFI expert committee.
- ◆ Analysis of AEFI data for completeness, timeliness, number of nil returns, rates of AEFIs, deaths and unusual events should be carried out monthly, quarterly and annually.
- ◆ Should present results at the Regional Epidemiologist's quarterly review and make arrangements to publish in the Quarterly Epidemiological Bulletin and WER (Weekly Epidemiological Report).
- ◆ Should provide guidance and training to the District and MOH staff.
- ◆ Regular reviews in the districts should be conducted to identify weak areas and to solve these problems.
- ◆ Should prepare detailed reports for the expert committee/ causality assessment committee meetings

3.1.9 National Level: National Regulatory Authority (NRA)

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. **In Sri Lanka Medical Technology & Supplies (MTS) is functioning as the NRA.**

WHO has defined six functions to be carried out by NRA as given below:

1. Marketing authorization and licensing activities: with clear written instruction for licensing products and manufacturers

2. Post marketing surveillance including AEFI: surveillance of vaccine field performance in safety and efficacy
3. NRA lot release: system for Lot release
4. Laboratory access: use of laboratory when needed
5. Regulatory inspection: Regular inspection of manufacturers for Good manufacturing Practices (GMP) compliance
6. Regulatory oversight of clinical trials: evaluation of clinical performances through authorized clinical trials

Responsibility of MTS:

- ◆ Should monitor all AEFIs reported by the Epidemiology Unit, Private institutions and registered vaccine suppliers.
- ◆ Should inform Epidemiology Unit any serious AEFI or vaccine reaction with a national significance reported by private institutions, vaccine suppliers or vaccine manufacturers.
- ◆ Should carefully consider vaccine safety profile of all vaccines at registration and extension of registration: advice shall seek from Drug Evaluation Sub Committee (DESC), Epidemiology Unit and NCL (MRI).
- ◆ Should assist investigations and causality assessment of deaths and unusual events conducted by Epidemiology Unit.
- ◆ Should report deaths and unusual events to the team of experts in the AEFI expert committee.
- ◆ Should prepare detailed reports for the expert committee/ causality assessment committee meetings

3.1.10 National Control Laboratory (NCL)

Medical Research Institute (MRI) functions as the NCL.

- ◆ Should monitor all AEFIs reported by the Epidemiology Unit, Private institutions and registered vaccine suppliers.
- ◆ Should inform Epidemiology Unit any serious AEFI or vaccine reaction with a national significance reported by private institutions, vaccine suppliers or vaccine manufacturers..
- ◆ Should carefully consider vaccine safety profile of all vaccines at registration and extension of registration: advice shall seek from Drug Evaluation Sub Committee (DESC), Epidemiology Unit and NCL (MRI).
- ◆ Should assist investigations and causality assessment of deaths and unusual events conducted by Epidemiology Unit.
- ◆ Should report deaths and unusual events to the team of experts in the AEFI expert committee.
- ◆ Should prepare detailed reports for the expert committee/ causality assessment committee meetings

3.2. TOR of the Expert Committee at the Epidemiology Unit

The committee consists of the Chief Epidemiologist, Assistant Epidemiologist and Consultant Epidemiologist.

- ◆ Should review aggregate reports and advise on analysis and reporting of AEFI data.
- ◆ Should advise on development and maintenance of National AEFI data base.
- ◆ Should review deaths, individual serious events and unusual AEFIs in order to assess the potential causal link between the event and the vaccine. This review will follow WHO guidelines and recommendations for causality assessment.

All deaths and any other AEFI cases with national significance will be investigated and submitted to national expert committee for further review.

- ◆ Conduct periodic evaluation of the AEFI surveillance system and recommendations for further strengthening.
- ◆ Keep up monitoring of reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events and make recommendations for further investigation.

3.2.1. TOR of the National Expert Committee on AEFI

The committee consists of a Director, Medical Technology & Supplies (National Regulatory Authority), a Paediatrician, a physician, a Neurologist, an Immunologist (NCL), a virologist (NCL), a Microbiologist (NCL), a Pathologist, an Epidemiologist, a Judicial Medical Officer and a Pharmacologist.

- ◆ Chief Epidemiologist will be the Secretary and the convener to the committee.
- ◆ The committee could invite other experts when necessary, depending on the technical matters to be discussed at the meeting
- ◆ The committee shall review all reported serious AEFI presented for expert opinion by the Expert Committee at Epidemiology Unit and make arrangements to investigate further to establish causality and to make necessary recommendations to rectify issues.
- ◆ Makes final decisions on causality assessment of unconcluded investigations; ensures quality control on AEFI surveillance system. Shall communicate with other national and international experts when requirements arise in establishing causality and vaccine quality issues.
- ◆ Shall advise the Chief Epidemiologist (National EPI manager) regarding AEFI related issues when requested by him/her.

- ◆ Shall advise Director General of Health Services regarding AEFI related matters when requested by him/her.
- ◆ The committee will meet at least twice a year and whenever necessary.
- ◆ A committee member will serve for a period of two years but could be extended as long as the committee feels his/her service is necessary

4.REPORTING AND INVESTIGATING OF AEFI

4.1 Reporting events

All adverse medical events following an immunization that is believed to be but not necessarily caused by immunization need to be reported.

All medical events should be reported if temporally related to immunization. Unless otherwise specified these include all such events occurring within 30 days following administration of a vaccine.

The events that are known to be identified as AEFI (case definitions are given in Annexure 1), events where a change in the nature, severity, frequency could be observed and also event which occur in clusters or cause major public concern should be reported using Adverse Events Following Immunization notification form (AEFI Form 1).

Any unexplained sudden death of a vaccine recipient temporally linked (**within 30 days**) to immunization, where no other clear cause of death can be established, should be reported. In addition, any unusual events should be reported.

As soon as health staff is informed of a AEFI or noticed any AEFI, it is important to ensure that recipient has received necessary health care including treatment if it is indicated.

4.1.1 Mass Immunization / Special immunization Programme

It is of utmost importance to report all AEFI to MOH in an event of mass immunization or special immunization programme, for 2 reasons:

- i. Mass Immunization and special immunization programme covers a large number of individuals in a particular target group in a specified given time period and therefore, an excess number of adverse events may be reported within a short time period. Unless, these are not properly investigated or analysed, it can cause undue concern among public and may affect the immunization programme.
- ii. During special immunization programmes, a new vaccine may be introduced with no prior experience or with little information on adverse reactions. There is a possibility of detecting signals through strengthening surveillance during such special immunization programmes. e.g. Narcolepsy reported following H1N1 influenza mass vaccination in Finland in 2009-2010.

4.1.2 Private sector reporting

As in government institutions, all private sector medical institutions handling immunization services and treating AEFI cases should report all AEFIs to the respective MOH. Reporting from private sector is encouraged for two reasons: (i) Public commonly seek out patient medical care from the private sector, following vaccines received at public institutions. (ii) It is important to monitor vaccine use in private sector.

For vaccines used only in the private sector

All AEFIs following these vaccines should be reported quarterly to the Medical Technology & Supplies (National Regulatory Authority) with a copy to Epidemiology Unit by the local agent of the relevant vaccine.

Serious AEFI from any vaccine should be reported to the Epidemiology Unit immediately by the relevant private hospital.

For vaccines used in EPI programme

Specialist/Medical Officer who treat the patient at the private hospital is responsible for sending information . Each private hospital should identify an officer to coordinate this mechanism. The responsibility and coordination could delegate to a senior nursing officer too. The reporting from private sector does not different from practice by government hospital; it is a case base reporting to the respective MOH.

4.1.3 How can reporting be encouraged?

Support of field staff is crucial for the success of any surveillance programme. Field staff should be encouraged to report adverse events without fear or penalty. Available AEFIs should be reported even if there is a delay in the submission of information by the field staff.

It is important that field staff should be given a feedback about the results of investigations and action taken. This has to be carried out at each level of the surveillance process and should include positive feedback such as an acknowledgement for reports received. Feedback also should include sharing information on management of child/recipient especially concerning future vaccination and the outcome of investigations or causality assessment when these are carried out.

4.2 AEFI case investigation

Ultimate goal of a case investigation is to find the cause of an AEFI or if there is clustering of AEFIs and to prevent the occurrence of similar events in future. If the cause is identified as a programme error, remedial action can be taken promptly and public can be assured of the integrity of the immunization services. Even if the cause cannot be identified or the cause of the event was attributed to some other reason, the fact that health workers had investigated the incident itself will increase public confidence towards immunization.

Purpose of investigating AEFI cases are:

1. To confirm the reported diagnosis or propose other possible diagnoses and clarify the outcome of the medical incident
2. To identify details of specifications of the vaccine used to immunize the affected recipient and most importantly to identify any vaccine related link for the given AEFI
3. To examine the operational aspects of the programme
Even if an event seems to be vaccine induced or coincidental, programme errors may increase severity in events.
4. To determine whether a reported event was a single incident or one of a cluster and if it is a cluster where the suspected immunizations were given and what vaccines were used
5. To determine whether unimmunized people are experiencing the same medical incidents.

4.2.1 What adverse events to investigate and when?

All trigger events following immunization should be investigated. It is important to note that the objective of AEFI surveillance is to ensure the quality and safety of vaccines used in both national immunization programme and the private sector. Therefore reporting and investigation of all vaccines used in both sectors are important and necessary.

Some of the events to be investigated are:

- ♦ All injection site abscesses
- ♦ All cases of BCG lymphadenitis
- ♦ All deaths that occur within one month of an immunization and attributed to that particular immunization

- ♦ All cases requiring hospitalization that occurs within one month of an immunization which are attributed to that particular immunization.
- ♦ All medical events that are believed to have been caused by an immunization and about which people are concerned.

4.2.2 How should an investigation take place?

It is important to initiate an investigation urgently whenever it is deemed necessary so that the cause may be determined (where possible) and in some events additional cases are prevented. MOH, RE, MO/MCH or Epidemiolog Unit or in case of minor AEFIs any officer (PHNS, SPHI or SPHM) assigned by MOH, may conduct the investigation. In case of a death, the district team should conduct the investigation and MOH shall assist the district team. If the event is of national interest, a team from Epidemiology unit will conduct the investigation with participation of the district team. Who ever initiates the investigation he/she should immediately notify the event to the relevant supervising officers. AEFI case investigation form is used for this purpose (Annexure 5). Although 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 any individual. Laboratory testing may sometimes confirm or rule out the suspected cause: the vaccine and diluent may be tested for safety, sterility and chemical composition and the needles and syringes for sterility. Testing should only be requested on a clear suspicion and not as a routine procedure.

On clear suspicion samples from vaccine and diluent should be sent for testing to the Medical Research Institute and if necessary to the international laboratories. The manufacturer should be informed. During transport of samples cold chain (2-8 C°) conditions should be maintained and they have to be sent to the laboratory as quickly as possible. Relevant information should be clearly written on the request of the sample. It is important that the used vial with remaining vaccine and diluent (if applicable and available) is sent for testing along with the unused 1-2 vials of the same batch.

On completion of the investigation cause of the event needs to be communicated to the relevant health officials, parents/relatives and 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.

4.2.3 Stages of the investigation:

4.2.3.1 Initial step

Immediately after any serious, unusual AEFI and death is reported, MOH and the field staff should re-assure the affected recipient/ parents/guardian that an investigation would be carried out.

4.2.3.2. Second stage

- ♦ MOH should verify the information and decide whether the event needs further investigation.
- ♦ If an investigation is warranted, initiation of the investigation should begin by proceeding to the location of the AEFI.
- ♦ The investigation should begin as soon as possible.
- ♦ AEFI case investigation form should be used for the investigation.

Following information should be obtained during the investigation:

- ♦ Inquire from the patient (if possible)/parents about the health condition of the patient
- ♦ Check about the vaccine that is attributed and other drugs received
- ♦ Inquire about other vaccines received
- ♦ Question about the quality of immunization services
- ♦ Observe the immunization sessions in action
- ♦ Inquire about similar events in unvaccinated persons
- ♦ Support case definition or establish a more specific case definition if needed
- ♦ Seek information from other recipients/community regarding any similar events

4.2.3.3 Collection of specimens

Collect specimens if relevant:

- (i) from the patient
- (ii) the vaccine/diluents
- (iii) syringes and needles
- (iv) post mortem samples

For histo-pathological examination and microbiological examination specimens should be handled at the local hospital or forwarded to Medical Research Institute (MRI). Specimens for toxicological examination are performed at the Government Analyst Department. Above activities could be coordinated through Epidemiological Unit and Regional Epidemiologist of the district. If facilities for essential laboratory testing are not available at national institutions, sending samples to an accredited laboratory abroad need to be considered.

Information regarding the identity of the deceased and the details of authorization (postmortem order by coroner) should be obtained and included in the report. Samples should be taken and investigated in cases such as alleged intoxications, allergy related incidents etc. Therefore, as soon as information is received clinical staff should be advised to preserve samples such as blood, urine, CSF, vomitus, faeces, sputum, swabs etc that have already been obtained. Samples (blood) for immunological studies in an anaphylactic reaction should be collected immediately after the reaction and also at 3 hrs and 6 hrs following the event optimally. Ward staff should be advised to document all therapeutic interventions.

