Yellow Fever Initiative
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Yellow fever

Surveillance of adverse events following immunization against yellow fever

FIELD GUIDE
for staff at the central, intermediate and peripheral level

World Health Organization

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Contents

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Foreword

This field guide is intended for health workers at the central, intermediate and peripheral levels (physicians, health workers and decision-makers) who may have to deal with cases of adverse events following immunization (AEFI) related to yellow fever vaccination.

This guide has been designed to help in planning and carrying out field investigations into AEFI related to yellow fever vaccination. This initiative has been made possible by the experience gathered over many years in different countries within the Expanded Programme on Immunization (EPI) framework, using other vaccines such as those against poliomyelitis and measles. Specific sections of the guide (e.g. the use of active surveillance) relate specifically to adverse events that may occur following yellow fever vaccination. The guide is therefore not intended to replace any existing guidelines for AEFI surveillance in general. Whenever possible, and to optimize the use of human and other resources, surveillance of adverse events related to yellow fever vaccination should be coordinated with routine AEFI surveillance activities in each country.

This guide contains practical information relating to adverse events on:

- planning and setting up a system of active and passive surveillance of yellow fever AEFI,
- carrying out investigations into AEFI,
- case management,
- communication with the public in regard to AEFI.

Users will find here an operational framework to adapt to local conditions as required.

Acronyms and abbreviations

AEFI: adverse event following immunization

ALAT: alanine aminotransferase

AMP: *Agence de Médecine Préventive* (Preventive Medicine Agency)

ASAT: aspartate aminotransferase

CDC: Centers for Disease Control and Prevention (USA)

CISSE: *Centres d'Information Sanitaire de la Surveillance Épidémiologique* (Centres for Health Information on Epidemiological Surveillance)

CPK: creatine phosphokinase

CSF: cerebrospinal fluid

EPI: Expanded Programme on Immunization

EPIVAC: *programme de formation-action en épidémiologie et vaccinologie* (practical training programme on epidemiology and vaccine technology)

GACVS: Global Advisory Committee on Vaccine Safety

GAVI: Global Alliance for Vaccines and Immunization

HIV: human immunodeficiency virus

IFRC: International Federation of Red Cross and Red Crescent Societies

IHR: International Health Regulations

MSF: *Médecins sans Frontières*

PATH: Program for Appropriate Technology in Health

UNICEF: United Nations Children's Fund

WER: Weekly Epidemiological Record

WHO: World Health Organization

Glossary

Adverse event following immunization (AEFI): a medical incident that takes place after an immunization, causes concern and is believed to be caused by immunization.

AEFI cluster: two or more cases of the same adverse event, linked by time, place of vaccination or the vaccine administered. National programme directors may need to develop a more precise definition in the context of an investigation. AEFI clusters may be due to programme errors and may be caused by error in the vaccine administration technique or a problem with the vaccine and/or diluent.

Coincidental event: an AEFI medical incident that happens after the immunization but is not caused by the vaccine or a programme error.

Minor AEFI: a benign and temporary adverse event following immunization.

Non-serious AEFI: includes benign and moderate temporary adverse events following immunization that are not classified as serious.

Programme error: an AEFI caused by error in vaccine preparation, handling or administration.

Serious AEFI: any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, or results in persistent or significant disability/ incapacity, or is life-threatening.

Vaccine reaction: an AEFI caused by some component of the vaccine; i.e. the active component, preservative or stabilizer.

Introduction

The purpose of immunization is to protect normally healthy individuals from vaccine-preventable diseases.

The vaccine products and equipment used in immunization are very reliable because they are subject to rigorous quality control and approval, i.e. official authorization, before they are put on sale and used.

Even if these precautions are taken, some people may be affected by adverse events following immunization (AEFI) caused by the vaccine composition or by an error in its administration. In most cases, it is very difficult to determine with certainty a causal relation between the immunization and the reaction observed.

As regards international pharmacovigilance, the Global Advisory Committee on Vaccine Safety (GACVS), a scientific and clinical body responsible for advising WHO on global problems of vaccine safety, has drawn attention to the need to improve global surveillance and analysis of adverse events following immunization (*1*).

Immunization against yellow fever is the principal means of controlling this notifiable epidemic disease (IHR 1969, 2005) which poses a threat of global spread. The yellow fever vaccine (17D) has been used for more than 70 years, and is a very reliable and effective attenuated live vaccine. It is contraindicated for (*2*):

- children aged under six months
  (and not recommended for those aged from 6 to 8 months);
- persons with severe allergy to eggs;
- severely immunosuppressed persons
  (persons with symptomatic HIV infection or who are severely immunocompromised).

On theoretical grounds, the yellow fever vaccination also is not recommended for pregnant women.

As a rule, adverse events caused by yellow fever vaccination are mild. However, reactions caused by hypersensitivity to the vaccine components are occasionally observed, as are systemic manifestations. The latter are extremely infrequent and rarely documented. Systemic involvement may be neurological, hepatic, renal or haemorrhagic (*2–5*). We lack information to evaluate post-vaccination events associated with immune deficiency among populations infected with HIV. In 2001, seven cases of vaccination-associated viscerotropic disease characteristic of yellow fever were reported (*2, 6*).

Cases of AEFI sometimes occur in groups known as AEFI clusters; these correspond to an unusual frequency of similar adverse events or occurrences in the same geographical area.

The widespread notion that vaccines are responsible for any medical incident that follows is false: most AEFIs are coincidental events or due to avoidable programme errors.

The Yellow Fever Initiative launched by WHO and UNICEF with the support of the Global Alliance for Vaccines and Immunization (GAVI) in December 2005 provides for preventive and responsive mass immunization campaigns. This disease between 2006 and 2010 will involve some 48 million persons in 12 countries in west and central Africa.

During mass immunization campaigns, we generally observe an increase (perceived or real) in adverse events following immunization. This increase is essentially attributable to two factors.

- The large number of vaccinations performed in a short period of time (from a few days to a few weeks) causes a temporary concentration of adverse events following immunization.

- Certain vaccination teams repeatedly fail to observe safe injection practices. These failures arise from (1) the constraints arising from the desired vaccination coverage objective, which seeks to vaccinate many people as quickly as possible; and (2) the temporary recruitment of additional health workers who are unqualified or without vaccination experience.

In developing countries, among populations ill-informed about the benefits of vaccination or actually hostile to it, the occurrence of AEFI may feed rumours and engender collective fear of vaccination, jeopardizing programme success.

Against this specific background, we need to enhance and standardize surveillance of adverse events following immunization against yellow fever in the countries supported by the Yellow Fever Initiative. This will enhance the possibilities (1) to document AEFI caused by yellow fever vaccination and (2) to take necessary remedial actions as soon as possible.

For whom is this guide intended?

This guide is specifically intended for officials and the organizers of yellow fever mass immunization campaigns and those involved in technical aspects of yellow fever immunization campaigns at the central, intermediate and peripheral levels.

Objectives of the guide

Purpose

To make it possible to obtain detailed, comprehensive and standardized information on adverse events following vaccination against yellow fever.

Operational objectives

This guide is intended to offer countries a methodology and tools to implement:

- an effective system for surveillance of yellow fever AEFI;

- measures for controlling and treating AEFI;

- effective communication with the public, including measures to combat rumours that jeopardize vaccination activities;

- investigations into yellow fever AEFI following mass immunization campaigns.

1. Planning surveillance of AEFI

Planning for surveillance of AEFI must be an integral part of immunization programmes. Serious AEFI may be detected and declared either as part of overall disease surveillance or within an ad-hoc framework.

Before taking action to detect and declare AEFI, political decision-makers should be made aware of the surveillance system's importance. It also is useful to draw up a list of activities to be carried out, ranked in order of priority, and to set up an ad-hoc AEFI committee.

1.1. Obtaining the backing of health officials for AEFI surveillance

When immunization campaigns are organized, political and health authorities' primary objective is to vaccinate the whole target population of the programme as quickly and cheaply as possible. Surveillance of AEFI is not a priority for some political decision-makers. Certain others question the value of monitoring adverse events following immunization, as to do so would reveal shortcomings in their programmes.

Thus to obtain the support of political authorities we need to show that AEFI surveillance is inseparable from immunization programmes and is key to their success. Immunization officials in the countries concerned also must persuade their superiors of the value of AEFI surveillance.

Scientific arguments alone are not sufficient to convince national political decision-makers. These officials also must understand that because of the size of the immunization programme's target population, AEFI are inevitable regardless of the efficacy and safety of the vaccines used.

To maintain the population's support throughout the immunization campaign and thus achieve the desired level of vaccination coverage, surveillance of yellow fever AEFI should be backed up by:

- proper management of the cases detected;
- rapid remedial action if error can be ascribed to immunization activities;
- a communication campaign to counter rumours or information that jeopardize immunization activities.

It is also important to explain that lack of surveillance of adverse events following immunization encourages rumours and public mistrust of immunization per se and may jeopardize not only the success of the yellow fever immunization campaign but also the country's other immunization programmes.

WHO recognizes AEFI surveillance as «a factor for improving the quality of immunization services» and urges that it be an integral part of all immunization programmes.

1.2. Establishment of ad-hoc national scientific committee on AEFI

An ad-hoc national scientific committee on AEFI should be appointed and charged with setting up, tracking and evaluating the surveillance of serious yellow fever AEFI.

1.2.1. Responsibilities of the national scientific committee on AEFI

Because the AEFI committee requires independence, it should not involve staff responsible for vaccination. This national scientific committee (NSC) has the following tasks:

- convincing political and health authorities to include surveillance of serious yellow fever AEFI as part of the immunization campaign;
- defining the methods of surveillance, reporting and investigation of serious yellow fever AEFI associated with the scheduled immunization campaign;
- helping to draw up an estimated budget and to seek funding from political decision-makers and donors for surveillance, investigation and treatment of serious AEFI;
- organizing field investigations when required;
- monitoring the input, management and analysis of AEFI data;
- deciding on methods of treatment for AEFI cases;
- where necessary, helping to take rapid remedial action where programme errors associated with immunization activities occur;
- rapidly dealing with any rumours generated by AEFI that may jeopardize vaccination;
- conducting an AEFI causality review;
- classifying and responding to reports of serious AEFI to decide whether or not they are linked to the vaccine;
- preparing a final report on all types and cases of AEFI.

1.2.2. Composition of and appointments to AEFI national scientific committee

To perform all tasks described above, the national scientific committee on AEFI will need to bring together a range of expertise from different fields: medicine, biology, epidemiology, public relations, social mobilization and clinical skills. Apart from these areas of expertise, we recommend that the following also be included:

- authorities from the central level, together with partners involved in epidemiological surveillance activities and vaccination;
- one or more clinical specialists;
- one or more members of the health products pharmacovigilance or safety service, if this exists in the country;
- one or more members of the immunization campaign's social mobilization or public communication committee to deal with rumours;
- one or more other academic specialists on questions of vaccination safety.

The appointment of AEFI committee members should be an agenda priority in early meetings to organize the immunization campaign. The committee members dealing with serious AEFI will share surveillance-related tasks depending on their fields of expertise, as detailed below.

1.3. Budgeting to implement AEFI surveillance

AEFI surveillance is a mandatory component of mass yellow fever immunization campaigns that receive financial support from GAVI; it must appear in the immunization campaign budget. The budget line for AEFI surveillance must encompass expenditure on surveillance activities as a whole and on AEFI treatment.

Annex 1 suggests a checklist of activities and items of expenditure that could be included in budget estimates for AEFI surveillance. The estimated costs of treatment for cases could be calculated using Annex 2's estimates of the incidence of each AEFI type; we recommend that treatment for non-serious and serious AEFI be offered free of charge. Countries are strongly recommended to provide injectable adrenaline free of charge for treatment of anaphylactic shock; in addition, some countries provide antihistamine treatment free of charge in case of acute hypersensitivity reaction associated with vaccines. In the rare cases of serious AEFI, the method of treatment should be determined on a case-by-case basis. However, treatment of events such as moderate pain and fever associated with vaccination is usually the responsibility of patients.

2. Introduction of AEFI surveillance

An adverse event following immunization is a medical incident that takes place after an immunization which is believed to be caused by immunization.

While neither AEFI surveillance nor most communicable disease surveillance systems offer ways to «control» epidemics, their aim is nonetheless to identify and document cases and to set in motion investigations, remedial actions and/or communication with the public or media to address concerns about immunization.

To determine the possible causes of an AEFI, the first requirement is to ensure that events are detected and declared.

In most countries, the routine surveillance system (AEFI surveillance system or national disease notification system) will not make it possible to detect all AEFI or to identify all serious AEFI cases following yellow fever vaccination in a timely manner. To remedy this, provisions must be made for more active case detection in health centres and hospitals, especially of serious AEFI following yellow fever vaccination. The recommended methods are described later in this document.

2.1. Definition of medical incidents to be monitored

Annex 3 lists medical incidents that may be observed following yellow fever vaccination, together with their clinical descriptions. Some of their characteristics are listed below.

- **Non-serious or minor/moderate AEFI** take several forms: temporary local reaction at the injection site (pain, redness, swelling), headaches, tiredness, muscle pain or moderate fever (< 39°C) not lasting more than 2 days. Alternately, these are allergic (rash, itching, asthma) or gastrointestinal (nausea, vomiting, diarrhoea) reactions or temporary convulsions lasting no longer than a week that are not life-threatening and leave no sequelae.
- **Serious AEFI** are medical incidents that are life-threatening or which require admission to hospital due to anaphylactic reaction or shock, encephalitis, Guillain-Barré syndrome, kidney failure, liver failure, respiratory failure, rhabdomyolysis and haemorrhage. Serious AEFI may also have sequelae causing disability, jaundice with fever or death.

Serious AEFI must be systematically reported; however, the team responsible for AEFI surveillance (comprising the national scientific AEFI committee and officials from the immunization programme) will need to decide whether serious and non-serious (minor/moderate) AEFI should also be reported.

To ensure that health workers at the peripheral level make no medical interpretations or decisions, it is advisable to draw up a list of the clinical signs suggestive of yellow fever AEFI for inclusion on the reporting form (Annex 3).

The description of the clinical signs, including the time they take to appear after vaccination and the time they take to disappear as indicated on the reporting form, will enable the clinician to make a standard diagnosis free from personal interpretation. Annex 3 lists medical incidents reported following yellow fever vaccination and the corresponding clinical signs.

2.2. Introduction of passive surveillance

2.2.1. Using existing national disease notification systems

To ensure the yellow fever AEFI surveillance system is operational and to simplify the tasks of health workers and officials at intermediate and peripheral levels, it is strongly recommended that the systems and human resources already in place for the surveillance of epidemic disease be used at each level of the health pyramid.

2.2.2. Passive surveillance system actors and their roles

In facilities providing treatment and vaccination, vaccinators and district health-care personnel are responsible for detecting, treating and reporting AEFI.

A focal point for AEFI surveillance should be designated **in the district health authority,** to be responsible for monitoring AEFI reporting in the district, putting out a regional alert in case of serious AEFI and transmitting data from reporting level to the regional/national level.

The following should be designated within the **regional health authority**.

(1) A focal point for AEFI surveillance is responsible for:

- following up reports of AEFI in the region;
- giving the alert at the national level in case of serious AEFI;
- transmitting data from reporting level to the regional/national level;
- assisting with investigations into AEFI in the region (directed by the yellow-fever AEFI investigation team).

(2) A referring clinician is responsible for:

- analysing medical data on serious or non-serious AEFI cases recorded on reporting forms or transmitted by health care personnel who reported the case;
- forwarding as quickly as possible to the national scientific committee the precise clinical and laboratory data on suspected serious AEFI cases;
- proposing and transmitting to the national scientific committee on AEFI a differential diagnosis;
- participating in the investigation of any serious AEFI in the region.

The following responsibilities should be designated **at the central level**.

- The national scientific committee should be proactively involved in setting up passive surveillance of AEFI and be ready to respond to any reports of serious events to direct necessary investigations (detailed responsibilities of the scientific and advisory committee on serious AEFI are listed in section 3.1);
- make a causality review of serious AEFI;
- national epidemiological surveillance officials must monitor AEFI reporting and organize input and analysis of reported data.

2.2.3. Setting a deadline for reporting

In coordination with vaccination programme officials, the national scientific committee on yellow fever AEFI will determine which AEFI are compulsorily notifiable on an immediate or weekly basis. The deadline for reporting will depend on what action is required in response to suspected AEFI.

A supplementary investigation should be carried out as quickly as possible into severe medical incidents or incidents which cause alarm about vaccination among the population.

Accordingly, it is strongly recommended to arrange for immediate reporting (by telephone, radio, or fax) of each severe medical incident as soon as an AEFI is suspected, as well as weekly reports of non-serious events.

2.2.4. Period for reporting AEFI

If actually associated with immunization, the adverse events following immunization described in Annex 3 appear within 4 weeks. Reporting yellow fever AEFI should thus begin on the first day of the immunization campaign and continue for four weeks after its completion (*7–9*).

2.2.5. Preparation of reporting documents

Vaccination card

The yellow fever vaccination card is an essential element for the investigation and reporting of an AEFI. When an AEFI is suspected, a check should be made to find out whether the patient's vaccination card is available. This is because only the information recorded on a properly completed vaccination card makes it possible to identify the vaccine and diluent concerned (batch number and expiry date), exact place and date of vaccination.

Reporting form

The reporting form (Ready Reference Card 1) must by filled out for each suspected case of a serious or non-serious AEFI by the health worker who treats the case.

The form should make it possible:

- to identify the case (surname, first name, address, contact details, age and sex);
- to identify the place, site and date of vaccination and the characteristics of the vaccine and of the diluent administered;
- to identify the health facility and the health worker who reported the case;
- to determine the date on which the symptoms appeared and on which treatment began;
- to determine the clinical signs observed. To avoid health workers making medical interpretations or decisions, it is preferable for a list of clinical signs suggestive of yellow fever AEFI to be provided on the reporting form. The referring clinicians (at the regional and central levels) will be responsible for suggesting a standardized diagnosis and for deciding, on the basis of the symptoms described and the information available as a whole, whether there is potentially a link between the event observed and the vaccination; and
- to describe the treatment provided and the clinical course of the case.

A model reporting form is provided (Ready Reference Card 1).

Serious AEFI report/evaluation form

The serious AEFI report/evaluation card (Ready Reference Card 2) is for:

- the emergency investigation mission (mobile team) organized by the district or region after a serious AEFI has been reported; and for
- the mobile team of investigators responsible for active case detection (Section 2.3).

The card will enable these investigators to report precise information on the case's medical history and clinical course, as well as on laboratory specimens taken during the investigation. This card is to be transmitted as soon as possible to the national scientific committee on AEFI, which will decide if complementary information is necessary.

Weekly AEFI summary

It is recommended that each health centre (or «reporting unit») use a weekly AEFI summary form (Ready Reference Card 3) to:

- collect data on non-serious and serious AEFI;
- identify serious AEFI which have not been immediately reported; and
- indicate, where appropriate, that no cases of AEFI have been detected («zero cases» notification).

This AEFI summary form is to be sent each week by health centres to district health authorities even if no cases have been detected.

Note: serious medical incidents which must be reported immediately, and for which the serious AEFI reporting form and report card must be completed in full, must also be included in the weekly summary of yellow fever AEFI.

2.2.6. Defining the practical details of the passive surveillance system

Documents on methodology that set out appropriate procedures should be prepared and provided to each staff member and health worker depending on their AEFI surveillance responsibilities.

At the health-care facility level (vaccination posts and hospitals), health workers should be shown:

- how to detect AEFI (Annex 3);
- how to treat cases of AEFI (Annex 8, Ready Reference Card 8);
- how to fill out the reporting forms (Ready Reference Card 1); and
- how to report cases of AEFI to specific district health authorities.

At the district health authority level, the methodology will explain:

- how to inform and train health workers in AEFI surveillance;
- how to monitor and supervise the AEFI surveillance system in the district;
- how to report AEFI at the regional level and to whom;
- how to react to a serious case of AEFI;
- how to respond to an AEFI cluster, which often indicates a programme error in the technique used to administer the vaccine or a problem in the vaccine (specific vial or batches) or diluent used (Annex 5).
  If the event also affects unvaccinated persons it may be a coincidence; this makes it important to determine whether unvaccinated persons in the same geographic area as the AEFI cases have developed the same symptoms during the same period; and
- when and how to carry out an investigation.

At the regional health authority level, the methodology will explain:

- why AEFI surveillance is important;
- how to monitor and supervise the AEFI surveillance system at the regional level;
- how to report AEFI to the central level, and to whom;
- how to respond to a serious case of AEFI;
- how to respond to AEFI occurrences which form a geographical or temporal cluster; and
- when and how to carry out an investigation.

2.2.7. Introduction of AEFI surveillance at the regional and district levels

When preparatory and training sessions on vaccination activities are organized for regional and district health authorities, it is advisable to schedule a special session on AEFI surveillance and notification. This session will be used to:

- Explain the importance of monitoring AEFI by describing its scientific and medical considerations, the problems posed by rumours, etc. The following should be stressed:
    - the importance of vaccine safety, for both scientific and ethical reasons;
    - the importance to the programme of (1) ensuring that vaccination activities go smoothly, (2) taking steps to deal with any rumours/opinions that jeopardize vaccination, and (3) using vaccination cards for surveillance of AEFI;
    - the medical importance of AEFI's as a notifiable «disease» (if necessary, refer to Ministry of Health directive) and of reporting AEFI to allow remedial action to be taken as quickly as possible.

- Describe the activities to be carried out at the district and regional levels to ensure the smooth running of the surveillance system. These activities include:
    - informing and training health workers in AEFI surveillance;
    - monitoring and supervision of AEFI reporting, which should be integrated into vaccination supervision activities, as well as follow-up and monitoring of reporting after vaccination activities;
    - investigating AEFI (see section on organizing investigations);
    - providing health workers and vaccinators with the documents needed for reporting (vaccination cards and reporting forms as well as practical details of surveillance, treatment and reporting) and with drugs to treat AEFI;
    - retrieving data from health facilities and vaccination posts; and
    - transmitting reporting data to the central level.

- List and describe the reporting tools/documents. These include:
    - methods of AEFI detection, treatment and reporting (including the reporting forms) intended for health workers;
    - methods of retrieval, management and transmission of reporting data from the district and regional levels to the central level; and
    - methods/methodology of yellow fever AEFI investigation.

- Identify one or several clinicians for referral of serous AEFI at the regional level.

Hospital clinicians specializing in gastroenterology, hepatology and neurology who are capable of carrying out investigation missions when serious viscerotropic or neurologic AEFI are suspected should be designated in advance.

2.2.7.1. Training vaccination staff to identify, treat and report AEFI

During the preparatory/training sessions for vaccination activities organized for the vaccination teams, a session on surveillance/notification of AEFI should be scheduled during which:

- the importance of AEFI surveillance will be explained;
- the mandatory requirement to immediately report serious AEFI will be explained (if necessary, refer to the national directive);
- an explanation of the procedure for detect detection and reporting of AEFI will be given; and
- the importance of using vaccination cards for AEFI surveillance and investigation will be explained.

2.2.7.2. Training non-vaccination staff to detect, treat and report AEFI

Although most health workers at the peripheral level are involved in vaccination activities, some categories of staff in hospitals are not involved and will not take part in the training sessions specially organized for the immunization campaign.