The area Medical Officer of Health (MOH), where the child was vaccinated needs to be informed to preserve and handover empty vials, diluents, syringes and needles used at the incriminating event along with control samples of the same batch. Regional Epidemiologist should coordinate this activity.

Date and time of collection of each sample and type of preservative used in each should be recorded. Reports of clinical investigations and medical records related to the incident such as microbiology, biochemistry, immunology, histopathology, haematology, radiology etc should be collected and documented.

A detailed history which includes past medical history, drug history, immunization history, history of allergies and findings of medical records etc of the patient should be obtained.

4.2.4 Investigation of Deaths:

In the event of a death following immunization, it should be notified to the Regional Epidemiologist and Epidemiological Unit immediately over the phone and the field investigation has to be initiated promptly by the district team with the participation of MOH.

Following information should be obtained during the investigation and format for investigation of death following immunization has to be completed (Annexure 8).

- ♦ Detailed history from the parents/guardian
 - ☞ Pre immunization health status
 - ☞ Sequale of the AEFI following immunization (Since details of the immediate events leading to death bears great importance in the causality assessment preferably this information has to be obtained by a medical personnel with a sound paediatric knowledge)
 - ☞ Significant past medical problems of the child
- ♦ Details of all medical interventions has to be obtained and preferably copies of Bed Head Tickets (BHT) and reports of laboratory investigation should be preserved for subsequent causality assessment.
- ♦ Information on storage conditions, maintenance of cold chain and handling of vaccines, diluents and syringes.
- ♦ Information on similar events among other recipients of vaccine in the same

clinic setting and the neighborhood.

A post mortem examination is preferred following all deaths suspected to have been caused by vaccine/immunization. It should be performed by a consultant Judicial Medical Officer (JMO) or a medical officer qualified with a diploma in legal medicine. Guidelines on conducting paediatric autopsies on deaths following immunization (Annexure 12) is available at the Epidemiology Unit website <http://www.epid.gov.lk>

- ♦ During such postmortem examinations macroscopic examination, histopathological examination and relevant microbiological and toxicological examinations has to be conducted as is deemed necessary. Specimen collection and storage has to be done according to the guidelines provided (Annexure 12) for paediatric autopsies on deaths following immunization.
- ♦ Post mortem specimens have to be preserved at the JMO Office at least for a period of one year, in case further investigation is required.
- ♦ Detailed death investigation report has to be forwarded by the regional epidemiologist in the given format, to the Epidemiological Unit for evaluation.

Table 6: Guide to specimen samples obtained following selected AEFIs

Event	Specimen from the patient*	Vaccine, diluent, syringe and needle
Severe local reaction	Blood	Yes
Abscess	Swab, Blood	Yes
Lymphadenitis	Blood	Yes
CNS symptoms with no paralysis	Cerebrospinal fluid, blood	Yes
CNS symptoms with paralysis	Stools**	Yes

Anaphylaxis	Blood	Yes
Toxic shock syndrome	Blood, blood culture	Yes
Death	Postmortem tissue specimen (Refer to the guideline on paediatric autopsies on deaths following immunization)	Yes

* This is given as an example and specimens to be collected based on clinical relevance (Refer the guideline ; (Annexure 7a).

** If paralysis follows administration of OPV, specimens of stools are important. Samples of syringes and needles may be irrelevant since it is an oral vaccine. Stools are to be collected as according to the guidance given for AFP surveillance (refer ‘Eradication of Poliomyelitis – A comprehensive guide for Medical officers’, Epidemiology Unit, 2005 Available at www.epid.gov.lk)

4.2.5 Basis of AEFI Investigation

The basis of investigation is to identify whether the;

- i. Adverse event is not related to the vaccine and vaccination
- ii. Adverse event is related to the vaccination; operational aspect of the programme
- iii. Adverse Event is related to the vaccine

Results of the investigation should be entered in AEFI form 3 and forwarded to the Epidemiology Unit with a copy to the Regional Epidemiologist as soon as possible.

There are many background factors / reasons involved in deciding whether an adverse event is actually caused by the vaccine. Vaccinations are carried out at an age when many underlying diseases become evident among children. The fact that the vaccine-

was administered within a reasonable time period of occurrence of signs and symptoms of a disease does not automatically suggest that the vaccine is the cause or aggravating or contributing factor. Systematic assessment of the patient and the relevant factors will determine the cause and effect relationship of the event.

4.2.5.1. Adverse events not related to the vaccine or vaccination

Some of the events may just coincide with the vaccine/vaccination; for instance, the event might have occurred even if the person had not received the vaccine. Occurrence of the event on a coincidental basis could be demonstrated if the same event also occurred in the unimmunized group in the population.

4.2.5.2 Adverse events related to vaccination

- ◆ Inadequate dosage/over dosage
- ◆ Inadequate quantity of diluents
- ◆ Reconstitution of the vaccines using the wrong diluents
- ◆ Improper preparation of vaccines
- ◆ Incorrect method of vaccine administration
- ◆ Substitution of vaccines or diluents with medicinal drugs or other substances
- ◆ Contamination of the vaccine or diluents
- ◆ Improper storage of vaccines following preparation
- ◆ Use of vaccine and diluents after their date of expiry
- ◆ Use of vaccine in contraindicated instances or use of wrong vaccine
- ◆ Use of reconstituted vaccine at a subsequent session without discarding at the end of an immunization session
- ◆ Misidentification of the vaccine recipient

It may also be related to Needles and Syringes

Unsafe use of needles and disposable syringes:

- ◆ Improper handling of needles and syringes
- ◆ Improper storage of the syringes and needles
- ◆ Syringes and needles used after their date of expiry

The factors which need to be considered

- ◆ Whether several cases occurred in the same clinic
- ◆ Whether the unimmunized population of the same age group presented with the same symptoms/events
- ◆ Whether other recipients vaccinated with the same batch of vaccine presented with the same symptoms/events

In any of the incidents mentioned, corrective measures should be initiated immediately in areas of logistics, training and supervision

4.2.5.3 Adverse events related to the vaccine

These are due to the inherent properties of the vaccine antigen or excipients (Adjuvant, preservatives, stabilizer, antibiotics or any other component). Minor events usually settle with treatment and have no long term consequences. Although serious events are very rare, it is important to investigate each case where the quality of vaccine is suspected to be the cause.

The factors to be considered during investigation of such cases;

- ◆ Frequency of occurrence (common/rare/not previously reported)-whether the events occur within the expected frequency range
- ◆ Known reaction to the vaccine
- ◆ Similar events reported among un-immunized population

- ◆ Event caused by the plausible mechanism due to biological properties of the vaccine
- ◆ Significant temporal relationship of the event and the immunization
- ◆ Past history of similar events; related or independent of vaccination
- ◆ History of drug therapy; concomitant/previous
- ◆ Concomitant or preceding medical condition which could explain the event e.g immunocompromised status of the recipient
- ◆ Any other factors that could explain the event; e.g. programme errors Laboratory results which help in the investigation.

If the event is serious, unexpected vaccine reaction or occurred with unexpected frequency;

- ◆ Contact Regional Epidemiologist / Epidemiology Unit immediately
- ◆ May temporarily suspend or withdraw the use of product at MOH level if recommended by Epidemiology Unit: the batch or lot of the suspected vaccine/ diluent/ syringe.
- ◆ Vaccine suspension or withdrawal at district or national level would be done only on recommendation of national AEFI expert committee
- ◆ Re-evaluate the quality of the vaccine with the Medical Technology & Supplies MTS (National Regulatory Authority)/MRI (National Control Laboratory) and communicate with the manufacturer, if necessary.
- ◆ Report findings of the investigation to the health staff and community

If causality cannot be determined, the reasons for such need to be indicated to the relevant concerned categories. e.g; MOH staff, Clinicians etc.,

4.2.6 Investigation of AEFI cluster

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administration. Exact nature of the relationship between the adverse events (e.g. duration of time, proximity of place); will differ by nature of events and the circumstances in which they occur. Investigation of a cluster follows the same principles as indicated above with following steps:

- ◆ Establishment of a case definition, if there is no case definition laid down previously
- ◆ Identification of all immunized and unimmunized population who meet the case definition
- ◆ Obtaining immunization history (when, where and which vaccines were given)

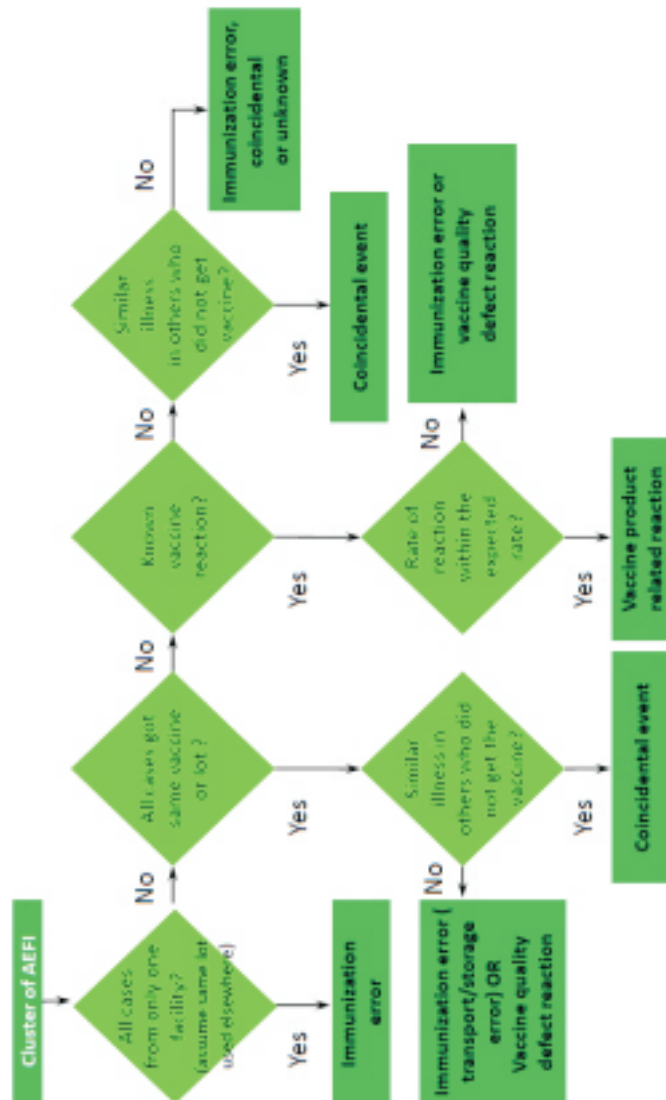
Identification of any other common exposures of the cases. If all cases received vaccines from the same health worker/ immunization clinic and there are no other cases – **Immunization related error is likely**

If all cases received the same vaccine or lot from the different clinics and there are no similar cases in the general community, a problem with the vaccine is likely – **vaccine defect**

If the event is a known vaccine reaction but occurring at an increased rate – **an immunization related error or a vaccine defect are likely causes.**

If cases include people in the same area in the same age group who were not immunized – **event was probably coincidental.**

Figure 2: Identifying cause of AEFI cluster



Source: WHO Aide Memore

5. ANALYSIS OF AEFI DATA

Analysis of data on AEFIs consists of following components :

- ◆ Completeness of AEFI forms to be received
- ◆ Identifying health institutions where AEFIs are not reported. Determine whether it is due to failure of reporting or whether there are no AEFIs to be reported. Check on “zero reporting”.
- ◆ Assessing AEFI reports received during stipulated time period
- ◆ Assessing number of events and calculating rate for 100,000 doses of antigen (vaccine) used.
- ◆ Categorizing the type of AEFI (by the new classification adopted in 2012)
- ◆ Analyzing immunization related error by number and rates by area and number of doses of relevant vaccines used
- ◆ Reviewing case investigation reports of each patient. Reviewing other data about the event and the community, where it took place may provide important clues to, making a final diagnosis and identifying a probable cause. It may not be possible to make a diagnosis, the cause might not be evident or there might be more than one cause.

5.1 Who should analyse the data?

Data analysis could be carried out at different levels in the AEFI surveillance system. MOH could carry out data analysis for the MOH area. District data is compiled and analyzed by Regional Epidemiologist while data analysis for the country is carried out by the Epidemiology Unit.

In analyzing data MOH plays an important part as it is the first and the best operational level where surveillance data can be used. All reports should be analyzed to identify the type of AEFI, particularly the programme errors. This is largely to carry out corrective action in a timely manner. Before the analysis, MOH needs to verify data and reassure its accuracy.

Regional Epidemiologist also needs to perform the same analysis for the district. Analysis by MOH area will help to identify issues and may focus on corrective action.