The possibility that they will have to deal with adverse events following immunization against yellow fever should be explained to these health workers, and they should be shown the proper procedure for treating and reporting suspected yellow fever AEFI.

2.3. Methods of active detection of serious AEFI

The AEFI reporting system should be supplemented by specific active detection of serious AEFI. This active case-detection activity is to be organized by the national scientific committee on AEFI. A protocol on active case detection will specify methods to be used.

2.3.1. Designing active case-detection systems for serious AEFI

The arrangement suggested consists of active, prospective and retrospective detection of suspected serious cases of AEFI using available health registers or hospital records, or by questioning workers in health care facilities. Any suspected cases of serious AEFI that are detected will be thoroughly investigated.

2.3.2. Sites for active case detection

Ideally, serious AEFI should be sought in each health facility in areas where vaccination is being carried out.

However, for practical and budgetary reasons, it will not always be possible to cover the whole of the vaccination area. In this case, selection of «referral sites» is recommended.

These sites should be chosen from among:

- the referral health facilities for all the districts and regions affected by vaccination (regional and district hospitals or district medical centres);
- the health facilities (medical and health centres) that serve for referral of large populations; and
- selected health centres in remote rural regions.

The national scientific committee on AEFI will select the sites to be included in active case detection.

2.3.3. Period for active case detection

When the adverse events following immunization described in Annex 1 are associated with vaccination, they occur within four weeks of vaccination. After this period, the probability of new cases of AEFI is very low (*10, 11*). In 95% of the cases of neurologic and viscerotropic AEFI described in the literature, the symptoms appear within less than 10 days of the vaccination.

Consequently, it is recommended that active surveillance of serious AEFI should begin on the first day of the immunization campaign and continue for 4 weeks after its conclusion.

If practical and budgetary considerations make is impossible to carry out active case detection for 4 weeks after the campaign, the period of surveillance may be limited to the duration of the campaign and a fortnight after it has ended. However, if a suspected case of serious AEFI is identified and reported by health care staff after this period of active detection, it still can be reported to the national scientific committee and investigated.

2.3.4. Methods of identifying suspected cases of serious AEFI

A team of investigators with medical training (interns, medical students) will be formed and given specific training in identifying and evaluating serious yellow fever AEFI. They will be instructed to collect data on forms (serious AEFI report/evaluation card and Ready Reference Card 2) and shown how to take clinical specimens.

The national scientific committee's coordinators will be responsible for organizing and supervising the investigators' work. In each health centre or hospital, investigators will examine the hospital records and/or medical files and question health care personnel. The epidemiological surveillance focal point or a district management team member may participate with investigators in active case-detection of serious AEFI.

The investigators will examine the data and reporting forms available in health centres or hospitals as well as those centralized in the district and regional centres for health information on epidemiological surveillance (CISSE) to identify suspected cases of serious AEFI.

A list of the clinical signs and symptoms to be looked for is proposed in Annex 4.

The national scientific committee on AEFI will decide, on the basis of the serious AEFI report/evaluation form, whether or not to carry out a thorough investigation.

3. Organizing the investigation

3.1. Why conduct an investigation?

Sometimes when AEFI is suspected, it will be necessary to supplement the information provided on the reporting form. These supplementary steps may include:

- confirming or identifying the cause of the AEFI: the composition of the vaccine itself or an error in the vaccination process, an AEFI occurring by coincidence, or even an AEFI of unknown origin (Annex 5 describes specific definitions of different AEFI causes);
- giving a more precise description of the signs observed and monitoring the clinical course of the case (Ready Reference Cards 4 and 5);
- taking the clinical specimens necessary to confirm the presumed diagnosis and assessing the link between the vaccination and the AEFI observed (see Annex 6, Ready Reference Card 6);
- reassuring the patient and patient's family;
- if need be, providing the population with information about the incident and reminding them of the benefits of vaccination (if rumours are an issue or the population is worried about vaccination); and
- taking immediate remedial action if the AEFI is caused by any shortcomings in vaccination activities (programme error).

3.2. In what circumstances should an investigation be conducted?

Investigations carried out as part of preventive immunization campaigns or campaigns in response to an epidemic are costly and time-consuming.

Because the regional and district health authorities who must also supervise the immunization campaign are not always available and AEFI surveillance is subject to budgetary constraints, it is not possible to carry out an investigation into each AEFI suspected and reported. Accordingly, we recommend that investigations be carried out in cases of:

- serious AEFI that results in death, hospitalization or prolongation of hospitalization, in persistent or significant disability/incapacity, or is life-threatening;
- AEFIs that may be an indication of a programme error (e.g. clusters of bacterial abscesses);
- serious unexplained AEFI occurring within 4 weeks after vaccination and not listed on product label;
- events causing significant parental or community concern;
- situations where any of the specific serious AEFIs defined in Annex 3 is suspected, regardless of whether this engenders public mistrust in vaccination.

The district or regional referral clinicians will be able to investigate the suspected case of AEFI first. Nevertheless the reporting form and the AEFI report/evaluation form on the case of serious AEFI should be sent as soon as possible to the national scientific committee on AEFI to allow it to decide whether to conduct and to organize an investigation.

3.3. Who is to conduct the field investigation?

The national scientific committee is responsible for organizing and carrying out investigations into serious AEFI (see responsibilities of the national scientific committee). The composition of the investigative team will depend on the type of AEFI suspected.

If a serious AEFI is suspected, a small team comprising a clinician, an epidemiologist and a laboratory expert from the central level should be formed. If rumours have started to spread or if the population is reluctant to be vaccinated, this small team may include a communication specialist. Lastly, we recommend that the investigation team should include the person responsible for the health facility that reported the AEFI, together with the referral clinician(s) in the region.

The epidemiologist, biologist and clinicians from the central level (who are members of the national scientific committee on AEFI) will be responsible for organizing the investigation mission in coordination with the regional and district health authorities.

3.4. Preparing the field investigation

Before starting the field investigation, some items of information should be checked. While having this information facilitates preparation for the field visit, it is important to note that these steps are part of the overall investigation and should not delay a field investigation, as the field investigation itself offers an opportunity to collect or verify missing information.

Using the reporting form (Ready Reference Card 1) and the serious AEFI report/evaluation form (Ready Reference Card 2) which have been completed and submitted, investigators should:

- check that the yellow fever vaccination has indeed been administered: did the patient present a yellow fever vaccination card?
- check that the medical incident or clinical signs described correspond to the AEFI case definition;
- complete any information missing from the reporting form which will be needed; and
- suggest one or more hypotheses for the probable cause of the AEFI.

Once the potential cause(s) of the AEFI have been determined, it is first necessary to draw up a list of the information needed to confirm or invalidate the AEFI cause(s). Then investigators should identify the tests and specimens necessary to confirm or invalidate the suspected cause (Annex 6 lists laboratory tests to be carried out depending on the suspected AEFI). Where a programme error is suspected, it might be worthwhile (1) to contact district health care facilities to seek information on the possible occurrence of similar AEFI, or (2) to determine a methodology for detecting similar AEFI or AEFI clusters.

From the practical/administrative angle, investigators should:

- inform the health worker responsible for the health centre/hospital that an investigation is being carried out;
- draw up the terms of reference for the investigation (objectives, duration, sites, persons to be interviewed, schedule for the activities to be carried out, members of the investigation team) and circulate these documents to the persons concerned by the investigation;
- if necessary, determine a budget for the investigation and request necessary funds from the central level;
- prepare the necessary materials and tools for the investigation (data collection forms, items for taking samples, etc); and
- decide on the communication strategy (and the key messages to put across) in the event of any rumours detrimental to vaccination.

3.5. Information to be collected during the investigation

Certain information must systematically be sought or confirmed when a suspected yellow fever AEFI leads to an investigation: information on the vaccination, on the vaccine given, on the state of health and on the case's social and demographic background. Any other information that needs to be collected will depend on the potential causes of the AEFI.

A list of information to be found and collected is suggested in Annex 7. If a viscerotropic or neurologic AEFI is suspected, precise clinical and laboratory information will be required to determine whether the vaccine is the cause. The proposed clinical and laboratory description of the neurologic and viscerotropic involvement (Ready Reference Cards 4 and 5) may be of use to clinicians and laboratory experts on the AEFI national scientific committee in the investigation (*12*).

The reporting forms (Ready Reference Card 1), the suspected serious AEFI report/evaluation forms (Ready Reference Card 2) and the forms for reporting data and the results of laboratory tests (Ready Reference Card 6) will be sent to the national scientific committee on AEFI. Although it is difficult to establish a causal link between a serious AEFI and the vaccine, every effort must be made to do so and to eliminate any other possible cause (coincidence).

On the basis of the clinical, epidemiological and laboratory information available, the committee will determine whether there is a link between the vaccination and the AEFI under investigation. The committee will determine what type of additional laboratory investigations are needed to confirm the correlation, in accordance with the guidance for detection and investigation of serious adverse events following yellow fever vaccination (*13*). Specimens intended to confirm a causal link with the vaccine virus are to be sent to a WHO reference centre (see laboratory input, type of specimen and preservation in Annex 6). It will be possible at the national level to analyse specimens for confirmation of clinical symptoms, e.g. liver, kidney, blood or neurology.

In the case of a serious AEFI, the search for and confirmation of a link between the vaccine and the AEFI require:

1. proof of a link in time;
2. a clear clinical and biological description which confirms the signs and symptoms presented by the patient;
3. identification of the viral antigens in the tissue of the organs involved; and
4. detection, either directly (i.e. viral culture, genetic sequencing) or indirectly (PCR, specific immunoglobulins) of the vaccine virus in the blood or tissue.

The presence of viral antigens or of the virus itself sometimes allows a causal link to be established.

3.6. Drafting and circulating a summary investigation report

The investigation report must concisely describe:

- the circumstances that triggered the decision to conduct the investigation: all the information available on the AEFI before the investigation and any hypotheses as to its potential cause;
- the names of those who took part in the investigation;
- the site and duration of the investigation;
- the methods and progress of the investigation;
- any additional information collected during the investigation concerning observance of the contraindications for yellow fever vaccination;
- the vaccination and the vaccine;
- the patient's state of health and the treatment administered;
- the laboratory tests carried out and the results available on the AEFI's identified cause;
- the remedial action taken; and
- the conclusions, recommendations and prospects.

The investigation report is to be sent:

- to the officer in charge of the immunization programme;
- to the staff responsible for organizing the campaign at the central level;
- to the (regional and district) health authorities in the area affected by the AEFI;
- to the head of the health facility that reported the AEFI;
- to the AEFI surveillance focal point in the district concerned; and
- to all members of the field investigation team.

4. Monitoring the AEFI surveillance system

4.1. At vaccination posts and health facilities

Throughout the immunization campaign, monitoring of yellow fever AEFI surveillance activities should be an integral part of activities to monitor the campaign. During each supervisory visit to a vaccination site, the supervisors must ensure that:

- the vaccination team has the relevant documents and materials for surveillance of yellow fever AEFI as well as documents regarding appropriate procedures in the event of anaphylactic shock (Ready Reference Card 8);
- the head of the vaccination team is familiar with the methods of detecting, treating and reporting yellow fever AEFI and knows which AEFI should be investigated;
- the vaccination post has the treatments needed for non-serious or serious AEFI (in particular adrenaline) available free of charge during the immunization campaign;
- a reporting form has been filled out and sent for each non-serious AEFI; and
- the vaccination team has a summary up-to-date list of non-serious AEFI.

As well as supervising immunization sites, the supervisory teams should visit each health centre or district referral hospital to ensure that the health care staff who are not involved in vaccination activities have actually received the AEFI surveillance documents and materials, that they have been informed and trained and that they have observed the procedure for detecting, treating and reporting yellow fever AEFI.

If necessary, the supervisory teams should:

- reiterate the existing procedure for surveillance and treatment of AEFI;
- if necessary, supply sites with medicines (analgesics, adrenaline and antihistamines) to be provided free of charge during the immunization campaign; and
- provide sites with documentation and reporting materials for surveillance of yellow fever AEFI.

We recommend that this checklist be appended to the immunization campaign supervision form.

On completion of the immunization campaign and for four weeks after the end of vaccination activities (the surveillance period for yellow fever AEFI), the district health authority and district surveillance focal point will ensure that health workers comply with procedures for reporting yellow fever AEFI. It is the responsibility of the district health authority to remind health workers to submit weekly yellow fever AEFI reporting forms.

4.2. In the district and regional health authorities

Each week, the health authorities or the district surveillance focal points shall:

- collect all (individual) reporting forms and weekly summary from each health facility; if necessary, remind those health facilities not sending their summary list of reports on time (a tool for tracking weekly declarations of yellow fever AEFI is proposed as Ready Reference Card 7);

- cross-check the information from the summary list against the individual report forms to ensure that detailed information is available on each non-serious or serious AEFI;

- check that the information on the forms is complete and consistent and, if necessary, request that the health worker who reported the case collect or correct any missing or inconsistent information; and

- transmit all the reporting data to the central level (in accordance with the requirements of the national reporting system).

4.3. At the central level

The national epidemiological surveillance service must ensure that reporting operates smoothly and in accordance with approved procedures throughout the specified surveillance period (up to four weeks after completion of the immunization campaign). If necessary, the head of epidemiological surveillance will prompt the regions to send yellow fever AEFI reports.

If a serious AEFI is suspected, the reporting forms and, if necessary, the serious AEFI report/evaluation forms must be immediately faxed to the head of epidemiological surveillance, who must forward them to the national scientific committee on serious AEFI for action.

5. Treatment of AEFI

Procedures for treating each type of AEFI are suggested in Annex 8.

In view of the practical difficulties of respecting contraindications for yellow fever vaccination in case of allergy to egg protein, we recommend that vaccination posts and hospitals be provided free of charge with treatments for anaphylactic shock and acute hypersensitivity reactions (anaphylactic reactions) which the vaccination might cause in patients who are allergic to eggs. When adrenaline is provided in vaccination posts and hospitals, a document on appropriate procedures should also be provided to enable health workers unfamiliar with management of anaphylactic shock and adrenaline use to comply with dosage and methods of administration.

A document on appropriate procedures in event of anaphylactic shock is suggested (Ready Reference Card 8). The programme directors are responsible for making sure that the equipment (syringes and needles) and medicines needed to treat anaphylactic reactions are available and that every member of the vaccination team has been trained to diagnose and treat them. A copy of the document (Ready Reference Card 8) should be on hand in all vaccination posts.

All patients with the serious AEFI described in Annex 3 must rapidly be admitted to hospital and treated.

6. Communication on AEFI

AEFI require a communication plan to:

- inform the population about the possible occurrence of temporary minor reactions after the vaccination;
- encourage the population to visit a health facility in the very rare case that a non-serious, serious or persistent AEFI occurs; and
- manage and refute rumours and misinformation about AEFI that are detrimental to vaccination activities.

6.1. Informing the population about AEFI

The purpose of the key messages delivered to the population during social mobilization activities is to inform them about the possible occurrence of temporary minor reactions without causing concern or compromising immunization.

Although the media may put across these key messages, they may also be repeated at the vaccination posts by the vaccination teams during the campaign.

More detailed and specific information on the nature of adverse reactions may be provided directly by vaccinators, who will encourage patients to consult their health facility if they experience a non-serious, serious or persistent adverse reaction. Vaccinators should emphasise that some treatments are free of charge.

6.2. Managing and quashing rumours

If one or more adverse events occur, they may give rise to rumours or misinformation that, if left unchecked, could sabotage the immunization programme.

To maximize the population's confidence in vaccination, the district or any other well-informed health authority must set up permanent public relations channels (direct contacts, press, radio) between the community and health workers such as vaccinators, health-care personnel, AEFI investigation teams, vaccination supervisors and the director or head of immunization activities. A constant stream of information must be provided to:

- combat the spread of false rumours;
- keep the population abreast of the progress and results of the investigation and any remedial action taken in response to a serious AEFI that causes public concern; and
- reassure the population by explaining that adverse events from immunization are the exception and that the risk to non-immunized persons from disease is far greater.

The population's confidence in the health service depends on the quality of information, which must be transparent, open and truthful.

If the cause of the AEFI has not been determined, this should be frankly admitted. If the AEFI is the result of a programme error, the measures taken to resolve the problem should be explained.

In crises, when the population of the entire area concerned by the immunization programme is reluctant to be vaccinated, a careful analysis of the situation must be made as quickly as possible. A broader communication effort may be warranted involving, for example, a press conference and TV or radio interviews to be broadcast nationwide.

To improve the credibility of information, the director of the immunization programme should appeal to the population. A contribution from the international health organizations present in the country may also help to convince the population.

If rumours or information that compromise immunization are circulating in a precisely defined area, the local press and radio might be a means of solving the problem without alarming neighbouring populations. In such cases, the director of the immunization programme (or their representative) and the relevant health authority should be involved in the public relations effort.

As a rule, if immunization is to be successful it must have the support of the media, opinion makers and religious leaders. These groups must be involved from the outset of the immunization campaign and should participate in social mobilization activities connected with the campaign. The overall public relations effort for the immunization campaign should be coordinated and organized by media specialists in association with immunization specialists.

Some practical advice on communication techniques and typical questions and answers on AEFI are suggested in Annex 9.

7. Conducting a retrospective (post-campaign) AEFI survey

Post immunization-campaign AEFI surveys are a means of retrospectively detecting serious AEFI. These surveys can offset the lack of sensitivity of passive and active AEFI detection during the immunization campaign, as they estimate the proportion of AEFI among the vaccinated population and characterize these AEFI. Among the vaccinated population, interviews will be conducted with vaccinated persons or their representatives. In health care facilities, personnel will be interviewed and consultation and admission registers examined.

The AEFI survey should be part of the evaluation survey (immunization coverage +/- qualitative evaluation) of the immunization campaign. Detection of AEFI among the population will be based on the sample selected for the immunization coverage survey.

Active detection of AEFI using consultation or admission registers will need to focus on the referral health facilities (regional and district hospitals). Visits should also be made to a representative group of more elementary health facilities, selected on the basis of the reporting data submitted (for example, it might be worthwhile to select health facilities which have not reported any AEFI) and evenly distributed throughout the area covered by the immunization programme.

It will be possible to compare the findings of the post-campaign AEFI survey with those of active and passive detection of AEFI during the immunization campaign to assess how exhaustive and representative the earlier results were.

8. Management and analysis of AEFI data

8.1. Types of data

There are three types of data: those collected via the AEFI surveillance system that operates during and after the campaign, data obtained and collected from the investigations carried out into specific AEFI and data from post-campaign investigations of AEFI clusters.

8.2. Data input

Data collected in AEFI surveillance activities should be entered at the central level. Overall data input may be performed on completion of surveillance, investigation and post-campaign survey activities. All reporting forms and other data-collection tools completed during the investigations and the survey must be submitted to the central level.

The data input software must permit separate entry of data from existing surveillance (individual reporting forms and weekly summary lists of AEFI), investigations and the post-campaign AEFI survey among the population.

A single identifying number will need to be established for each AEFI. Each AEFI reported and documented by the surveillance system, investigations and the post-campaign survey must be assigned the same identification number to allow cross-referencing between the databases.

For data input purposes, we recommend the choice of user-friendly software with which the epidemiological service is already familiar (Excel or Epi-info).

The epidemiological service's data manager may be mobilized to supervise data input.

8.3. Data analysis

Data analysis will be performed by the epidemiologist at the central level with the assistance of the other members of the AEFI national scientific committee.

The data analysis should give the following indicators:

- total number of AEFI, broken down into non-serious and serious AEFI;
- reporting rate of AEFI (non-serious/serious) among the population vaccinated (Ready Reference Card 9);
- distribution of AEFI by cause (vaccine reaction, programme error or coincidental);
- distribution of reported cases by specific AEFI (e.g. septicaemia, anaphylaxis);
- distribution of AEFI by time and place;
- characteristics of AEFI by age and sex of patient;
- outcome of AEFI cases (death, recovered fully, recovered with sequelae); and
- description of case management for each etiology.

Lastly, data analysis will also involve comparison of the reporting data and the data from the post-campaign AEFI survey.

A meeting of the national scientific committee on AEFI should discuss and validate the results, draw conclusions and make recommendations.

9. Drafting the AEFI surveillance report

The national scientific committee on AEFI responsible for surveillance activities will be required to prepare a final report on all types and cases of AEFI that have been detected. The report will be circulated to all those involved in surveillance at the central, regional and district levels.

This report will describe:

- the background of yellow fever AEFI surveillance;
- the activities carried out and the methods and tools employed;
- the results of AEFI surveillance; and
- the conclusions, recommendations and prospects of yellow fever AEFI surveillance.

10. References

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11. Ready reference cards and annexes

Ready reference cards

READY REFERENCE CARD 1: Yellow fever AEFI notification report

READY REFERENCE CARD 2: Serious AEFI report/evaluation

READY REFERENCE CARD 3: Weekly summary of yellow fever AEFI

READY REFERENCE CARD 4: Viscerotropic and neurologic yellow fever AEFI case definitions

READY REFERENCE CARD 5: Serious AEFI investigation record

READY REFERENCE CARD 6: Request to perform laboratory tests

READY REFERENCE CARD 7: Monitoring of weekly AEFI reports

READY REFERENCE CARD 8: Procedure in the event of anaphylactic shock

READY REFERENCE CARD 9: Incidence of AEFI by age group

Annexes

ANNEX 1: List of AEFI surveillance activities

ANNEX 2: Estimate of expected number of cases by AEFI type

ANNEX 3: Definition of AEFI types

ANNEX 4: Detection of serious AEFI/warning signs

ANNEX 5: Etiology of AEFI

ANNEX 6: Laboratory input: clinical specimens collection and management procedures

ANNEX 7: Information to be obtained during an investigation

ANNEX 8: Treatment of AEFI

ANNEX 9: Some advice on communicating about AEFI

READY REFERENCE CARD 1.
Yellow fever AEFI notification report

Health facility information	**Patient information**
Health region:	Surname:
Health district:	First name:
Health facility:	Address and contact information:
If general infirmary, specify unit:	Age: years. Sex: ☐ M ☐ F
Health worker:	
Date of notification: ... / ... /	

Vaccination information

Vaccination card: ☐ Yes ☐ No,

if No, other source of information:

Place of vaccination/village/vaccination point:

Date of vaccination: ... / ... / .....

Vaccine:

Mode of administration: ☐ Subcutaneous ☐ Intramuscular

Site of administration: ☐ Right arm ☐ Other:

	Manufacturer	**Batch number**	**Expiry date**
Vaccine			... / ... / .....
Diluent			... / ... / .....

Description of AEFI observed

Date of onset of initial symptoms: ... / ... / .....

Fever: ☐ Yes ☐ No, if Yes, specify:_____°C, Date of fever peak: ... / ... / .....

Headaches: ☐ Yes ☐ No

Local reaction at injection site: ☐ Yes ☐ No,

if Yes, specify: ☐ Pain ☐ Redness

☐ Swelling/oedema ☐ Skin lesion, if Yes, purulent? ☐ Yes ☐ No

☐ Other local reaction:_____

Skin or mucous tissue reaction: ☐ Yes ☐ No, if Yes, Specify, Date of onset: ... / ... / .....

Rash/itching: ☐ Yes ☐ No, if Yes, Site:_____

Eczema: ☐ Yes ☐ No, if Yes, Site:_____

Conjunctivitis: ☐ Yes ☐ No. Other skin/mucous tissue reaction:_____

Swelling/oedema: ☐ Yes ☐ No, if Yes, Date: ... / ... / ..... Site:_____

Respiratory problem: ☐ Yes ☐ No, if Yes, Date: ... / ... / ..... Specify:_____

Gastrointestinal problem: ☐ Yes ☐ No, if Yes, Date of onset: ... / ... / .....