5.2 How should analyse the data ?

The first step in analysis is to diagnose the case, which is done by the MOH at MOH level. Patient's signs and symptoms, the history of the event, patient's past medical history, data on suspected immunization and laboratory results all may contribute to the diagnosis. Standard case definitions should be used. (Annexure 1)

Secondly, all reported AEFI data need to be line listed and followed by tabulating by place (PHM/PHI divisions), person and time. Thirdly analysis by antigens and by type of reported adverse events (high fever, abscess) should be done. Number of doses administered for each antigen is the denominator for calculating reported AEFI rates for each antigen in a given time period (by month, quarter or year). Fourthly, analysis shall expand to the AEFI rates by first or second or third dose, when the antigen is administered more than once. For this, the number of doses administered of the given antigen as first, second or third dose need to be used as the denominator.

Available expected rates for each type of AEFI for a given antigen will provide a guide to make decisions on corrective action to be taken on reported AEFIs (Tables 3-4).

It is also important to know about background rates of reported medical events in the country. Comparison of such background rates with reported rates of AEFI may provide a possibility of developing hypothesis of a coincidence. e.g Febrile seizures of varying aetiologies are common among young children and also may be possible following some vaccines (DTwP). Therefore it is important to know the rate of febrile seizures due to other reasons and expected rates following a given antigen. This comparison will essentially lead to describe the causality.

Tables 7 and 8 shows how to calculate AEFI rates by different antigens, by different doses for given adverse events by country and a selected MOH area.

5.3 How should a cause be determined?

Until the investigation is complete a 'working hypotheses could be formulated. Later it will be possible to analyze the data and assign a 'cause' and then to further classify into one of the categories of AEFI. For a few medical events, the diagnosis itself will show the cause whether it is programme related, vaccine induced, coincidental or injection reaction. In others, external evidence may be required to identify the cause.

Recommendations will be made on the findings and conclusions. These recommendations should include the action that should be taken to remedy the problem identified. Action should be taken by the programme managers at each operational level.

Table 7: Calculating adverse event rates by selected antigen in Sri Lanka –2010

Antigen	Number of doses administered	Fever (>39°C)	Fever rates /1000 doses Administered	Allergic reactions	Allergic reactions rates /1000 doses administered
DPT	459,892	734	734/459,892 X1000 =1.6	373	373/459,892 X1000 =0.8
Penta	891,472	740	740/891,472 X1000 =0.8	240	240/891,472 X1000 =0.26
Measles	344,235	54	54/344,235 X1000 =0.15	287	287/344,235 X1000 =0.8

Table 8: Calculating adverse events rates by selected antigen in a defined area

Antigen	Number of doses administered	Fever (>39°C)	Fever rates /1000 doses Administered	Abscess	Abscess rates /1000 doses administered
Penta 1	1681	1	1/1681x1000 =0.59	1	1/1681x1000 = 0.59
Penta 2	1703	4	4/1703x1000 = 2.35	0	0/1703x1000 = 0
Penta 3	1637	2	2/1637x1000 = 1.22	0	0/1637x1000 = 0
Penta	5021	7	7/5021x1000 =1.39	1	1/5021x1000 = 0.19

6. CAUSALITY ASSESSMENT OF AEFI

Causality assessment is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine/s received. It is a critical part of AEFI monitoring and enhances confidence in the national immunization programme among health sector and public. Steps that need to be taken to address the event would be decided on the fact that it is attributable to the vaccine or the vaccination programme.

All reported AEFIs require verification of the diagnosis; coding, review, collation and storage of data; if an AEFI is serious it requires a systematic, standardized causality assessment.

Causality assessment is important for:

- ◆ Identification of urgent problems for investigation/action
- ◆ Identification of immunization related errors and batch problems
- ◆ Testing of hypothesis and research
- ◆ A basis for estimation of rates of serious AEFIs
- ◆ Comparison of AEFIs between vaccine brands
- ◆ Pre and post marketing surveillance

The quality of the causality assessment process depends on several factors:

1. Effectiveness of the reporting system
2. Quality of the causality review process

6.1 Levels of causality assessment

Causality assessment of AEFIs may be performed at different levels:

- (I) At the level of the individual AEFI case report, in order to estimate the probability that the occurrence of a reported AEFI in a specific individual is causally related to the usage of the vaccine. It is usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report.

(II) At the population level, using a surveillance data and appropriate statistical methodology in order to test the hypothesis that there is a causal association between the usage of a vaccine and a particular AEFI. This may sometimes be combined with causality assessment at the individual level (of AEFIs collected within that system) whereby some or all of the cases of interest could undergo individual case review and causality assessment before inclusion in a group analysis.

(III) In the context of the investigation of signals, the assessment of whether a particular vaccine is likely to cause a particular AEFI, takes into account all evidence from individual AEFI cases, surveillance data and, where applicable, cluster investigations as well as non-clinical data.

In settings where causality assessment is undertaken it is important to consider all possible explanations for an event and the degree of likelihood for each before addressing the question of whether or not a vaccine product, quality defect, the immunization process or immunization anxiety caused a given event or if it was due to something else such as an inter-current infection. This is true whether the assessment is done for one or multiple cases of an expected or unexpected AEFI.

Evidence for a causal link exists for some vaccines and AEFIs (e.g. measles vaccine and thrombocytopenia). This does not ensure, however, that causality can be assessed on an individual basis. Most often this is because of missing or imprecise data in the AEFI report(s) resulting in a case being deemed unclassifiable. In other cases the final designation of an AEFI as to causality may be unknown due to lack of evidence for a causal link. It is still important to gather reports on such events because at some point they may be considered a signal and lead to hypotheses regarding a link between a vaccine and the event in question with specific studies designed to test for a causal association.

6.2 Criteria for establishing causality

Five **criteria** by Bradford-Hill will provide logical way to assess the association and test the hypotheses during the causality assessment.

Criteria (Evidence) for establishing Causality:

- ◆ Strength of the association
- ◆ Consistency of the association
- ◆ Specificity of the association
- ◆ Temporal sequence
- ◆ Biologic plausibility (coherence with existing information)

Causality assessment aims to classify the likelihood of a causal association between a vaccine and an adverse event.

6.3 Causality assessment method

In 2012, WHO developed a method, allows the National Committees for AEFI case review and causality assessment to screen serious cases reported by their surveillance system for completeness and quality of information, ensuring the objectiveness of the assessment.

There are four steps in causality assessment; (Annex I: Causality assessment method)

Step 1: Eligibility

To proceed with causality assessment, it is necessary to have a diagnosis for the reported AEFI. The diagnosis should meet a standard case definition. The case definitions can be adopted from standard medical literature, national guidelines or adopted locally. If possible, it is best to adopt the Brighton Collaboration case definition. This can be accessed online at <https://brightoncollaboration.org/public>.

Step 2: Checklist

The checklist contains elements to guide the Committee or the assessor to collate the evidence needed for case review. It is designed to assemble information on patient-immunization-AEFI relationship in the following key areas:

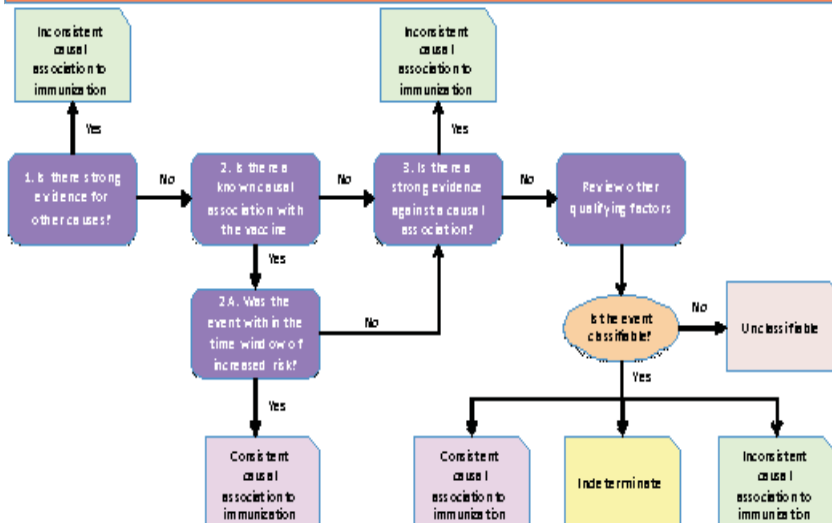
Once the checklist is systematically completed, the answers in the checklist are applied to the algorithm.

	Yes	No	Unkn own
1. Is there strong evidence for other causes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Is there a known causal association with the vaccine / vaccination? a. Relationship with vaccine ingredients b. Immunization Error c. Injection Reaction	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
3. Was the event within the time window of increased risk?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Is there strong evidence against a causal association?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Other qualifying factors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Step 3: Algorithm

The algorithm is based on key questions given in the checklist. Stepwise approach in algorithm helps determine if the AEFI could be *consistent* or *inconsistent* with an association to immunization, *indeterminate* or *unclassifiable*.

Step 3: Algorithm



Step 4: Classification

The final classification is based on the availability of adequate information

I. Case with adequate information for causality conclusion can be classified as follows

A. Consistent Causal association to immunization

- A1: Vaccine product related reaction or
- A2: Vaccine quality defect related reaction or
- A3: Immunization error related reaction or
- A4: Immunization anxiety related reaction

B. Indeterminate

- B1. *Temporal relationship is inconsistent but diagnosis is consistent with published literature

C. Inconsistent causal association to immunization

- C1. Diagnosis inconsistent and temporal relationship inconsistent or
- C2. *Diagnosis is inconsistent with published literature but temporal relationship is consistent

**B1 and C2: These are potential signals and maybe considered for investigation*

II. Case without adequate information for causality conclusion is “Unclassifiable” and requires additional information for further review of the causality

7. FOLLOW-UP ACTION

AEFI detection, investigation, analysis and causality assessment must lead to action if the credibility of immunization services is to remain high. These follow-up actions include diagnosis, treatment, reporting, communication and corrective actions.

7.1 Treatment

Treatment must be the first response to an AEFI. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. PHNS, PHM and PHI should also know how to identify serious AEFIs and when to refer to the relevant authorities. It is very much important that all field health staff be aware with the General Circular on managing anaphylaxis on field setting (Annexure 2) and be prepared accordingly.

7.2 Corrective actions

When the investigation is completed and cause of AEFI is identified, it could be included into the relevant category and remedial action taken. Table 9 illustrates some corrective action to be taken after investigating AEFI.

Table 9: Corrective actions to be taken after investigating AEFI

Vaccine quality defects	<p>If a higher reaction rate than expected is being reported from a specific vaccine or batch then obtain information from the manufacturer and consider</p> <ul style="list-style-type: none"> ◆ Withdrawal/temporary suspension of the suspected batch of vaccine. ◆ Arrange for return of implicated vaccine, if appropriate ◆ Change manufacturing specifications or quality control ◆ Replace the vaccine with a new stock of quality reassured vaccine
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Immunization related errors (Programme Errors)	<p>Correcting the cause of the error</p> <ul style="list-style-type: none"> ◆ Proper maintenance of cold chain ◆ Intensify monitoring and supervision of health staff ◆ Training of field health staff ◆ Change procedure at the immunization clinics: <p>Whatever action is taken, it is important to review at a later date to check that the immunization errors have been corrected.</p>
Coincidental	<ul style="list-style-type: none"> ◆ Main task is to exclude other causes for AEFI ◆ Communication with parents/community/field staff is crucial to impress that the cause and effect relationship is just coincidental ◆ Patient should be referred to a clinician if the medical condition warrants treatment and medical care.
Injection Reaction	<ul style="list-style-type: none"> ◆ This is due to the anxiety and fear of injection, which is usually common during school immunization programmes ◆ Effective communication with children to relieve their anxiety is important
Unknown /Undetermined	<ul style="list-style-type: none"> ◆ Depending on the nature of the event, its extent and whether it is ongoing, further technical assistance from an expert may be needed to assist the investigation or causal assessment ◆ If necessary a special study needs to be conducted (to study possible signals)

7.3 Training & awareness

AEFI is an opportunity for training and awareness for staff. Irrespective of type or outcome of AEFI, it can use to update knowledge and develop skills and confidence among the staff. Awareness can expand to involving all stakeholders link to the immunization programme such as: academia, teachers, volunteers, policy makers, politicians and media.

7.4 Management of crisis situations

A crisis is a situation in which a real or potential loss of confidence in the vaccines or in the vaccination service occurs, precipitated by information about an adverse event. Usually, crisis can be avoided through foresight, care and training. Proper management of the crisis will strengthen the immunization programme and improve public confidence. Proper prior planning for a crisis situation with a draft document will enhance crisis management.

Steps on prevention of crises

- ♦ Anticipate. Do not wait until a crisis occurs. Prepare for the unavoidable.
- ♦ Train vaccination personnel at all levels to respond adequately
- ♦ Confirm all the facts before making any public statements
- ♦ Prepare a plan to react to a crisis when it occurs

7.5 Sharing AEFI information with stakeholders

Vaccine safety information needs to be shared with other stakeholders in order to ensure dissemination of correct information and thereby to ensure smooth functioning of national immunization programme in the country. This may be done at two stages: sharing preliminary information at initial stage and final data/report after completion of investigation/causality assessment at a later stage.

- Ministry of Health (Higher officials:Secretary,Director General of Health Services, Deputy Director Generals)
- Medical Technology & Supplies (National Regulatory Authority)
- Medical Research Institute/(National Control Laboratory)
- Professionals /Academia
- International agencies: WHO, UNICEF
- Manufacturers
- Other stakeholders

Sharing information may be on routine or event basis. At present, Sri Lanka is actively reporting all investigated cases routinely to WHO Post-marketing Surveillance (PMS) network, Upasala center.

Further, all AEFI data are available online on Unit website www.epid.gov.lk and published in Weekly Epidemiological Report (WER) and Quarterly Epidemiological Bulletin (QEB) of the Epidemiology Unit.

7.6 Communication

Communication with parents, other members of the community and health staff need to be carried out under all circumstances. They should be kept informed about the investigation, results and action being taken or to be taken regarding the AEFI. It is crucial to highlight the benefits of immunization while communicating with the public/medical staff/stake holders.

Key points to consider when communicating with parents/relations of the recipient, community and health staff:

- ♦ Listen to parents and their concerns empathetically
- ♦ Reassure and support the parent or recipient but do not make false promises

- ◆ Assist the parents/guardian for hospitalization if necessary
- ◆ Maintain frequent communication with the parents/guardian regarding the progress of the patient.
- ◆ Prepare a fact sheet on adverse event for parents, community, health staff and media
- ◆ Inform parents about possible common adverse events and how to handle them
- ◆ Communicate continuously with parent, community and media during the investigation period to ensure their understanding of the risk-benefit balance of vaccination
- ◆ Avoid blaming health workers and focus on corrective action and quality of the EPI system
- ◆ Communicate among health authorities involved
- ◆ Field health staff also needs to be reassured and informed of the results of the investigation.
- ◆ Build up and maintain confidence among health staff

Be prepared to answer all questions relating to AEFI.

Usual questions are;

- ◆ WHO is affected and what is responsible?
- ◆ WHAT has happened and what is being done about it?
- ◆ WHERE has it happened?
- ◆ WHEN did it happen?
- ◆ WHY did it happen?
- ◆ WILL it happen again?

Communication /Sharing AEFI information with Media

Media plays an important role in disseminating information and in developing public awareness. Use of media for the benefit of an immunization programme is necessary. Therefore, AEFI data may be shared with the media, when it is deemed necessary. However, sharing AEFI information with media is the responsibility of Ministry of Health and Chief Epidemiologist may act on behalf of the Ministry. According to the departmental regulations, sharing any information with media should be done only with prior approval from the Ministry. This does not apply to health awareness/public educational programmes carried out with media, because maintaining professional relationship with media is important.

Communication with the community: In communicating with the community, it is useful to develop links with community leaders (local government members, religious leaders), district staff (RDHS staff) and divisional staff (MOH staff) so that information can be disseminated as is necessary. MOH should support and provide appropriate information to his/her field staff to respond directly to community concerns. When there is a high level concern about a vaccine, known benefits of immunization in preventing serious vaccine preventable diseases compared to the uncertainty over vaccine adverse reactions (communication in risk-benefit of vaccines) can be emphasized through communication with the community.

8. EVALUATING 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 be include:

- ◆ Timeliness, Completeness and accuracy of AEFI reporting
 - ◆ By monitoring information from reports and site visits
 - ◆ Comparing reports with the Clinic and MOH AEFI registers and BHTs
 - ◆ Talking to health workers and observing their work
 - ◆ (Refer: WHO/EPI manual *Training for Mid-Level Managers: Disease Surveillance WHO/IVB/08.08*)
- ◆ Timeliness, completeness of investigations
 - ◆ Check reports to ensure that those meeting the investigation criteria were investigated
 - ◆ That investigation was begun within the defined time criteria
 - ◆ Confirm the adequacy of the investigation and soundness of the conclusion reached and correction 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 immunization related 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. AEFI surveillance should be evaluated regularly and should lead to remedial actions. Main indicators used for evaluation of effectiveness of the programme are:

- ◆ Percentage of completeness, nil returns and timeliness of routine AEFI returns
- ◆ Timeliness of serious AEFIs/death investigations carried out
- ◆ Percentage of investigations conducted out of all reported investigative AEFIs within the stipulated time
- ◆ Rate of AEFI reported from 100,000 doses used from respective antigens
- ◆ Rate of AEFIs due to programme errors
- ◆ Rate of formation of injection site abscesses by each antigen
- ◆ Rate of development of BCG lymph-adenopathy following BCG vaccination
- ◆ Timeliness of analysis /Timely feed back
- ◆ Immunization coverage / Incidence and prevalence of events

Websites on immunization safety

Brighton Collaboration	www.brightoncollaboration.org
Centre for Disease Control (CDC), USA	www.cdc.gov/nip/vacsafe www.cdc.gov/vaccinesafety/Activities/VSD.html http://www.cdc.gov/vaccines/recs/acip/default.htm
Council for International Organizations of Medical Sciences (CIOMS)	http://www.cioms.ch/
Dept of Health, UK	http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/
Epidemiology Unit MoH, Sri Lanka	www.epid.gov.lk
Public Health Agency of Canada	http://www.phac-aspc.gc.ca/im/index-eng.php
Public Health, Depart of Health, South Australia	www.health.sa.gov.au/pehs
World Health Organization	www.who.int/gpv-safety www.who.int/immunization/sage/en http://www.who.int/vaccine_safety/en/

References

National Immunization Guideline, Sri Lanka, 2012

ANNEX 1

List of Working definitions to be used in AEFI surveillance

Local adverse events

a. Injection Site Abscess

Occurrence of a fluctuant or draining fluid filled lesion at the site of injection with or without fever.

- ♦ **Bacterial:** Existence of purulence, inflammatory signs, fever, positive Gram stain, positive culture, or finding of neutrophil predominance of content will support a bacterial site abscess, but the absence of some of these signs will not rule it out.
- ♦ **Sterile:** there is no evidence of bacterial infection following investigation.

b. Lymphadenitis (includes supportive lymphadenitis)

Occurrence of either:

- ♦ At least lymph node, 1.5cm in size (one adult finger width) or larger, 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)

c. 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 or
- ♦ Requires hospitalization

Local reactions of lesser intensity may occur commonly and are generally of little consequence. For monitoring purpose, priority should be given to severe local reactions as defined above.

Central nervous system adverse events

Vaccine-Derived Paralytic Poliomyelitis:

Acute onset of flaccid paralysis within 4-30 days of receipt of oral polio virus vaccine (OPV), or within 4-75 days after contact with a vaccine recipient, with neurological deficits remaining 60 days after onset or death.

Guillain barre Syndrome (GBS)

Acute onset of rapidly progressive, ascending, symmetrical flaccid paralysis, without fever at onset of paralysis and with sensory loss. Cases are diagnosed by cerebrospinal fluid (CSF) investigation showing dissociation between cellular count and protein content. GBS occurring with 30 days after immunization should be reported.

Encephalopathy:

Encephalopathy is an acute onset of major illness temporally linked with immunization and characterized by any two of the following three conditions.

- ♦ Seizures;
- ♦ Severe alteration in level of consciousness lasting for one day or more; and
- ♦ Distinct change in behavior lasting one day or more.

Cases occurring within 72 hours after vaccination should be reported.

Encephalitis:

Encephalitis is characterized by the above mentioned symptoms and signs of cerebral inflammation and, in many cases, CSF pleocytosis and /or virus isolation. Any encephalitis occurring within 1-4 weeks following immunization should be reported.

Meningitis:

Acute onset of major illness with fever, neck stiffness/positive meningeal signs (Kerning, Brudzinski). Symptoms may be subtle to similar to those of encephalitis. CSF examination is the most important diagnostic measure. CSF pleocytosis and/ or detection of microorganism (Gram stain or isolation)

Seizures:

Seizures lasting from several minutes to more than 15 minutes and not accompanied by focal neurological signs or symptoms.

- ♦ Febrile seizures or Afebrile seizures

Other adverse events requiring investigation**Anaphylactic shock**

Circulatory failure (e.g. alteration of the level of consciousness, low arterial blood pressure, weakness or absence of peripheral pulses, cold extremities secondary to reduced peripheral circulation, flushed face and increased perspiration) with or without bronchospasm and / or laryngospasm/laryngeal oedema leading to respiratory distress occurring immediately after immunization.

Persistent screaming

Inconsolable continuous crying lasting at least 3 hours accompanied by high-pitched screaming

Hypotensive-hyporesponsive episode (shock collapse)

Sudden onset of pallor or cyanosis, decreased level or loss of responsiveness, decreased level of muscle tone (occurring within 48 hours of vaccination). The episode is transient and self limiting

Osteitis / osteomyelitis

Inflammation of the bone either due to BCG immunization (occurring within 8 to 16 months after immunization) or caused by other bacterial infection.

Toxic- shock syndrome

Abrupt onset of fever, vomiting and watery diarrhea within a few hours of immunization, often leading to death within 24-48 hours.

Adverse events not requiring investigation**Allergic reaction**

Characterized by one or more of the following (1) skin manifestations (e.g. hives, eczema); (2) wheezing; (3) facial or generalized oedema

Arthralgia

Joint pain usually including the small peripheral joints.

- ♦ Persistent: Joint pain lasting longer than 10 days
- ♦ Transient: Joint pain lasting up to approximately 10 days.

High fever (>39 C/ 102F)

The Endogenous elevation of at least one measured body temperature >39 C/102 F

Nodule at the injection site

Presence of a discrete or well demarcated firm soft tissue mass or lump at the injection site that is sometimes referred to as a subcutaneous nodule, antigen cyst or granuloma, in the absence of abscess formation, erythema and warmth.

ANNEX 2

General Circular No: 01-20/2001
Provincial/ Regional Directors of Health Services,
Medical Officers of Health,
All Heads of Medical Institutions

Guidelines for Initial Management of Anaphylaxis at Field Settings

Anaphylaxis is one of the most acute life-threatening hypersensitivity reactions that could occur following administration of a vaccine or any pharmacological agent. This could occur very rarely following vaccination, as an allergic reaction to the vaccine or its components. On average when a million is immunized one may develop anaphylaxis. Usually an anaphylactic reaction occurs within minutes of vaccination but in rare instances it could occur even after 12 hours of immunization.

Some people are more prone to develop anaphylaxis. e.g. persons who had developed an allergic reactions to a drug, vaccine or a food previously or those with a history of asthma or eczema. However some people without any such known risk factors could also develop anaphylaxis for the first time.

A person who develops anaphylaxis should be treated immediately to prevent lifethreatening reactions and death. Hence it is very important to recognize the condition immediately in field clinic settings by the vaccinator, age appropriate first dose of adrenalin 1:1000 to be given immediately and the patient to be taken to the closest hospital for further management as soon as possible. To implement the contents of this guideline you are kindly requested to adhere to the following.

- a) Ensure competency of the field health staff including Medical Officers, Nursing Officers, Public Health Inspectors and Public Health Midwives to recognize anaphylaxis early and administer the first dose of adrenaline, by thorough training of all field health staff as per national guidelines.
- b) Estimate, procure and make available required quantities of Adrenaline 1: 1000 vials and 1 CC disposable syringes with 23 Gauge one inch needles.
- c) Authorize field health staff in charge of field clinics to hire a vehicle in an emergency to transport the patient to the nearest hospital. The vehicle hire could be reimbursed to the field health staff subsequently.

Signs and symptoms of Anaphylaxis

Signs and symptoms of anaphylaxis are not distinctive to this condition alone. Signs and symptoms of anaphylaxis could be grouped according to the system of the body that is affected.

Skin and mucous membranes.

In over 80 % to 90 % of anaphylaxis reactions, skin and mucous membranes are affected. When only skin and mucous membranes are affected without involvement of other systems it could not be called anaphylaxis. However anaphylaxis could occur without the skin being affected.

- Tingling sensation around the lips
- Oedema of lips
- Itching of skin
 - o specially in small children
 - scratching of forehead
 - scratching of hands
 - scratching of eyes & ears
- Generalized skin erythema
- Urticaria and oedematous patches
- Swelling in the throat (angio oedema)
- Hoarseness of voice

Respiratory system

If a person prone to asthma develops an acute attack of asthma or difficulty in breathing after immunization it should be assumed that this could be a sign of an anaphylaxis reaction instead of assuming it as another attack of asthma and should manage accordingly.

- Cough
- Wheezing
- Difficulty in breathing
- Hoarseness
- Rapid breathing
- Stridor

Circulatory system

- Weak peripheral pulse
- Lowered blood pressure
- Increased heart/pulse rate
- Cold and clammy hands and feet

Nervous system

- Feeling of Anxiety and distress
- Loss of consciousness

Digestive system

- Stomachache (specially in small children)
- Vomiting
- Abdominal cramps
- Diarrhoea

Diagnosis of anaphylaxis

Following administration of a vaccine to a healthy recipient, if criteria mentioned below are met it could be suspected that the person is suffering from anaphylaxis.