☐ Nausea ☐ Vomiting ☐ Diarrhoea

☐ Stomach pain ☐ Other:_____

Anaphylactic shock (collapsus): ☐ Yes ☐ No

Muscle pain: ☐ Yes ☐ No

Jaundice: ☐ Yes ☐ No, if Yes, Date of onset: ... / ... / .....

Neurological involvement: ☐ Yes ☐ No, if Yes, Specify type:_____Date of onset: ... / ... / .....

Mental status change: ☐ Yes ☐ No, if Yes, Specify:_____

Seizures: ☐ Yes ☐ No

Viscerotropic disease: ☐ Yes ☐ No, if Yes, Describe:_____

Haemorrhage: ☐ Yes ☐ No, if Yes, Describe:_____

Other signs observed or other laboratory test results:_____

Presumed diagnosis:_____

Treatment and outcome

Treatment(s) administered:_____

Patient hospitalized: ☐ Yes ☐ No, if Yes, Date of admission: ... / ... / .....

Date of discharge ... / ... / ..... (If exact dates unavailable, duration:_____days)

Status of patient on discharge: ☐ Cured ☐ In remission

☐ Other:_____

Patient recovered fully: ☐ Yes ☐ No, if Yes, Date: ... / ... / .....

Patient recovered with sequelae: ☐ Yes ☐ No,

if Yes, describe sequelae and date of assessment:_____

Patient deceased: ☐ Yes ☐ No, if Yes, Date: ... / ... / .....

Cause of death:_____

Autopsy done: ☐ Yes ☐ No, if Yes, Date of autopsy: ... / ... / .....

Results (if available):_____

READY REFERENCE CARD 2.
Serious AEFI report/investigation (mobile team)

Team No._____or District/regional clinician name:_____

Date: ... / ... / .....

Demographic data

Surname	**First name**	**Date of birth** (dd/mm/yy) **Notification number:** ... / ... / ...
Address:		Sex:
District:		Province/region:
Health centre:		Health worker:
Place of vaccination:		

Details of vaccine

Vaccine			**Diluent**		
Batch number	**Manufacturer**	**Expiry date**	**Batch number**	**Manufacturer**	**Expiry date**

Details of vaccination/evaluation

Date of vaccination	**Date of onset of AEFI**	**Date of evaluation**	**Date of notification**	**Date specimen taken**
... / ... /	... / ... /	... / ... /	... / ... /	... / ... / .....

History: Medical:_____
Vaccination:_____

Clinical history and other relevant information
(other cases, symptomatic treatment received, etc.)

Development: Recovery: ☐ Yes ☐ No Hospitalization: ☐ Yes ☐ No
Death: ☐ Yes ☐ No

Name and signature of investigators:

Committee of experts on AEFI

Date report received:	Seen by:
Investigation necessary: ☐ Yes ☐ No,	if Yes, when?

READY REFERENCE CARD 3.
Weekly summary of yellow fever AEFI (serious and non-serious)

Week from: ... / ... / ..... to: ... / ... / .....

Health district:_____.Health facility/hospital:_____.Number of declared AEFI:_____

No.	Surname, first name	Age (years)	Vacc. card (Y/N)	Date and place of vaccination	Vaccine batch no.	Date of AEFI	Description of AEFI	Treatment	Hospitalized	Cinical development	Notification (Y/N)

Name of person notifying:_____Date and signature:

READY REFERENCE CARD 4.
Viscerotropic and neurologic yellow fever AEFI

I) VISCEROTROPIC YELLOW FEVER AEFI

Warning signs during epidemiological surveillance	**Fever (> 38°C, > 24h duration) and one or more of the following signs:** • Nausea • Vomiting • Malaise (duration > 72 hours) • Muscle pain (duration > 24 hours) • Arthralgia (duration > 24 hours) • Dyspnea
Clinical signs and symptoms of disease	• Jaundice (total bilirubin ≥ 1.5 times normal) • Liver failure (elevation of AST and ALT ≥ 3 times above normal) • Kidney failure (BUN and creatinine ≥ 1.5 times above normal with no history of renal disease) • Tachycardia (heart rate > 100 beats per minute) or bradycardia (< 50 beats per minute) • Rhabdomyolysis (≥ 5 times normal CPK) • Respiratory distress (shortness of breath, ventilation or oxygenation impairment) • Thrombocytopenia (platelets < 100 000 / µl) • Hypotension (systolic blood < 90 mm Hg for adults or less than fifth percentile by age for children < 16 years; diastolic blood pressure ≥ 15 mm Hg at rest, orthostatic syncope or dizziness) • Myocarditis (abnormalities indicated by ECG, ECHO or cardiac enzyme changes, or inflammation visible on tissue biopsy) • Disseminated intravascular coagulation (elevation of prothrombin time or activated partial thromboplastin time with fibrin split products) • Haemorrhage

II) NEUROLOGIC YELLOW FEVER AEFI

Warning signs during epidemiological surveillance	At least one of the following signs: • Fever (> 38°C, > 24 hours) and headache (> 24 hours duration) • Focal neurologic dysfunction (including but not limited to: ataxia, aphasia and paralysis) • Mental status change (confusion, lethargy or personality change > 24 hours) • New onset seizure or recurrence of previously controlled seizures • CSF pleocytosis (≥ 5WBC / mm^3) • Elevated CSF protein (> 1.5 times normal limit)
Neurotropic disease clinical signs and symptoms	At least one of the following signs: • Neuroimaging consistent with inflammation • EEG finding consistent with encephalopathy
Autoimmune disease with central nervous system involvement (signs of disease)	One of the following signs: • Neuroimaging consistent with multifocal or disseminated areas of demyelination
Autoimmune disease with peripheral nervous system involvement (signs of disease)	**Does NOT require presence of altered mental status or seizures and some the following signs:** • Limb weakness with decreased or absent tendon reflexes • Cranial nerve abnormalities • Autonomic dysfunction (including but not limited to: postural hypotension, arrhythmias, abnormal sweating, gastric motility abnormalities) • Numbness or paresthesias • Electromyography finding consistent with GBS • Confirmed neuromuscular respiratory failure (pulmonary function testing, arterial blood gas, diaphragmatic elevation) or the need for ventilatory support

READY REFERENCE CARD 5.
Serious AEFI investigation record (hospitalization)

Notification number:_____ Presumed diagnosis:_____

DEMOGRAPHIC DETAILS

Surname:	First name:	Date of birth:	Sex: ☐ Female ☐ Male
		... / ... /	
District of residence:		Village:	
Address:		Contact (tel):	
Date of vaccination: ... / ... /	Vaccine manufacturer and batch no.:	Diluent manufacturer and batch no.:	Date of onset of AEFI: ... / ... / .....

INVESTIGATION

Investigators and job titles:	**AEFI investigation No.:**
	Date of investigation: ... / ... / .....
	Site(s) of investigation:

Cause of suspected AEFI: ☐ Vaccine reaction ☐ Programme error ☐ Coincidental event ☐ Unknown

Specify type of serious AEFI suspected *(tick box)*

☐ Encephalitis	☐ Thrombocytopenia	☐ Death
☐ Encephalopathy	☐ Rhabdomyolysis	☐ Anaphylactic shock/reaction
☐ Cranial nerve abnormalities	☐ Kidney failure	☐ Other:
☐ GBS	☐ Liver failure	

1. Clinical examination: ☐ Yes ☐ No,

if Yes, clinical description:_____

2. Additional investigation results:

General tests:	**Specific tests:**

3. Results of laboratory tests carried out prior to the investigation:_____

4. Condition of patient: ☐ Alive ☐ Comatose ☐ Recovered ☐ Deceased, Date: ... / ... / .....

5. Treatment(s) prior to investigation:

6. Specimens for laboratory analysis

☐ Blood,	Date: ... / ... / .....
☐ CSF,	Date: ... / ... / ....., aspect:
☐ Urine,	Date: ... / ... / .....
☐ Stool,	Date: ... / ... / .....
☐ Tissues:	Date: ... / ... / .....
☐ Vaccine, batch:	Date: ... / ... / .....
☐ Diluent,	Date: ... / ... / .....

7. Laboratory tests *(complete the laboratory test request form, Ready Reference Card No. 6)*

Specimen	Laboratory test(s) considered	Laboratory test(s) requested	Date specimen received at laboratory/ies
Blood			... / ... / .... / ... / .....
CSF			... / ... / .... / ... / .....
Urine			... / ... / .... / ... / .....
Stool			... / ... / .... / ... / .....
Tissues:			... / ... / .... / ... / .....
Vaccine			... / ... / .... / ... / .....
Diluent			... / ... / .... / ... / .....

8. Conclusions of investigation (based on information available at time of investigation)

Diagnosis:

Cause:

- **Vaccine reaction:** ☐ Yes ☐ No,
  if Yes, assess likelihood: ☐ Very likely ☐ Likely ☐ Plausible ☐ Doubtful
- **Coincidental event:** ☐ Yes ☐ No
- **Programme error:** ☐ Yes ☐ No,
  if Yes, specify reason (tick as appropriate):
  ☐ Defective cold chain
  ☐ Vaccine reconstitution error
  ☐ Incorrect injection technique
  ☐ Non-sterile handling
- **Unknown:** ☐ Yes ☐ No

Remedial action taken:

Investigators and job titles:	Signatures:

READY REFERENCE CARD 6. Request to perform laboratory tests

(for clinical specimens and samples of vaccine, diluent, needles or syringes)

Patient's surname: **Patient's first name:**

Address/village:

District: **Region:**

Date of birth: ... / ... / ..... *or* age: years Sex *(circle)*: Female - Male

Date of onset of initial symptoms: ... / ... / .....

Description of symptoms:

Specimens taken and dates: *(circle specimens taken)* Blood/serum: ... / ... / ..... CSF: ... / ... / ..... Stool: ... / ... / .....

Vaccine specimen: ... / ... / ..... Diluent specimen: ... / ... / ..... Other: ... / ... / .....

Describe transport arrangements
(dry ice, thermal accumulators?):

Tests requested:

Blood/serum:

CSF:

Vaccine specimen:

Diluent specimen:

Other:

Presumed/preliminary clinical diagnosis:

Contact details of person forwarding the results:

Surname and first name:

Full address:

Telephone number: Fax number:

E-mail:

READY REFERENCE CARD 7.
Monitoring of weekly AEFI declarations

Every week, this table will enable the district focal point for AEFI surveillance to collate notification data communicated by health facilities.

Region:	**District:**		
Week from: ... / ... /	**to ... / ... / .....**		
	Data communicated	**Number of non-serious AEFI**	**Number of serious AEFI**
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Health facility	☐ Yes ☐ No		
Total communications			

This weekly summary should be completed by the person responsible for AEFI surveillance in the district and forwarded every week to the regional level.

READY REFERENCE CARD 8.
Procedure in the event of anaphylactic shock

Anaphylaxis is a very rare (estimated as 0.8 / 100 000 doses of vaccine given) but serious and potentially fatal allergic reaction. **When anaphylaxis does occur, the patient must be diagnosed properly, treated and managed urgently by trained staff and transferred to a hospital setting.**

Patients in anaphylactc shock have a life-threatening condition; intravenous solutions should be administered and possibly an endotracheal intubation performed. These interventions should preferably be performed in a hospital setting. A qualified physician may in addition use other medicines: hydrocortisone, antihistamines, salbutamol spray (for bronchospasm) and adrenaline spray (for laryngeal oedema). Persons unfamiliar with these treatments should not administer them in a primary care context.

If the patient is already unconscious, place in the recovery position and ensure airways are unblocked.