1. with rapid onset of occurrence of signs and symptoms
2. when two or more of the above systems are affected

Treatment of anaphylaxis

The vaccine recipient with suspected anaphylaxis should never be left alone. Obtain help from those who are around and should ask to arrange transport the patient to the nearest hospital immediately. Vaccine recipient should be stretched out with the airway clear. If the vaccine recipient is conscious he/she should be kept supine with the feet raised higher than the head. If the patient is unconscious he/she should be kept in the left lateral position.

Adrenaline is the most important and effective drug in the treatment of anaphylaxis. Complications and death could be prevented by giving this drug as soon as possible (with the exception of infants).

Adrenaline 1:1000 solution should be given intra muscular (IM). **It should NEVER be given subcutaneous (SC) or intravenous (IV).**

It should be given on the middle 1/3 of the anterolateral aspect of the thigh. In immunization field clinic settings **ONLY ONE DOSE** of adrenaline should be given. Dosage of adrenaline 1:1000 Anaphylaxis among infants (less than 1 year of age) is very rare and infants should not be given adrenaline in field clinic settings.

Age	Dose of Adrenaline (1:1000)
12 months to 06 years	0.15 mg (0.1ml)
06 years to 12 years	0.2 mg (0.2ml)
12 years and over	0.3 mg (0.3ml)

Dose of adrenaline should not be changed even if the child is obese. A one inch 23 Gauge needle could be used to inject adrenaline to make sure it is delivered into the muscle. Before injecting the piston of the syringe should be drawn back to make sure that there is **NO** blood drawn into the syringe and hence the needle is not in a vein. 4 Immediately after administration of adrenaline patient should be taken to the closest hospital.

Management of a case of anaphylaxis

Keep the patient in the supine position and ensure the airway is clear and keep the feet elevated higher than the head. If vaccine recipient is unconscious, keep in the left lateral position Give a single, age appropriate dose of adrenaline intra muscular (IM) Take the patient to the closest hospital immediately

Differentiation between anaphylaxis and a fainting attack.

Adults and adolescents could faint due to their fear of the anticipated pain or fear of the injection itself. In the case of infants and preschool children fainting is rare. Hence if an infant or preschool child becomes unconscious after immunization anaphylaxis should be suspected first

	Fainting Attack	Anaphylaxis
Onset of signs and symptoms	Before immunization Or While immunizing Or Minutes after immunizing	Generally within minutes after immunization Could also occur a few hours after
skin and mucous membranes	Generalized pallor Cold and clammy hands	<ul style="list-style-type: none"> Generalized skin erythema Itching of the skin (in children specially forehead, hands, eyes and ears) Tingling sensation around the lips Urticaria Swelling of lips (Angio-oedema)
Respiratory system	Rate of respiration normal Shallow breathing	<ul style="list-style-type: none"> Rapid respiratory rate Difficulty in breathing Cough Wheezing Stridor Hoarseness of voice Constrictive feeling of the chest In drawing of the chest

Circulatory system	<ul style="list-style-type: none"> Reduced heart rate Weak pulse Transient absence of peripheral pulse Carotid pulse is strong and easily felt Blood pressure could drop but when keeping the patient in supine position blood pressure soon returns to normal 	<ul style="list-style-type: none"> Increased heart rate Weak pulse Pulse not felt sometimes Carotid pulse weak Hypotension. When keeping the patient in supine position blood pressure does not return to normal
Nervous system	<ul style="list-style-type: none"> Fiendishness or feeling faintish Light headedness Loss of consciousness. When keeping the patient in a supine position he soon becomes conscious 	<ul style="list-style-type: none"> Patient is anxious and distressed Becomes unconscious and keeping the patient in supine position makes no difference
Digestive system	<ul style="list-style-type: none"> Vomiting 	<ul style="list-style-type: none"> Vomiting Diarrhoea Stomachache (specially in small children) Abdominal cramps

Please be kind enough to bring the contents of this circular to the notice of all concerned in your institution.



Dr. Ajith Mendis
 Director General of Health Services
 cc : 01. DDG/PHS I
 02. DDG/PHS II
 03. Director MCH
 04. Chief Epidemiologist
 05. Director/ HEB
 06. Director/ NIHS
 07. Regional Epidemiologists
 08. Medical Officers (MCH),
 09. Medical Officers of Health

ANNEX 5

AEFI Form 2

Monthly surveillance report on Adverse Effects Following Immunization (AEFI)

RDHS Division : MOH area : Month : Year 201...

Adverse Events	BCG	OPV	Penta/DPT (Mark 'P' for Penta or 'T' for DTP in the row below against the dose)			HeHp B	Measles	MMR	MR	DT	aTd	JE		Influenza
			1	2	3							4	1	
1. Local Adverse Events requiring investigation														
a. Injection site abscess														
b. BCG lymphadenitis														
c. Severe local reactions														
2. Central Nervous System Adverse Events requiring investigation														
a. Vaccine associated paralysis poliomyelitis														
b. Guillen-Barre syndrome														
c. Encephalopathy														
d. Encephalitis														
e. Seizures														
Febrile														
Afebrile														
3. Other Adverse Events requiring investigation														
a. Death														
b. Anaphylactic shock														
c. Persistent screaming														
d. HHE														
e. Osteitis/Osteomyelitis														
f. Toxic shock syndrome														
4. Adverse Events not requiring investigation														
a. Allergic reaction														
b. Arthralgia														
c. High fever (>39 C° / 102°F)														
5. Others (specify)														
a.														
b.														
c.														

Instructions:

- Before reporting an AEFI, please refer to the definition for the relevant AEFI given in overleaf and make sure that reporting event agrees with the criteria stipulated in the definition.
- Please correctly identify and enumerate the adverse events by correct antigen.
- If a child/person has developed more than one adverse event, indicate only the most serious/important event here. (in this report under each adverse event reported will represent single individual)
- AEFI Form 3 (Case Investigation Form) should send to the Epidemiology Unit for each AEFI reported under categories 1-3 in this report. It is recommended to send all investigated forms with this monthly surveillance report.
- If any important observation is noted, please provide your comment (eg. Adverse events under category 4 here, if any clustering is observed)

Comments :

Name : Designation :

Signature : Date :

(This form should be completed by MOH/DDHS and sent to the Epidemiologist before the 10th of the following month with a copy to the Regional Epidemiologist of the area)

ANNEX 6

REGIONAL EPIDEMIOLOGIST'S MONTHLY CONSOLIDATE AEFI RETURN

Regional Epidemiologist Monthly Consolidate Return of AEFI

RDHS Division:		Month:																		
Serial No.	MOH Area	Adverse Events Requiring Investigation										Adverse Events Not Requiring Investigation								
		Local Adverse Events		CNS Adverse Events					Other Adverse Events Requiring Investigation			Others								
		Injection site abscess	BCG lymphadenitis	Severe local reaction	V.D. paralytic poliomyelitis	Guillen - Barre syndrome	Encephalopathy	Encephalitis	Meningitis	Febrile	Afebrile	Anaphylactic	Persistent screaming	Hypotonic Hyporesponsive Episode	Osteitis/Osteomyelitis	Toxic shock syndrome	Allergic reaction	Arthralgia	High fever (>39 c/102 F)	Nodule at the injection site
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
Total																				

(This form should be completed and sent to the epidemiology Unit on or before the 20th of the following month)

Date:

Regional Epidemiologist Signature.

ANNEX 7

AEFI Form 3

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) CASE INVESTIGATION FORM EPIDEMIOLOGY UNIT, MINISTRY OF HEALTH

The MOH should do the investigation personally. Necessary data should be obtained from the parents / patient / hospital by reference to the BHT / physician or from the diagnosis card. Early investigation and return is essential.

A. PARTICULARS OF PATIENT (Please (✓) appropriate box where applicable)

- Name of patient (IN BLOCK LETTERS):
- Residential Address:
- Date of Birth: □□ / □□ / □□

4. Age □□ / □□ y y / m m	5. Sex <input type="checkbox"/> 1. Male <input type="checkbox"/> 2. Female <input type="checkbox"/> 3. Unknown	6. Ethnic group <input type="checkbox"/> 1. Sinhalese <input type="checkbox"/> 2. Tamil <input type="checkbox"/> 3. Moor <input type="checkbox"/> 4. Others <input type="checkbox"/> 5. Unknown	7. RDHS Division □□	8. MOH area □□
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B. PRESENT ILLNESS / OUTCOME

09. What is the AEFI reported? 10. Date of onset: □□□□□□ d d m m y y 11. Where was the patient treated? <input type="checkbox"/> 1. Govt. hospital <input type="checkbox"/> 2. Pvt. hosp/practitioner <input type="checkbox"/> 3. Other (specify)	12. Was patient admitted to hospital? 1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/> 3. Unknown <input type="checkbox"/> 13. If yes, date of admission: □□□□□□ d d m m y y 14. Name of hospital:	17. Outcome of the case 1. Cured <input type="checkbox"/> 2. Died <input type="checkbox"/> 3. Unknown <input type="checkbox"/> 18. Date of discharge, transfer or death □□□□□□ d d m m y y 19. If transferred name of hospital
---	---	--

C. CLINICAL DATA

(Case definition: An adverse event following immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine)

20. Symptoms and signs <input type="checkbox"/> 1. Fever <input type="checkbox"/> 2. Inconsolable cry <input type="checkbox"/> 3. Painful swelling at the injection site <input type="checkbox"/> 4. Enlarged tender axillary lymph nodes <input type="checkbox"/> 5. Convulsions <input type="checkbox"/> 6. Altered sensorium Any other symptoms and signs	21. Date of onset □□□□□□□□ □□□□□□□□ □□□□□□□□ d d m m y y y y	22. Laboratory investigations	23. Treatment
---	--	--	--

D. PAST MEDICAL AND FAMILY HISTORY

	Yes	No	Unknown	If yes (specify) No. and place
24. Existing congenital disorders	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Persisting underlying disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Previous history of significant illnesses	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Family history of similar event	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Previous history of similar event	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

E. OTHER RELEVANT HISTORY

	Yes	No	Specify
(i) Delays in taking the patient to the hospital	<input type="checkbox"/>	<input type="checkbox"/>
(ii) Delays in transferring patient to another hospital for specialized treatment	<input type="checkbox"/>	<input type="checkbox"/>
(iii) Delays in receiving treatment	<input type="checkbox"/>	<input type="checkbox"/>

F. IMMUNIZATION HISTORY

29. Date and time of immunization □□/□□□□□□ (dd/mm/yy) Time: □□□□

30. Place of immunization MOH clinic Government Hospital
School Private Clinic Any other.....

31. Designation of the vaccinator MOH PHNS PHM
RMO PHI MO Others

32. Type of vaccine (Please ✓ appropriate box)	33. Dose	34. Expiry Date Please indicate the Vaccine No. on the dotted line from the Question 32	34. Batch No.	35. Manufacture	36. Diluents Batch No & Expiry date
<input type="checkbox"/> BCG <input type="checkbox"/> OPV <input type="checkbox"/> Penta <input type="checkbox"/> MMR <input type="checkbox"/> MR <input type="checkbox"/> DPT <input type="checkbox"/> DT <input type="checkbox"/> aTd <input type="checkbox"/> TT <input type="checkbox"/> Hep B <input type="checkbox"/> JE <input type="checkbox"/> Influenza <input type="checkbox"/> Others (specify)	<input type="checkbox"/> 1 st <input type="checkbox"/> 2 nd <input type="checkbox"/> 3 rd <input type="checkbox"/> 4 th <input type="checkbox"/> 5 th	Vaccine Vaccine Vaccine Vaccine Vaccine d d / m m / y y

G. INFORMATION ON COLD CHAIN / STORAGE / VACCINATION TECHNIQUE

37. Vaccine and diluents stored in the <input type="checkbox"/> 1. MOH office <input type="checkbox"/> 2. Clinic <input type="checkbox"/> 3. Others <input type="checkbox"/> Specify	38. Vaccines transported in a <input type="checkbox"/> 1. Vaccine flask or vaccine carrier <input type="checkbox"/> 2. Cold box <input type="checkbox"/> 3. Others (Specify)	39. Status of the data lodger for 1 month period prior to the date of immunization. Maximum temperature Minimum temperature	40. Failure to maintain cold chain as indicated in the 40.1 VVM; Stage..... <input type="checkbox"/> 40.2 Thermometer at the Main Compartment of refrigerator <input type="checkbox"/>
--	---	---	--

At the time of observation of the immunization	Satisfactory	Unsatisfactory	Not observed
41. Maintenance of Cold Chain			
1. Packing of vaccine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Maintenance of cold chain in unopened vials during immunization	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
42. Vaccination procedure			
1. Reconstitution	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Drawing of vaccine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Injection technique	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
43. Please ✓ the appropriate box Reusable <input type="checkbox"/> Disposable <input type="checkbox"/> AD syringes <input type="checkbox"/>			

H. AEFI IN THE CLINIC CENTRE / FIELD

Any history of similar events reported among those vaccinated

44. At the same clinic session	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
45. Using same vaccine at previous clinic sessions at the same clinic centre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
46. Using same vaccine at the other clinic centers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
47. History of similar events reported among those unimmunized (in the Field/Community)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I. CONCLUSION AS TO THE CAUSE OF AEFI

Immunization errors related reaction Event caused by an error in vaccine preparation handling or administration	Vaccine product related reaction Event caused by the inherent properties of the vaccine	Vaccine quality defect related reaction Event caused due to quality defects of the vaccine product	Immunization anxiety related reaction Event from anxiety about or pain from the injection itself rather than the vaccine	Coincidental events Event that happens after immunization but not caused by the vaccine – a chance association	Unknown
If possible, describe the cause in below given area					
.....					