1. Note heart rate, breathing rate and blood pressure; if the carotid pulse is strong, it is probably not anaphylactic shock.
2. If necessary, start CPR.
3. Administer adrenaline 1:1 000 (see table below for correct dosage for age or weight) by deep intramuscular injection in the limb opposite the limb where the vaccine was administered (subcutaneous administration is acceptable in benign cases), and inject an additional half-dose around the injection site to slow the absorption of antigens.
4. If the patient regains consciousness following administration of adrenaline, place feet at a level above the head and keep warm.
5. Administer oxygen by face mask if this equipment is available.
6. Call for assistance, but never leave the patient alone. Call an ambulance (or find another means of transport) and a physician if necessary, following the first injection of adrenaline or earlier if the person administering the adrenaline is not alone. As soon as anaphylactic shock has been diagnosed, do not wait for more qualified personnel to attend before administering adrenaline.
7. If the patient's condition does not improve within 10 or 20 minutes of administering the initial injection, repeat the adrenaline dose (three times maximum). Recovery from anaphylactic shock is generally rapid following injection.
8. Note or ask another person to record vital signs (pulse, breathing rate and blood pressure) and note the time of administration and the exact dose of all the medicines used. These details should not be lost when the patient is transferred. Give sufficiently clear warning on the vaccination card that the holder should never again be given the vaccine that triggered the anaphylactic shock. At an appropriate time, explain to close relatives or friends that the same vaccine should on no account be administered again.
9. Once the situation has returned to normal, alert the relevant official at the Ministry of Health by telephone, radio or fax that an anaphylactic shock has occurred.

Adrenaline dosage

Adrenaline **1:1 000** corresponds to a dose of **0.01 ml / Kg**, with a **maximum dose of 0.5 ml**, injected intramuscularly (or subcutaneously in truly benign cases). If the patient's weight is not known, refer to the table below for approximate weight based on the patient's age.

Age of patient	Dosage
< 2 years	0.0625 ml (1 / 16 ml)
2 – 5 years	0.125 ml (1 / 8 ml)
6 – 11 years	0.25 ml (1 / 4 ml)
> 11 years	0.5 ml (1 / 2 ml)

READY REFERENCE CARD 9.
Incidence of AEFI by age group

Age group	Number of AEFI	Number of doses distributed	Incidence per 100 000
< 1 year			
1 – 4 years			
5 – 14 years			
15 – 59 years			
> 60 years			
No information			

ANNEX 1. Checklist of AEFI surveillance activities

- **AEFI surveillance activities and tools**
  - Preparation and publication of guidance material and resources for AEFI surveillance.
  - Training/awareness-raising for periphery-level health workers in detection and notification of AEFI.
  - Administrative costs connected with notification activities.
  - Monitoring/control of AEFI surveillance.
  - Data input, management and analysis.
  - Drafting the AEFI surveillance report and disseminating results.

- **Serious AEFI investigation activities**
  - Forecasting costs connected with preparation of investigation missions.
  - Transport of blood and tissue samples from organs.
  - Forecasting costs associated with investigation missions (including drafting investigation reports).

- **Management of certain AEFI**
  - Free availability of medicines to treat AEFI at health and vaccination facilities.

- **Communication in response to rumours may include**
  - Communication with local and national media.
  - Press conference.
  - Print media, posters.

- **Conducting an AEFI survey**
  - Elaboration of protocol.
  - Preparation and publication of survey materials.
  - Training investigators.
  - Remunerating investigators.
  - Supervision of the survey.
  - Data input, management and analysis.
  - Preparation of survey report and dissemination of results.

ANNEX 2. Estimate of expected number of cases by AEFI type

	Non–serious AEFI	Serious AEFI	Hypersensitivity reactions	Neurologic problems	Viscerotropic diseases	Anaphylaxis reaction
Signs	Oedema and/or pain, hematoma, induration/swelling	Death, life-threatening, hospitalized, significant disability	Rash, urticaria, asthma	Neurotropic disease (meningoencephalitis); Autoimmune disease (acute disseminated encephalomyelitis) Guillain-Barré syndrome	Mimic yellow fever wild-type disease, typically progresses to hypotension or shock and multi-organ failure associated with jaundice and/or bleeding.	Anaphylactic shock, a life-threatening condition
No. of cases/ No. of doses	25 / 100[1]	1.6 / 100 000[2]	1 / 130 000 to 1 / 250 000[1]	0.4-0.8 / 100 000[3]	0.4 / 100 000[4]	0.8 / 100 000[5]

These estimates will help to facilitate preparation of the budget for surveillance, treatment and investigation of AEFI.

1. Kelso JM. *J Allergy Clin Immunol* 1999;103:698-701
2. Khromova et al. *Vaccine* 2005;23:3256-63
3. Mc Mahon AW et al. *Vaccine* 2007;25:1727-34
4. WHO. *World Epidemiological Review* 2008;32:285-92
5. Hayes E. *Trans R Soc Trop Med Hyg* 2007;101:967-71

ANNEX 3. Detecting a serious adverse event following yellow fever vaccination

1. Non-serious AEFI		
Adverse event	**Signs or symptoms**	**Onset**
Fever	Fever is defined as the endogenous elevation of at least one measured body temperature of ≥ 38°C.	1-5 days
Muscle pains	Muscle pains, often diffuse. In 30% of cases they may be psychogenic. If they are severe and long-lasting, they can lead to rhabdomyolysis, with high levels of serum potassium and kidney failure.	5-10 days
Local reaction at injection site	Any description of morphological or physiological change at or near the injection site.	0-7 days
Gastrointestinal syndrome (nausea and vomiting)	Nausea: unpleasant sensation of wanting to vomit. Various synonyms such as gagging, retching or heaving; vomiting: ejection of the contents of the stomach and sometimes the upper small intestine via the mouth.	0-5 days
Abscess at injection site	Abscess at injection site is a localized soft tissue collection of material occurring at the site of immunization and defined by abscess of infectious etiology, where there is spontaneous or surgical drainage of material from the mass AND laboratory confirmation (Gram stain, culture or other tests) of microbiological organisms with or without polymorphonuclear leukocytes in material drained or aspirated from mass. Abscesses may be accompanied by fever and/or regional lymphadenopathy.	0-7 days
Seizure	Case definition of generalized convulsive seizure • witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.	0-15 days

2. Serious AEFI vaccine-related			
Yellow fever vaccine-associated neurologic disease			
Neurologic syndromes and definitions	**Signs or symptoms**	**Laboratory findings**	**Onset**
Encephalitis – inflammation of the Brain	Fever, altered mental status (encephalopathy) and/or focal neurologic findings, focal weakness, cranial nerve palsies, seizures	• Cerebrospinal fluid (CSF) pleocytosis • CSF protein elevation • Clear CSF with negative gram stain	Approximately 2-30 days
Meningitis – inflammation of the covering of the brain	Fever, headache, meningismus (nuchal rigidity, photo/phonophobia)	• Cerebrospinal fluid (CSF) pleocytosis • Clear CSF with negative gram stain	Approximately 2-30 days
Anterior myelitis – inflammation of spinal cord motor neurons	Asymmetric limb weakness/paralysis, sensory loss generally absent	• CSF pleocytosis, • CSF protein elevation	Hours to days
Guillain-Barré syndrome (GBS) – autoimmune disease of peripheral nerves	«Ascending» weakness, legs to arms, generally symmetric, hypo - or areflexia, ascending pain or dysesthesias, objective numbness generally absent	Cytoalbuminologic dissociation – elevated CSF protein in absence of pleocytosis	Onset generally 1-4 weeks after event
Acute disseminated encephalomyelitis – autoimmune CNS demyelinating process	Altered mental status, cranial nerve palsies, focal weakness, ataxia	CSF: pleocytosis (often less than acute encephalitis), elevated protein	3-30 days

Yellow fever vaccine-associated viscerotropic disease			
Clinical syndromes	**Signs or symptoms**	**Laboratory findings**	**Onset**
Haemorrhage	Epistaxis, bleeding gums, purpura, petechiae, ecchymosis or other signs of spontaneous bleeding	Elevation of prothrombin time or activated partial thromboplastin time	1-10 days
Hepatic insufficiency	Jaundice, abdominal pain, nausea, vomiting, diarrhea, bleeding	Transaminases AST (SGOT) and ALT (SGPT) levels ≥ 3 times normal Total serum bilirubin ≥ 1.5 times normal	1-10 days
Hypotension/shock	Cool extremities, poor/absent pulse	Capillary refill time > 3 seconds, systolic blood pressure < 80, tachycardia	1-10 days
Myocarditis	Hemodynamic instability	ECG abnormalities	1-10 days
Renal insufficiency	Oliguria, anuria, hematuria, proteinuria	Serum creatinine ≥ 1.5 times normal oliguria < 500 cc / 24 hours Urinalysis reveals hematuria, proteinuria	1-10 days
Respiratory insufficiency	Dyspnea, hypoxia	Abnormal chest X-ray	1-10 days
Rhabdomyolysis	Myalgias, red/brown urine due to myoglobinuria	CPK > 5 times normal; hyperkalaemia and hyperphosphatemia result from the release of potassium and phosphorus from damaged muscle cells Pigmented casts Metabolic acidosis is common	1-10 days

3. Severe hypersensitivity reaction		
Adverse event	**Signs or symptoms**	**Onset**
Anaphylactic shock/anaphylactoid	Cardiovascular collapse (e.g. altered consciousness, low blood pressure, weakness or absence of peripheral pulse, cold extremities) may be accompanied by bronchospasm, laryngospasm, laryngeal edema or all of these symptoms with respiratory insufficiency that manifests immediately after the vaccination.	Immediate

Sources: WHO. *Detection and investigation of serious adverse events following yellow fever vaccination: Guidance from an informal consultation of experts.* 18-19 November 2008 Geneva; Brighton Collaboration Anaphylaxis Working Group *(http://www.brightoncollaboration.org/internet/en/index/definition___guidelines.html)*

ANNEX 4. Detection of serious AEFI/warning signs

Adverse event	**Warning signs**	**Laboratory/*clinical examination***
Encephalitis	Mental status change, convulsions, behavioural problems: agitation, prostration	Cytobacteriology of CSF *Convulsions or mental status change*
Guillain-Barré syndrome	Ascendant flaccid paralysis	Cytobacteriology of CSF *Abnormalities of gait initially (duck walk), ascendant paralysis subsequently*
Paresis of cranial nerves	Signs of neurological deficiency	*Paralysis of one of the XII cranial nerves, impaired sense of smell, acute loss of vision, facial paralysis, trouble swallowing, hearing problems, double vision etc.*
Liver failure	Jaundice (with or without encephalopathy)	AST (SGOT) and ALT (SGPT) > 1 000 IU / L Bilirubin, alkaline phosphatases, gamma GT. *Jaundice or digestive symptoms (nausea and vomiting)*
Rhabdomyolysis	Dark red-brown urine	Myoglobulinuria, CPK, hyperkalaemia
Kidney failure	Oligo-anuria (volume of urine < 500 cc)	Creatininemia reaching concentrations of 3-12 mg / dl, proteinuria, oliguria < 500 cc, haematuria consistent with cylindruria. *The patient consults for haematuria (or oliguria).*
Thrombocytopenia	Bleeding from nose, gums, skin or other signs of haemorrhage	Platelet count < 50 000 / ml; blood count: leucocytosis (neutrophils and large numbers of immature neutrophils), possible leucopenia (with lymphocytosis + eosinophilia)
Death		Detection of viral involvement in the organs (viral Ag in tissues); detection and culturing of virus in tissues and blood; genome sequencing

ANNEX 5. Etiology of AEFI

AEFI due to programme error

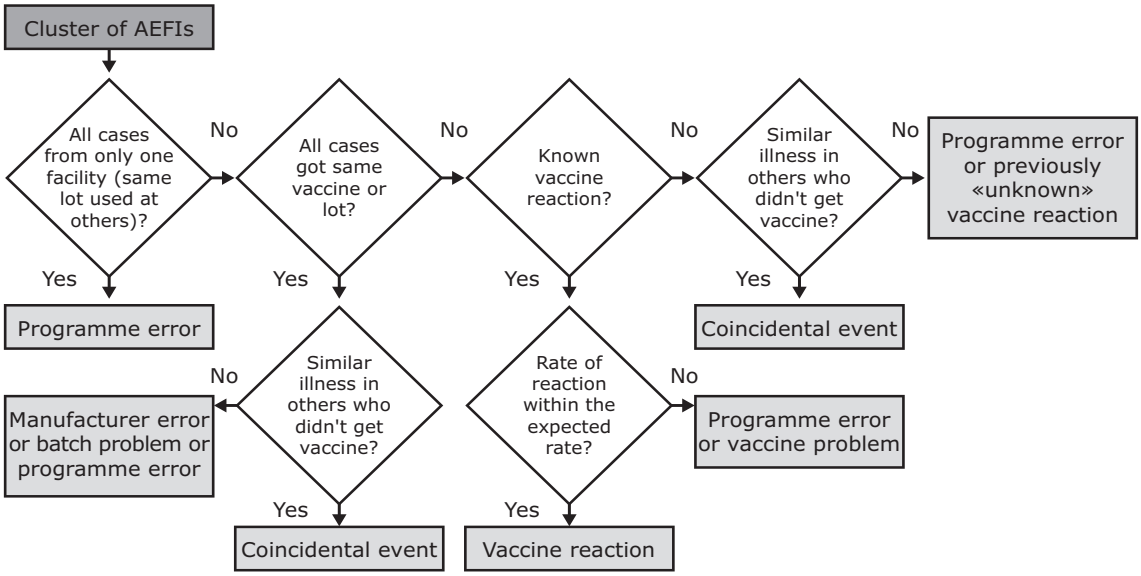
During a mass immunization campaign, programme-related faults are the most frequent cause of AEFI. Consequently, the investigation team should begin by looking for evidence of faults in the storage, handling or administration of vaccines.

Here is a list of common faults that could guide the investigation team if the cause of the AEFI is not immediately apparent:

- administration of too much vaccine;
- vaccination performed at the wrong site;
- poorly sterilized syringes or needles;
- careless handling of used needles;
- reconstitution of the vaccine using the wrong diluent;
- incorrect quantity of diluent;
- incorrect preparation of the vaccine;
- use of a medicine instead of the vaccine or the diluent;
- contaminated vaccine or diluent;
- incorrect storage of vaccine;
- failure to observe contraindications for the vaccine, such as specified for the vaccination campaign;
- reuse of vaccine left over from a previous vaccination session (which should have been disposed of).

Additionally, in the case of a cluster of AEFI, the team should carefully review all cases in the cluster to determine the likely cause; Figure 1 below is provided as guide to arriving at the most likely cause. It is important to note that this is not intended as a firm conclusion on the cause for the scenarios depicted. The team should be able to arrive at conclusions for each investigation based on the specific details of the cluster and other information obtained. If the investigation team is unable to exclude the possibility of a programme error, it should proceed to examine the possibility of a vaccine reaction or a coincidence.

Figure 1. Suggested steps for the identification of the most likely cause of a cluster of AEFI*



Vaccine reactions

Vaccine reactions occur when an individual experiences a reaction to a particular vaccine. It is unlikely that more than one person will experience the same reaction to the same vaccine administered during the same session. This category of AEFI also includes *incidents precipitated by vaccines* (extremely rare cases): these are, these are incidents for which the vaccinee has a pre-existing risk but which were brought on by the vaccination (for example, simple febrile convulsion in a child with a family history of the same symptom). Most vaccine reactions are mild and of short duration. They involve, for example, minor generalized reactions such as fever and exanthema and local reactions such as redness, sensitivity and pain at the injection site. Reactions at the injection site occur in fewer than 10% of vaccinated persons. Deaths following vaccination, either resulting from a reaction to the vaccine or a programme error, are rare.

In the case of vaccine reactions, as for other AEFI, it may be that no definitive conclusion is possible based on the available information.

Coincidental AEFI

These are due to neither a programme error nor a true vaccine reaction. They are incidents that would have occurred even if no vaccine had been administered. The only connection between this type of AEFI and vaccines and vaccinations is coincidence in time.

AEFI of unknown origin

The final category includes incidents of unknown origin, where it is impossible to determine whether the adverse event is due to a vaccine, a programme error or a coincidence.

*Reproduced from *Immunization safety surveillance : guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization*, Manila, World Health Organization, Regional Office for the Western Pacific, 1999.

ANNEX 6. Laboratory input: clinical specimens collection and management procedures

The laboratory's most important function in AEFI surveillance is to confirm medical incidents and to confirm or rule out whether adverse events are attributable to vaccination.

Clinical specimens relating to AEFI are normally collected at the time of the investigation; in rare cases (as when the patient is hospitalized) the results of laboratory tests are available before the investigation.

Clinical specimens should be collected from patients experiencing serious AEFI. The specimens to be collected depend on the AEFI observed. Arrangements for specimen preservation are described in Table 1 below. Where investigators suspect a serious AEFI (i.e. one of those listed in Annex 3, with the exception of anaphylactoid reaction and anaphylaxis), suggested steps can include the following:

- Detection of the yellow fever virus using a specimen of the patient's serum (in a yellow fever reference laboratory) should be routine procedure.
- Samples of the vaccine and the diluent used (from the same batch number) should also be collected and forwarded to the laboratory (tests will normally be carried out in a specialized reference laboratory; see Table 2).
- Some comprehensive laboratory tests on specimens cannot be performed in the country; they must be sent to a specialized laboratory, normally a WHO Collaborating Centre. The arrangements for the preservation and forwarding of clinical specimens to specialized international laboratories are set out in Table 3.

Testing of the specimen makes it possible to determine whether:

- the vaccine in the vial corresponds to the description on the label;
- the vaccine has been incorrectly handled (for example, whether it has been frozen or stored at a temperature in excess of the recommended limit); or
- the vaccine has been contaminated.

Table 1. Collection and storage of specimens for testing at a national laboratory

Adverse event	Type of specimen to be collected	Recommended volume	Preservation	Temperature	Diagnosis	Comments
Encephalitis	CSF	5 ml	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture	
Guillain-Barré syndrome	CSF	5 ml	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture	
Paresis of cranial nerves	CSF and serum	5 ml of CSF 5 ml of serum	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture, serological tests	
Liver failure (jaundice)	Serum	5 ml	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Serological tests	
Rhabdomyolysis	Urine, serum	10 ml of urine 5 ml of serum	Cold packs for urine specimens to be processed in < 24h; otherwise frozen; specimen of CSF frozen	+4°C Freezing at -80°C (if possible, otherwise -20°C)	Urine test (myoglobin), serological tests (CPK)	
Kidney failure	Urine, serum	10 ml of urine 5 ml of serum	Cold packs for urine specimens to be processed in < 24h; otherwise frozen; specimen of CSF frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture, serological tests	
Thrombocytopenia	Serum, plasma	5 ml of serum 5 ml of plasma	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture, serological tests	
Mental status change	LCR, serum	5 ml of CSF 5 ml of serum	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture, serological tests	
Anaphylactic reaction	Serum	5 ml	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture, serological tests	History of allergy to egg protein
Anaphylactic shock	Serum	5 ml	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Detection of viral RNA, viral culture, serological tests	History of allergy to egg protein
Death	**Tissue specimens** (in order of preference): 1. Liver 2. Brain with meninges 3. Kidney 4. Spleen 5. Pancreas 6. Heart 7. Lung 8. Suprarenal glands 9. Skin 10. Thymus	3-4 cm of each organ (~ 1g of each organ)	a) Snap frozen (liver tissue)	a) Freezing at -80°C (if possible, otherwise -20°C)	a) Detection of viral RNA and viral culture	• For fresh organs (not yet fixed), the specimens should be frozen immediately. • Fixing in formol is not recommended for viral diagnosis because prolonged immersion (> 24H) of tissue in formol leads to deterioration of RNA. • DO NOT FREEZE solid organs fixed in formol or any other preserving medium
			b) Solid organ fixed in RNA Later (Ambion)	b) RNA Later at +4°C	b) Detection of viral RNA	
			c) Solid organ fixed in formol	c) Formol at +4°C	c) Detection of viral RNA	
			d) Solid organ fixed in paraffin	d) Paraffin at +4°C	d) For anatomico-pathological investigation	
	Blood specimens • Cardiac puncture	1 specimen of 2 ml of blood 2 specimens of 5 ml of serum	• Freezing of one blood specimen and one serum specimen • One fresh serum specimen	1 specimen of blood at -80°C (if possible, otherwise -20°C); 1 specimen of serum at -80°C (if possible, otherwise -20°C); 1 specimen of serum at +4°C	Serological tests	Freeze immediately at -80°C.
	Lymph node specimens Two nodes from the side on which the injection was performed	2 specimens of lymph fluid, 2 ml each.	Freezing, preservation in formol	Freezing at -80°C (if possible, otherwise -20°C); formol at +4°C	Detection of viral RNA	

Table 2. Storage and transport of vials of vaccine (from same batch as administered to patient) to international reference laboratory

Vaccine	Recommended volume	Storage	Transport	Others
In freeze-dried form (preferable)	Vial	+4°C	Cold pack	Freeze-drying is preferable to rehydration
In rehydrated form	At least 1 ml by vial	-70°C	Dry ice or cold packs	Freeze immediately at -70°C.

Table 3. Storage and transport of specimens to the international reference laboratory

Type	Recommended volume	Storage	Temperature	Transport	Comments
Serum, CSF, pleural liquid	1-2 ml	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Dry ice or cold packs	Use test tubes appropriate for storage at low temperature (e.g. cryotubes)
Whole blood		Ambient temperature			Currently, sending whole blood presents no diagnostic advantages
Fresh solid organ (liver, brain with meninges, kidney, spleen, pancreas, heart, lung)	~ 1 g	Ambient temperature	Ambient temperature	Dry ice or cold packs	Use test tubes appropriate for storage at low temperature (e.g. cryotubes); freeze specimens immediately after removal
Solid organs (liver, brain with meninges, kidney, spleen, pancreas, heart, lung) fixed in formol or similar preserving medium (for example, **RNA Later**)	Representative specimens	Ambient temperature	Ambient temperature	Cold packs	• **RNA Later (Ambion)** solution stabilizes RNA and facilitates extraction of viral RNA for detection. • Fixing in formol is not recommended for diagnosis because prolonged immersion (> 24H) of tissue in formol leads to deterioration of RNA. • DO NOT FREEZE solid organs fixed in formol or any other preserving medium.
Solid organs (liver, brain with meninges. kidney, spleen, pancreas, heart, lung, thymus) in paraffin	Portions of representative specimens	Ambient temperature	Ambient temperature	Cold packs	DO NOT FREEZE solid organs in paraffin
Skin fixed in formol or other similar preserving medium	Representative specimens	Ambient temperature	Ambient temperature	Cold packs	DO NOT FREEZE solid organs fixed in formol or any other preserving medium
Postmortem cardiac serum (using direct cardiac puncture)	2 ml	Frozen	Freezing at -80°C (if possible, otherwise -20°C)	Dry ice or cold packs	Freeze IMMEDIATELY at -80°C.

Management, preparation and transport of yellow fever AEFI specimens

General observations

Each clinical specimen should be:

- individually labelled with a unique identification number (AEFI number, for example);
- marked with a collection date (dd/mm/yyyy); and
- packaged separately from other specimens.