Corrective action taken:.....

Remarks:.....

Signature: Name: Date: Designation:

Please return to: Epidemiology Unit, 231, De Seram Place, Colombo 10. email: epidunit@stnet.lk Tel: 011-2695112/2681548 Fax: 011-2696583

ANNEX 7a

Guidelines on case investigation

1. Notes on how to carry out an investigation

These notes should be used to fill the Case Investigation Report. Information marked is important to collect but is not included on the case investigation report form.

1.1 Demographic Details

Record:

- ◆ date of birth (DD MM YY)
- ◆ sex
- ◆ family name
- ◆ first name
- ◆ address
- ◆ date of notification, date of immunization, and interval to onset of symptoms.

1.2 Investigation and collection of data

Record about the patient:

a) Type of reaction

- ◆ local reactions
- ◆ central nervous system
- ◆ other adverse events
- ◆ other severe or unusual events occurring within 4 weeks after immunization

b) Medical *

- ◆ immunization history
- ◆ history and clinical description of Severe AEFI
- ◆ prior history of similar reaction or other allergies
- ◆ treatment, whether hospitalized, and outcome.

Record about the suspected vaccine

- ◆ Name and number of doses of all vaccines given on that day e.g. Penta-2
- ◆ Lot or batch number, manufacturer's name and expiry date.
- ◆ For vaccines which are reconstituted, the same information is required about diluents.
- ◆ Length of time the lot has been used
- ◆ List of vaccination centers receiving this lot
- ◆ Reports of other centers supplied with the lot and reporting of AEFI
- ◆ The 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, from where it was received from higher up the cold chain, vaccine monitor card.

Record about local immunization services

- ◆ Vaccine storage and distribution
- ◆ Diluents distribution and storage
- ◆ Reconstitution (maximum period allowed after reconstitution)
- ◆ Storage of opened vials
- ◆ Disposal of used vials
- ◆ Use of AD syringes and waste disposal
- ◆ Name of vaccinator(s)
- ◆ Details of training in immunization practice
- ◆ Whether there is supervision

Observe the service in action

- ◆ What else is stored in the refrigerator
- ◆ What vaccine are stored with other drugs
- ◆ Whether any vials have lost their label
- ◆ Whether similar containers are stored next to vaccine vials which could be confused with them
- ◆ How reconstitution of vaccine is carried out
- ◆ How and where the diluents are stored.
- ◆ How the injections are administered
- ◆ How needles and syringes are re-sterilized or disposed of
- ◆ What happens to opened vials
- ◆ Whether any open vials were contaminated.

Ask about other people in the area

- ◆ Whether others received the same vaccine
 - ◆ Whether others fell ill
 - ◆ Name of health worker(s) who gave immunization which resulted in AEFI
- Formulate a working hypothesis (so far) as to what was the probable cause of the AEFI for example:
- ◆ Programme related
 - Vaccine transportation or storage error
 - Reconstitution error
 - Unsterile practice
 - Incorrect administration technique
 - ◆ Vaccine induced
 - Vaccine manufacturer error
 - Vaccine associated (but not manufacturer error)
 - ◆ Coincidental
 - ◆ Other
 - ◆ Unknown

1.3 Collection and dispatch of specimens

Once a working hypothesis is arrived at, it should be apparent whether specimens are required to confirm or rule out the suspected cause. Only appropriate specimens shou-

-Id be taken, and a clear explanation should be sent to the laboratory on why they were collected and what information is required.

Record the following

- ◆ what specimens have been collected
- ◆ date of collection
- ◆ date of dispatch
- ◆ destination laboratory

1.4 Result and conclusions

- ◆ Laboratory results
- ◆ Clinical findings
- ◆ Findings of in-site investigation
- ◆ Summary of finding

2 Notes on specimen taking

Only specimens which are absolutely necessary for the investigation should be collected and dispatched. Their selection depends on the working hypothesis related to the events:

From the patient

- ◆ blood, urine, CSF, swab from wound /abscess site as appropriate
- ◆ autopsy specimens (If death occurred) as above, plus tissue samples for histology.

The **vaccine** in use at the vaccination center:

- ◆ Collect the actual opened vials of vaccine and diluents used to inject the child (or children) who suffered AEFI. If the clinic systems is working properly, investigators should not be able to locate them. Nonetheless, a through search must be made to try to locate them.
- ◆ Collect some unopened vials, two from the health center and five from central stores, of the same vaccine and diluents from the same refrigerator where the implicated vaccines were stored.

The vaccine may be tested for toxicity, sterility and adjuvant (e.g. aluminum content) and the diluents for sterility and chemical composition. The testing of vaccine should be requested on a clear suspension and not as a routine.

The syringes and needles

As with the vaccine, the needles and syringes may not be readily located and a thorough search must be made to try to locate them. Unless the AEFI occurred immediately after immunization, a properly functioning clinic will certainly have disposed of, or sterilized the used syringes and needles.

- ◆ If located all needles should be capped with extreme caution (beware of needle stick injury)

- ◆ If disposable or auto destruct syringes are used, collect a sample of unopened needles and stringers. They will usually be tested for bacterial contamination.

Notes on dispatch of specimens

- ◆ All specimens (whether of human origin, vaccines, diluents or equipment) should be **labeled** and **sealed** in containers or plastic bags.
- ◆ Specimens containing liquid should be kept **upright**.
- ◆ They should be transported in **ice** to the central laboratory for analysis.
- ◆ Be sure the transport time is less than the **cold life** of the ice.
- ◆ Attach in a separate envelope a copy of the **Case Investigation** Form to help the laboratory perform the correct tests as well as the model laboratory request form Appendix H.
- ◆ **Send a copy** directly to the laboratory, ahead of the specimens. Once at the central laboratory, a decision will be made whether to send specimens to international laboratories for toxicology etc.

ANNEX 8

Format for Investigation of Deaths Following Immunization

Part A	Background information
Part B	Investigation of the sequelae leading to death/Past History of the child
Part C	Investigation of the Hospital Management of the death
Part D	Investigation of the vaccine management and cold chain monitoring of the MOOH
Part E	Autopsy findings
Part F	Causal assessment of the death

Part A Background Information

1. Name of the child:-----

2. Date of Death: -----

3. Details of source of information

	Date	Informant/source
First notification to MOOH		
First notification to RE		
First notification to Epid Unit		

4. Information regarding the death investigators/investigation

Name & Designation Contact No.	Name & Designation Contact No.	Date(s) of investigation

Part B Investigation of the sequelae leading to death/Past History of the child

1. Identification and Related Basic Information

Name, address and contact no. of parent or guardian			
Date of Birth			
Age on the date of immunization			
Sex:			
Ethnic Group			
Gestational Age			
Birth Weight			
Weight at the time of immunization			
RDHS Division			
MOH Area			
Incriminated Vaccines			
Date of immunization	Time		
Time interval between immunization and death			

2. Clinical description/sequelae of the event as described by the mother

2.1 Assessment of the child prior to immunization

2.1.1 Feeding:-----

2.1.2 Activity:-----

2.1.3 Features suggestive of any acute illness (please specify)

2.2 Any Medication within 24 hours prior to immunization: Y/N If yes, please specify.

Drug	Dose/frequency	Last dose given at (time)_

3 Assessment of the child during immunization

3.1 Details of the immunization procedure

- i. Incriminated vaccine/s:-----
- ii. Place and time of immunization:-----
- iii. Medication simultaneous with immunization: Y/N
If yes please specify

2.3.2 Post immunization observation (Any adverse events noted)

2.3.3 . Assessment of the child during post immunization period

i. Feeding:-----

ii. Activity:-----

iii. Urine output:-----

2.3.4 Description of significant adverse events noted by the mother following

immunization

- i.-----
- ii.-----

2.3.5 Measures taken by the mother/guardian to overcome the above adverse event:

i. Traditional medication: Y/N(if yes please specify)

ii. Treatment at GP/ Govt. Hospital OPD/ Other : Y/N
if yes, please specify

- When was medical advise seek:-----
- medical advise provided/tentative diagnosis:-----
- medication prescribed/dose/frequency/how many doses given/when was last dosage

iii. Any other measures? (Please specify)-----

2.3.6. Out come of the above measures on observed adverse event (please specify)

2.4 Was the child hospitalized? YES /NO

If yes please specify details according to mother/guardian

2.5 Description of the final event according to the mother/guardian

	Date	Time	Person
When the child was last seen alive?			
When was child first seen unresponsive?			
When was child pronounced dead?			

2.5.1 Details of death confirmation:

2.5.2 If child had been asleep during death, please inquire following details

- i. Sleeping place:-----
- ii. Sleeping position-general:-----
- iii. Position child found dead/position during last sleep:-----

- iv. Other people who slept in the same place with the child:-----

3. Antenatal, and birth History

3.1. Antenatal Complications:-----

3.2. Natal period

Place of delivery: -----

Period of gestation:-----

Mode of delivery:-----

(if mode is other than normal vaginal delivery please mention the indication)

Birth weight:-----

Apgar at birth:-----

Any significant finding detected by neonatal examination

Any PBU admissions: Y/N

If yes, please specify details (Indication for admission, duration, management and Follow up visits, outcome of the child) & annex a copy of diagnosis/follow up notes

.....

4. Dietary History

4.1. Duration of exclusive breast feeding:.....

4.2 Details of introduction to weaning foods:.....

4.3 Current diet (brief description):.....

4.4 Any identified food allergies:.....

5. Development History

Highest milestone developed at the time of death:

Gross motor	
Fine motor	
Hearing, Vision	
Social development	

6. Past medical problems of the child

6.1 Hospitalizations

Disease/disorder/Diagnosis	Duration of illness	Institution/Medical Personnel involved

(Please annex copies of diagnosis cards)

6.2. Underlying congenital /acquired diseases or disorders for which child was currently on treatment/follow up

Disease/disorder	Duration of illness	Institution/medical Personnel involved	Management

6.3. Past history of evidence of abuse/ harm/ neglect/ accidental injury/ previous need for child protection.

Injury	Period	Institution/medical Personnel involved	Management

7. Previous immunizations

Vaccine	Date of administration	Batch No.	Adverse events

8. Family History / Social History

8.1. Details of parents

	Mother	Father
Name		
Age		
Educational Level		
Occupation		
Income		
Smoking/alcohol use		

8.2. Details of other siblings

			Number	Age
Number of siblings	Elder	M		
		F		
	Younger	M		
		F		

8.2.1. Any neonatal deaths in the family :(YES/ NO)

If yes please mention details and cause of death

.....

8.2.2. Any infant deaths in the family: (YES/NO)

If yes please mention details and cause of death

.....

8.2.3. Deaths or any other medical problems/hospitalizations among other children:

.....

e. Similar deaths among close genetic relatives: (YES/NO)

.....

Part C Details of the management of the case at medical institution

1. Identification and Related Basic Information

Name of the Institution	
Date & time of admission	
Name & Designation of the admitting officer	
Name & Designation of the medical officer in charge of the subsequent follow-up	

2. Clinical description and examination findings as per medical records/by admitting officer and immediate management

.....

3. Details of examination findings and subsequent management as per medical records

.....

3.1. Examination findings

General Examination	
Cardiovascular system	
Respiratory system	
Abdomen	
Central Nervous system	
Pulse Oximeter reading	

3.2. Investigations:

	Investigation	Interpretation
Radiological		
Haematological		
Bio chemical		

3.3 Management

3.3.1 Pharmacological

.....

3.3.2. Non-Pharmacological

.....

3.3.3. Tentative diagnosis/identified problems

.....

Part E Autopsy findings

1. Description of the autopsy

- 1.1 Autopsy performed: Y/N
- 1.2 Autopsy protocol used: Y/N
- 1.3 Offices involved in autopsy:

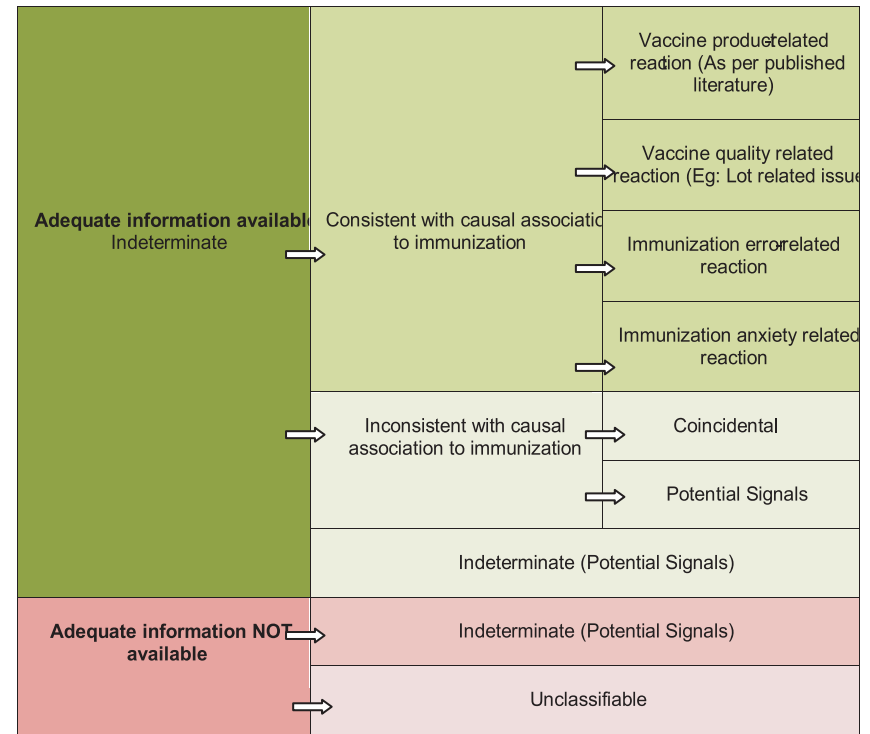
	Name/s	Designation	Institution
Medical officer conducted the autopsy			
Medical officer who conducted the histopathology Examination			
Other officers involved in death investigation(specify)			

1.4. Detailed description of autopsy findings

	Detailed description of autopsy findings
Gross pathology	
Histology	
Toxicology	
Microbiology	
Radiology	
Metabolic screening	
Biochemistry	
Other	

Part F Causality assessment by Expert Committee

Date of causality assessment by expert committee: -----



Conclusion:

ANNEX 9

Anaphylaxis Event Record (To be completed by a Medical Officer)

Patient details						
Name:		MOH Area:		RDHS Area:		
Age	Date of birth	Sex	Ethnicity	Hospital:	BHT number:	
Past allergic history: Has patient had previous allergic reactions? <input type="checkbox"/> Yes <input type="checkbox"/> No If 'Yes', Allergen (Drug/Vaccine/Food/Other) - <i>specify?</i>						
Part I: Clinical features						
Date & time of clinical examination: Date(dd/mm/yy)				Time : am/pm		
Skin &	<input type="checkbox"/> Urticaria <input type="checkbox"/> Erythema <input type="checkbox"/> Pruritus <input type="checkbox"/> Prickle sensation			Specify the site of reaction:		
	Eye	<input type="checkbox"/> Red bilateral <input type="checkbox"/> Red unilateral <input type="checkbox"/> Itchy				
Mucosa	Angioedema					
	<input type="checkbox"/> Tongue <input type="checkbox"/> Throat <input type="checkbox"/> Uvula <input type="checkbox"/> Larynx <input type="checkbox"/> Lip <input type="checkbox"/> Face <input type="checkbox"/> Limbs <input type="checkbox"/> Other					
Respiratory system	<input type="checkbox"/> Sneezing <input type="checkbox"/> Rhinorrhoea <input type="checkbox"/> Sore throat		<input type="checkbox"/> Hoarse voice <input type="checkbox"/> Stridor	<input type="checkbox"/> Sensation of throat closure <input type="checkbox"/> Cough	<input type="checkbox"/> Tachypnoea <input type="checkbox"/> Difficulty in swallowing <input type="checkbox"/> Rhonchi	<input type="checkbox"/> Wheezing <input type="checkbox"/> Indrawing / retractions <input type="checkbox"/> Chest tightness
					<input type="checkbox"/> Grunting <input type="checkbox"/> Cyanosis <input type="checkbox"/> Difficulty in breathing	
					<input type="checkbox"/> Capillary refill time >3secs <input type="checkbox"/> Heart rate (m)	<input type="checkbox"/> Tachycardia
Circulatory system	BP (mmHg)	<input type="checkbox"/> Measured hypotension	<input type="checkbox"/> Decreased central venous pulse			
CNS	<input type="checkbox"/> Loss of consciousness <input type="checkbox"/> Distress <input type="checkbox"/> Other(<i>specify</i>):					
GIT	<input type="checkbox"/> Diarrhoea <input type="checkbox"/> Nausea <input type="checkbox"/> Abdominal pain/cramp <input type="checkbox"/> Vomiting					
Diagnostic Criteria	<input type="checkbox"/> Rapid onset of occurrence of above sign & symptoms <input type="checkbox"/> Two or more systems are affected					
Part 2: Suspected Product and exposure Information						
Date & Time of drug/vaccine administration: Date(dd/mm/yy)				Time : am/pm		
Drug	<input type="checkbox"/> Oral <input type="checkbox"/> Parenteral	<input type="checkbox"/> Vaccine	<input type="checkbox"/> Serum	<input type="checkbox"/> Other (<i>specify</i>).		
Generic name :			Trade name :			
Batch number :	Expiry date :	For vaccine: VVM status <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV <input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> 3 rd dose <input type="checkbox"/> 4 th dose				
If diluent used, specify batch number & expiry date:						
If parenteral medicine/vaccine: <input type="checkbox"/> Single dose <input type="checkbox"/> Multi dose <input type="checkbox"/> Liquid <input type="checkbox"/> Lyophilised						
Route of administration: <input type="checkbox"/> Oral <input type="checkbox"/> IV <input type="checkbox"/> IM <input type="checkbox"/> SC <input type="checkbox"/> ID <input type="checkbox"/> Other(<i>specify</i>)						
Site of Administration: <input type="checkbox"/> Deltoid <input type="checkbox"/> Thigh <input type="checkbox"/> Buttock <input type="checkbox"/> Other (<i>specify</i>)						
Person who administered: <input type="checkbox"/> Doctor <input type="checkbox"/> Nurse <input type="checkbox"/> PHI <input type="checkbox"/> PHM <input type="checkbox"/> Other(<i>specify</i>)						
Place of administration/reaction: <input type="checkbox"/> Hospital <input type="checkbox"/> MOH <input type="checkbox"/> Clinic <input type="checkbox"/> Private Hospital <input type="checkbox"/> GP <input type="checkbox"/> Other(<i>specify</i>)						

If 'Yes', Route : IM SC IV Other (<i>specify</i>)		Dose:.....ml
Place: Clinic MOH Hospital Other (<i>specify</i>)		Time (of 1 st dose):.....am/pm
Person who administered adrenaline: Doctor Sister/Nurse PHI/PHM Other		
Was a repeat dose of adrenaline given?	If 'Yes', describe (<i>including the time</i>)	
Yes No		
What other medicines were administered?	If 'Yes', describe (<i>including the time</i>)	
Yes No		
Any other details concerning medicines/management (<i>including CPR</i>)?		
Investigation	Blood taken for mast cell Tryptase: Yes No If 'Yes' specify the time interval after event: <i>(Note: Serum Tryptase levels peak 60-90 min after the onset of anaphylaxis and persist to 6 h. Therefore It is recommended that blood should be taken between 1 and 2 h after the initiation of symptoms.)</i>	
Part 4: Outcome		
Onset of first symptom: Date (dd/mm/yy)		Time: am/pm
Outcome: Full recovery Not fully recovered Recovered with sequelae Death		
Specify details:		
Time at outcome (recovery/death) Date (dd/mm/yy)		Time: am/pm Unknown
Highest impact of Adverse drug event/Adverse Event Following Immunization:		
Did not interfere with daily activities	Interfered, but did not prevent daily activities	Prevented daily activities
Part 4: Any other comment		
Details of Reporting Source		
Name:	Designation:	Institute:
Signature	Date:	Telephone:

Definition: Anaphylaxis is defined as a severe, life-threatening, generalized or systemic hypersensitivity reaction, characterised by rapidly developing life-threatening airway and/or breathing and/or circulation and or gastrointestinal problems usually (not always) associated with skin and mucosal changes.

ANNEX 11

MOH OFFICE AEFI REGISTER

Date of Birth (DD/MM/YY)		
Address (10)		
Name of Child (9)		
Source of Notification(8) (CAR/MI/GP/OS)		
Place of Immunization (7)		
Date of Immunization(6) (DD/M/YY)		
Batch No/Lot No(5)		
Related Vaccine(4)	Dose	
	Antigen	
Adverse Event(3) [PI Specify]		
Date of Entry(2) (dd/mm/yy)		
Serial No (1)		

ANNEX10

CLINIC AEFI REGISTER

Remarks (10)			
Address (9)			
Name of Child (8)			
Date of Immunization(dd/m)(7)			
Batch No/Lot No (6)			
Related Vaccine(5)	Dose		
	Antigen		
Adverse Event(4)			
Date of Report/Detection(3)			
Registration Number of the CHDR (2)			
Serial No (1)			

ANNEX 12

CHILD HEALTH DEVELOPMENT RECORD

புதிதானவர்களின் தடுப்பூசி மருந்து அட்டவணை Immunization

பிந்த காலம் வரையில் குழந்தைகளை தடுப்பூசி செய்தல் மூலம் அவர்களுக்கு நிகழக்கூடிய நலவாத நிகழ்வுகளைத் தடுப்பதற்கும், சுகாதார தடுப்பூசி மருந்துகளுக்கும் குறிப்பிட்ட காலத்தில் கொடுக்கப்பட வேண்டும்.

வயது Age	பிந்தானவருக்கு Type of vaccine	திகதி Date		பிந்தானவருக்கு தடுப்பூசி Batch No.	பிந்தானவருக்கு தடுப்பூசி பின்னல் Adverse effects following immunization	பிந்தானவருக்கு பிந்தானவருக்கு B. C. G scar	
		வ. ம. ஆ.	பி. சி. ஆ.			பிந்தானவருக்கு B. C. G scar	பிந்தானவருக்கு B. C. G scar
பிறந்த At Birth	பிந்தானவருக்கு B. C. G					பிந்தானவருக்கு Present	
	பிந்தானவருக்கு 6 மாதங்களுக்குள்ளே பிந்தானவருக்கு 2வது தடுப்பூசி B.C.G 2nd dose (if no scar even at 6 months)					பிந்தானவருக்கு Present	
2 Months Completed	பிந்தானவருக்கு 1வது தடுப்பூசி DPT 1 or பிந்தானவருக்கு 1வது தடுப்பூசி OPV 1 பிந்தானவருக்கு 1வது தடுப்பூசி Hepatitis B1						
4 Months Completed	பிந்தானவருக்கு 2வது தடுப்பூசி DPT 2 or பிந்தானவருக்கு 2வது தடுப்பூசி OPV 2 பிந்தானவருக்கு 2வது தடுப்பூசி Hepatitis B2						
6 Months Completed	பிந்தானவருக்கு 3வது தடுப்பூசி DPT 3 or பிந்தானவருக்கு 3வது தடுப்பூசி OPV 3 பிந்தானவருக்கு 3வது தடுப்பூசி Hepatitis B3						
9 Months Completed	பிந்தானவருக்கு Measles						
12 Months Completed	பிந்தானவருக்கு Live JE						
18 Months Completed	பிந்தானவருக்கு 4 DPT 4 பிந்தானவருக்கு 4 OPV 4						
3 Years Completed	பிந்தானவருக்கு Measles & Rubella						
5 Years Completed	பிந்தானவருக்கு D.T பிந்தானவருக்கு 5 OPV 5						
13 Years Completed	பிந்தானவருக்கு Rubella						
14 Years Completed	பிந்தானவருக்கு atd						
Other							

ANNEX 13

Guidelines for paediatric autopsies on deaths following immunization

General
16 May 2012

Circular

No: 01-25/2012

Guidelines for paediatric autopsies on deaths following Immunization

Surveillance of Adverse Events Following Immunization (AEFI) is an important part of the National Immunization Programme (NIP) to ensure vaccine safety. It is of utmost importance to identify and establish causes of all serious AEFI including deaths to carry out timely follow-up and corrective action to safeguard the vaccine recipients and also to maintain public trust on the NIP.

On a recommendation by the national expert committee on vaccine safety and AEFI, it is advised to carry out a comprehensive autopsy for the establishment of cause of death whenever the cause of death is suspected with a vaccination. Investigation of suspected infant deaths following immunization is an issue of great national importance with regard to the Immunization programme, as the proper causality assessment would enable to differentiate vaccine related deaths from deaths due to other causes. The assistance that could be provided by a comprehensive autopsy in the establishment of the cause of death is immense, and adherence to a standard protocol would enable obtaining that assistance to the optimum. The College of Forensic Pathologists in Sri Lanka has drafted a detailed protocol on paediatric autopsy and this guideline will function as an interim guideline based on the detailed protocol and until it is available for implementation.

Considering the importance of autopsy in the investigation of infant/child deaths following immunization, head of the institution needs to make arrangements for a death inquest and conducting an autopsy. In an event of infant/child death following immunization at home, conducting an autopsy. In an event of infant/child death following immunization at home, conducting an autopsy is important and the respective authority shall be aware of this guideline and followed the same. Where possible, autopsies of all deaths following immunization should be carried out by a specialist in forensic medicine. Where a specialist is not available the autopsy should be performed by a medical officer qualified with Diploma in Legal Medicine,

who is also trained in performing such post mortems. Where both are not available the hospital authorities should make arrangements with the closest specialist in forensic medicine regarding conducting the post-mortem. It is the responsibility of the hospital authority to make transport arrangements.

This guideline provides measures to be followed and adhered to in a standard autopsy protocol which would enable conduct of a comprehensive causality assessment of a reported death following immunization.

In an event of all such deaths a detailed autopsy should be performed including the following;

- ♦ review of detailed preclinical and clinical history including laboratory and radiological findings,
- ♦ if necessary visit to the death scene for additional evidence,
- ♦ radiological, histopathological, toxicological and microbiological investigations.

Microbiologist and Histopathologist of the local institution will be the focal point for microbiology and histopathology examinations respectively. Where a specialist Microbiologist and/or Histopathologist is not available at the local level, or when virological / immunological investigations need to be carried out focal point for such examinations will be the MRI (Tel: 112693532-4).

Also, in situations where the cause of death is inconclusive or not straightforward, obtaining a second opinion on histopathological examinations from another pathologist is recommended. Department of Government Analyst (Tel: 2694786, 2694787, 2695881, 2699753) will be the focal point for toxicological examinations. It is advisable to contact the respective institutions on detailed information on collection, storage and transport of specimens.

Where possible samples of the organs should be preserved for further evaluation at the institution where the postmortem is conducted.

The epidemiology Unit should be informed (Tel: 112695112, Fax: 112696583) by the head of the institution and the Regional Epidemiologist of the district to be contacted to coordinate assistance. In situations where local facilities are insufficient to perform such examinations, assistance from the Epidemiology Unit could be obtained to seek external assistance.

The Medical Officer of Health (MOH) or MOH staff who carried out the vaccination shall provide all necessary information to carry out the autopsy, but their presence during the autopsy is not mandatory.

Basic Information

Information about the identity of the deceased and the details of authorization should be obtained and included in the report.

Preliminaries

Antemortem samples should be taken over and investigated in cases such as alleged intoxications, allergy related incidents etc. Therefore, as soon as information is received the clinical staff should be advised to preserve the antemortem samples such as blood in a plain bottle, urine, CSF, vomitus, faeces, sputum, swabs etc that have already been obtained and hand them over to the forensic specialist at the earliest. In an anaphylactic reaction, ante-mortem samples collected between 30 min to preferably 3 hours after reaction (up to 6 hours) and 24 hour baseline samples (if available) are to sent for immunological investigations. If there is a delay in transport centrifuge the sample and refrigerate at 4^o C.

Ward staff should be advised to document all therapeutic interventions. The area MOH, where child is vaccinated need to be informed by the head of the institution to preserve and handover empty vials, diluents, syringes, needles, with control samples of same batch. Regional Epidemiologist should coordinate this activity.

- ♦ Ensure maintenance of the chain of custody throughout the investigation (collected by, custody of, dispatched to).
Record date and time of collection and type of preservative for each and every ante-mortem sample collected
- ♦ Document reports of clinical investigations and medical records related to the incident such as microbiology, biochemistry, immunology, histopathology, haematology, radiology etc.

Pre autopsy information

Obtain a detailed history which includes past medical history, drug history, immunization history, history of allergies and findings of medical records etc.

Pre autopsy preparation

Preserve autopsy blood – untreated and spun – in case required for later analysis. Make arrangements to take photographs at the autopsy. Be prepared to take X-rays if and when necessary while dissection (specially in cases of suspected air embolism). Be prepared to preserve the heart after careful dissection if the cause of death cannot be ascertained at the end of the autopsy.

External examination

In addition to routine external examination, record features of allergic

reaction, anthropometric parameters when relevant (Weight, Height/Crown-heel length, Crown-rump length, Foot length, Occipito-frontal circumference, Chest circumference at nipple level, Abdominal circumference at umbilicus),

Congenital abnormalities, nutritional and developmental state, features of neglect, therapeutic interventions, and paraphernalia, features of complications of therapy such as presence of subcutaneous emphysema etc. It is important to examine vaccination/ injection site regarding local reaction.

Internal examination

In addition to routine internal examination, record features of allergy and anaphylaxis such as laryngeal oedema, petechial haemorrhages, froth / secretions in upper airway, mucus plugging of the bronchi, effusions in body cavities, tissue oedema and the degree of local reaction at the vaccination/ injection site etc.

Look for complications of therapy such as pneumothorax, degree of haemorrhage in relation to puncture sites. Look for congenital abnormalities

Whenever possible record the weights of internal organs including thymus (children).

Post-mortem samples

Samples for microbiology, immunology, histopathology and virology, should be collected according to the instructions from the relevant laboratories. (Details of instruction on sending samples to MRI is available on laboratory manual issued by the SLCM or could be obtained from the respective departments at the MRI by telephone 112693532-4). All samples should be clearly labelled and dated. The request form should have the patient's information, a short history including clinical presentation, duration of illness and date of death. Indicate the necessary tests (if known) to be performed. In case special investigations are needed, contact the laboratory for instructions prior to sending samples. If possible mention the tentative /provisional diagnosis. MRI will accept the samples for special investigations 24 hours / day, 7 days of the week.

7.1 Histopathology

Samples for histopathology *obtained from all major organs are as follows:* any macroscopically visible lesions should be described in detail and sample extensively. Sample should be taken in 10% formal saline or in dry ice for frozen section. *Specify the required special stains when necessary.*

- ♦ *Central nervous system: Brain (If the brain is to be examined after fixation suspend in 20% formal saline for two weeks).* Sections from Middle frontal gyrus, hippocampus, basal ganglia (putamen+globus pallidus)+ insular cortex, mamillary bodies, thalamus, left cerebellum, dentate nucleus, mid brain, pons, and medulla should be obtained.

- ♦ *Cardio-vascular system:* Myocardium (LV, RV, RA, LA, septum, other areas where relevant), cardiac valves, coronary arteries, conduction system and others
- ♦ *Respiratory system :* Epiglottis, Tonsils, Larynx, Trachea, Bronchi and Lungs- (at least one sample from each lobe including hilum and periphery) Hilar lymph nodes
- ♦ *Digestive system:* liver, pancreas,
- ♦ *Genitourinary system:* Kidneys including cortex and medulla
- ♦ *Mononuclear Phagocyte system:* Spleen, thymus, bone marrow
- ♦ *Endocrine system:* Adrenal gland, pituitary, thyroid gland
- ♦ Other: eg. Injection sites, including control, injuries and others

7.2 Microbiology

7.2.1 Bacteriological Investigation

Type of specimens and tests: Blood for culture, CSF and body fluids for culture, pus for culture, tissues for culture and blood for serology

Collection and transport:

- ♦ Blood and Body- fluids for Culture after death should be collected as early as possible and preferably before the body is sent to the morgue.
- ♦ If the body is already at post-mortem, following guidelines should be followed: Blood, CSF and Body- fluids should be collected before the dissection is started. Follow standard precautions for collection of samples. Clean the over-lying skin with 70% alcohol. Draw the sample using a sterile disposable needle and syringe. For Blood-culture 3-5ml blood (heart or venous) should be added into a blood-culture bottle with 30-40 ml BHI and mix carefully.
- ♦ CSF and other Body- fluids also should be sent in sterile screw capped containers. (Send these samples as soon as possible at room-temperature).
- ♦ Tissue samples should be sent in sterile N Saline in screw capped containers.
- ♦ Pus samples / swabs in sterile screw capped containers.
- ♦ Blood for serology and bacterial testing: Plain blood in sterile containers.

7.2.2 Immunology

A post mortem sample for serum tryptase should be taken from femoral vessels, and not heart blood. Serum should be separated and stored at 4°C, or frozen if the assay is delayed.

The circumstances regarding the death are important, as tryptase levels are also increased after myocardial infarction, trauma, amniotic fluid embolism and sudden infant death. Serum tryptase rises in anaphylaxis, if shock is present, or after insect stings, or in circumstances where the allergen enters the body parenterally.

Anaphylaxis following ingestion of an allergenic food does not usually lead to an increase in tryptase levels.

Information on allergy to foods (particularly beef, pork, milk, gelatine, previous vaccination) should be obtained. A blood sample should be sent to the Medical Research Institute for testing for allergen specific IgE.

7.2.3 Mycological (fungal) investigations

- ◆ **Blood:** 5-10 ml of venous blood should be collected under strict aseptic precautions. The lid should be wiped with 70% alcohol before inserting the needle to inoculate the blood into a culture bottle containing Brain Heart Infusion (BHI) broth. Mix well and keep at room temperature till dispatched. Smaller volumes of blood from neonates should be collected into paediatric BHI bottles (1-5 ml). (send as soon as possible to the laboratory)
- ◆ **Bone marrow:** 2-3 ml of bone marrow aspirate should be placed in a sterile screw capped container with 0.5 ml of 1:1000 heparin. (Send within 24 hours to the laboratory)
- ◆ **CSF:** 3-5 ml of CSF should be collected into a sterile screw capped bottle.
- ◆ **Body fluids:** Chest, abdominal fluid and any drain fluid should be collected aseptically in to a sterile screw capped bottle
- ◆ **Respiratory tract:** Tissues should be collected into a sterile screw capped bottle containing normal saline. Another sample should be sent in formal saline for histology.
- ◆ **Blood for serology:** 1-2 ml of blood should be collected into a plain bottle.

7.2.4. Virology Investigation

General Considerations: Most antigen / antibody detection assays in virology are compatible with serum / plasma. If the blood is haemolysed as it happens when blood is taken during the post mortem (PM) examination, these tests cannot be performed. Therefore it is recommended to the clinicians, to take a blood sample just before or immediately after death if possible. Similarly other samples like CSF, lung tissue etc, also are recommended to be collected just before or after death. If the facilities are available, serum should be separated before transport.

It is recommended to take multiple specimens including blood, CSF, respiratory secretions, stool, lung tissue etc. Plural fluid, peritoneal fluid, pericardial fluid etc has limited value as antigen / antibody detection assays cannot be performed using these samples. Tissue samples, swabs, respiratory secretions are collected into virus transport medium (VTM). VTM can be collected from the Department of Virology, MRI. It can be kept for few weeks at + 40 C (Do not use if the colour has changed from yellowish orange to pink) All samples, especially the samples intended for virus isolation / molecular assays should be collected with sterile precautions to prevent contamination (If tissue samples are taken, use separate sterile instrument set for each site).

All samples should be transported early to the laboratory at + 40 C. Samples should be stored at + 40 C until transport is arranged. For the transport of specimens, ice packs are preferred than ice cubes, to maintain the temperature. If ice cubes are used the samples should be packed in polythene bags separately so that there is no leaking once the ice gets melted.

- ◆ **Blood:** Ideally collected just before or just after death or during the autopsy and should be collected into dry, sterile bottle (for PCR collect into lysis buffer). Also blood sample can be collected from heart during the PM. Allowed to clot at room temperature. If facilities are available separate the serum.
- ◆ **CSF:** Ideally collected just before or just after death or during the autopsy, should be collected into dry, sterile bottle and to be sent to the laboratory early.
- ◆ **Respiratory specimens** (Nasopharyngeal swabs, tracheal swabs, bronchial aspirates or swabs): Ideally collected just before or just after death or during the autopsy and should be collected into virus transport medium (VTM). Use sterile throat swabs. Rub the surface with the swab to collect the epithelial cells. Insert the swab with the specimen into the container with VTM.

- ♦ **Faeces:** Collect during the autopsy into dry, bottle. Collect 5 -10 g of faeces (rectal swabs are not satisfactory) in to a leak proof container and sent to the laboratory early. However, anal swabs are not useful in viral diagnosis and not encouraged.
- ♦ **Vesicular fluid / scrapings / swabs:** Collect during the autopsy into virus transport medium (VTM).
- ♦ **Tissue specimens (lung, spleen, lymph nodes, myocardium, brain):** Collect during the autopsy. Use true cut biopsy needle & collect lung necropsy specimens just before or just after death in fatal case of suspected pneumonia. Take 3 specimens one into VTM, one into 70% alcohol, one into formalin. Should collect into container with virus transport medium (VTM). Collect tissue of 1cm x1 cm x 1 cm size from suspected areas.

7.2.5 Samples for electron microscopy

Mast cell degranulation is an important finding in allergy and anaphylaxis.

Presence of this in myocardium specially around coronary arteries can be fatal and has to be differentiated from myocarditis. Therefore a section from the myocardium for this is essential and the sample should be 3mm thick tissue in gluteraldehyde.

Please bring the contents of this circular to the notice of all officers concerned in your Province/ District/ Institution/ Unit.



Dr. U. A. Mendis
Director General of Health Services