Information

The following information should be provided for each patient:

- identification of the specimen collected;
- surname and first name, or surname code (3 letters) and first name code (2 letters) to ensure personal confidentiality (names can be sent separately from the specimens by e-mail);
- sex;
- date of birth;
- date of vaccination;
- date specimen collected;
- nature of specimen and quantity (volume); and
- patient's clinical signs and detailed clinical history (the information on AEFI notification and investigation records).

Clinical specimens

Efforts should be made to ensure that clinical specimens are collected and processed in hygienic conditions to avoid contamination. Autopsy specimens should be frozen immediately after collection (Table 1).

Preservation and transport of specimens

Use strong, leakproof plastic containers (with caps if possible) resistant to low temperatures (freezing); for example, Nunc or CryoTube vials. It is possible to use glass containers but these are vulnerable to breakage in transport. If possible, make up several 500 µl or 500 mg aliquots from the original specimens.

All the specimens should be wrapped in cloth and placed in a second container to avoid contamination in the event of leakage. The packages should be properly insulated and thermal accumulators added if necessary to ensure that the specimens are properly preserved in transport.

Exchange of information before sending

The laboratory receiving the specimens should be notified in advance that they have been shipped. As soon as the package has been deposited with the carrier, the carrier's name and package reference number should immediately be communicated to the receiving laboratory by e-mail or fax.

Solid organ specimens

Organ specimens can only be tested if they are frozen immediately after collection and remain frozen until arrival at their destination. It is recommended that specimens be collected from the following organs (Table 1):

1. Liver
2. Brain
3. Kidney
4. Spleen
5. Heart/pancreas/skin

Vaccine

A specimen of the batch of vaccine that was administered to the patient with a suspected serious AEFI should also be sent to the laboratory if possible. The vaccine specimen should be stored according to the manufacturer's instructions (or at +4°C) (Table 2).

Differential diagnosis

All specimens relating to suspected yellow fever AEFI should be tested for the following diseases:

- Hepatitis B, C, D
- Yellow fever
- Malaria
- HIV
- Leptospirosis
- Viral haemorrhagic fevers
- Typhoid fever
- Dengue

ANNEX 7. Information to be obtained during an investigation

Information	Source
1. Information to be obtained in all cases	
Proof of vaccination and details of vaccine administered (manufacturer, batch number, expiry dates of vaccine and diluent)	Vaccination card
Age, sex and contact address	Vaccination card/patient or relative/friend
State of health at time of vaccination	Patient, relative/friend or vaccinator
Past history of similar reactions (description)	Patient or relative/friend
Clinical course/results of clinical examination/patient's state of health at time of investigation/diagnosis at time of investigation (specific clinical and laboratory tests can be carried out depending on the AEFI suspected and the likely cause)	Patient or relative/friend, medical file, health worker
Results of laboratory tests conducted prior to and during the investigation (Annex 6 lists laboratory tests to be performed by type of AEFI suspected)	Health worker/medical file/test laboratory
Similar reaction among patient's relatives or friends or in the same geographical area (description)	Patient or relative/friend and neighbouring health centres/hospital
2. Information to be obtained where vaccine reaction is suspected	
Preservation/management of the cold chain	Depending on the vaccination facility/post, obtain temperature readings from the various vaccine storage sites; Cold chain indicators of unused vaccines stored at the same sites
Method used to reconstitute the vaccine	In each vaccination team, the health worker who diluted the vaccine
Method used to keep track and dispose of opened vaccine vials	Vaccination team leader
Number of vaccines from the same batch, storage facilities and vaccination posts concerned	Immunization campaign supervisory teams, person responsible for logistical operations/vaccine supply
Whether the vaccine caused the problem (number of doses administered from the same batch of vaccine)	Vaccination teams that used the vaccine from the same batch/record sheet
Result of comprehensive laboratory test on a specimen from the batch of vaccine and the batch of diluent	Specimen/vial of vaccine and diluent with the same batch numbers as those administered to the patient (for subsequent laboratory testing)
Known severe allergy to eggs	Patient or relative
Other known allergy	Patient or relative
3. Information to be obtained where programme error is suspected	
Vaccination post and team (team members) concerned	Vaccination post (card)
Other material and items stored in the vaccine storage refrigerator	Vaccination team and supervisory team
Vaccination post	Vaccination card and AEFI case
Vaccinator's qualifications and training to administer the vaccine in question	Vaccination team leader
Method of disinfecting vaccine injection site	Vaccinator
Model/type of syringe used	Vaccinator
If syringe is not self-blocking, method of managing and disposing of used syringes	Vaccination team
Method of preparing syringes	Vaccinator/health worker on vaccination team
Method of reconstituting the vaccine	Vaccinator/health worker on vaccination team
Method of injecting the vaccine (obtain a detailed description of how injection is carried out)	Vaccinator
Method of ensuring that opened vials are accounted for and disposed of	Vaccination team leader
Number of yellow fever vaccine doses administered to the case in question	AEFI case or relative/friend or vaccinator
Other similar AEFI in the same geographical area	AEFI case or relative/friend and surrounding population; District-level AEFI surveillance data (notification records and weekly summaries of yellow fever AEFI)
Other similar AEFI in patients vaccinated by the same team	Health centres and hospitals close to the sites where the vaccination teams in question worked; District-level AEFI surveillance data (notification records and weekly summaries of yellow fever AEFI)
Other similar AEFI in patients vaccinated with the same batch	Health centres and hospitals close to vaccination sites that used the same batch of vaccine or diluent; District-level AEFI surveillance data (notification records and weekly summaries of yellow fever AEFI)

ANNEX 8. Treatment of AEFI

Adverse events	Treatment
1. Non-serious AEFI	
Fever	Paracetamol
Muscle pain	Analgesics
Local reaction at injection site	Analgesics
Gastrointestinal syndrome (nausea and vomiting)	Rehydration if required
Abscess at injection site	Incision, antibiotics (if abscess of bacterial origin)
Convulsions	Supportive care, paracetamol and cooling if febrile; rarely, anticonvulsants may be needed
Septicaemia	Hospitalization, antibiotics intravenously
2. Serious AEFI (vaccine-related)	
Anaphylactoid reaction	Antihistaminics, adrenaline
Anaphylactic shock	Adrenaline, corticosteroids
Encephalitis	Evacuation/hospitalization (antibiotics)
Encephalopathy	Evacuation/hospitalization
Guillain-Barré syndrome	Evacuation/hospitalization
Paresis of cranial nerves	Evacuation/hospitalization
Thrombocytopenia	Evacuation/hospitalization
Rhabdomyolysis	Evacuation/hospitalization
Kidney failure	Evacuation/hospitalization
Liver failure	Evacuation/hospitalization
Death	No treatment but autopsy required

ANNEX 9. Some advice on communicating about AEFI

1. Interviews/press conferences

When the media become closely interested in an adverse event following immunization, it is wise to organize a press conference or agree to an interview. If all journalists have equal access to information, without «exclusives», they tend to attach less importance to the incident and cover it less sensationally. A press conference is particularly useful when media interest is intense, because such events enable a message to be communicated to a large number of journalists simultaneously. Press conferences also provide a chance for representatives of other organizations to express their support for immunization and the approach that has been adopted to deal with the issue. In some situations, professional bodies have more credibility than the government. The media are often more interested at the beginning, when there is still relatively little hard information on the facts and possible causes. In these situations, rumours can spread and the negative consequences can be incalculable. It is wise to call a press conference fairly quickly, even if there is not much information to impart, so that rumours can be quashed and contacts established with journalists. At the end of the press conference, state that another conference will be called in a day or two to give out more information about the incident and the enquiry. Regular contact should be maintained with the media to enable them to keep up with developments. Conclude by summing up the results and any remedial action that has or will be taken.

2. Sixteen «style» tips

Here are some practical tips on style and techniques to use when dealing with the press:

- Be honest. Never lie. If you do not know something, admit it and promise to find out the answer.
- Be frank and open. For example, you can say: «This hasn't worked. We are trying to find a solution.» This is important for building long-term relationships and inspiring confidence in immunization. A lie or cover-up is more likely to make the front page of the newspapers than the event itself.
- Be human. Project an image of yourself and the immunization service as strong, caring and competent.
- Be responsible. Do not be defensive: «Let's see if what the report says is true.» Accept the responsibility that comes with your post and do not try to blame somebody else.
- Be cooperative. If necessary, organize a daily press conference to satisfy the expectations of the public and the media. This can be a way of building up a relationship of trust with the latter.
- Remain at ease, even in situations where you are uncertain of the answer: «For the time being we don't know, but we are trying to find out.»
- Be aware of the importance of body language; for example, facial expression, eye contact, gestures and body posture.
- Be positive. Whenever possible, describe the situation in positive terms. Avoid negative or remarks, offhand comments and aggressiveness, and use terms such as «vaccine safety» (which has a positive connotation) rather than «adverse event». Adopt a positive turn of phrase. Even if the media portray an incident negatively from the standpoint of immunization, with care and thought the same incident can be reframed in a positive light. However unpromising the initial contact with a journalist may be, the situation can be turned to the immunization programme's advantage.
- Be ready to communicate your core message. Come well prepared. Know what you want to say and take the initiative in turning the discussion to the topic you want to talk about. Give your version of the facts. Anticipate difficult questions and have answers ready. Prepare your answers in advance (see below).
- Be serious. A joke can be fatal. In any event, the subject is rarely amusing.
- Stay calm. Do not overreact. Do not give out information that has not been requested or which could be embarrassing.
- Be sure of your ground and maintain control of the discussion.
- Stay polite, even if things turn ugly. The audience will be more impressed if you refrain from using inappropriate language and do not react to provocation.
- Know your weak points and be prepared to respond when pressed on this subject.
- Stick to matters with which you are familiar and can give answers to.
- Make a «link» to pass from difficult topics to firmer ground (see «Difficult questions» below for an explanation of how to make this link). Reframe the question in your own terms if necessary.
- Be clear. Avoid jargon. When referring to a complex medical concept, use simple phrases. Give easily comprehensible examples if these help to clarify the meaning.

3. Skills

All persons having contact with the media should possess the following skills:

- The ability to communicate on risk perception;
- The ability to explain complex topics clearly;
- Interpersonal skills (empathy);
- Particular skills in dealing with the media (television interviews); and
- The ability to digest and process relevant information quickly.

4. Drafting a press release

All information to be communicated at a press conference should be prepared in advance and summarized in a press release. This will include:

- A full account of the facts (in comprehensible language for those unfamiliar with health or immunization services) placed in the appropriate context (isolated incident, coincidence) to prevent any concerns from compromising the entire immunization programme;
- Details of how the incident is likely to develop, i.e. if it is continuing or if there are new cases;
- An overview of action already taken or in preparation (depending on the stage reached, this could be a plan of action or a completed enquiry);
- Some indication of the cause of the incident (if this has been ascertained with sufficient certainty and is no longer just a working hypothesis), in addition to any remedial action that has been or will be taken.

5. Preparing for a press conference

Before agreeing to take part in a discussion, it is important to choose the topics that will be addressed and how the data will be presented. Anticipate questions and rehearse replies. When preparing for a press conference, you should:

- Define the core messages you want to communicate;
- Designate a spokesperson or spokespersons;
- Prepare a press pack for journalists and community leaders with: (1) a brief press release containing all essential information, (2) additional basic information such as on the benefits of immunization, and (3) a list of «frequently asked questions» featuring questions that have been or are likely to be asked by the groups concerned.

Communicating on the subject of risk presupposes dialogue, active listening and discussion. Everyone perceives risk differently depending on their level of experience and knowledge, and different people may judge certain risks more acceptable than others. It is important to emphasize that the risk of true vaccine reactions is small in relation to the risks occasioned by the disease itself, and that these risks are in no way equivalent.

The core messages regarding the benefits of immunization include:

- The benefits of immunization in disease prevention are well known.
- The risk associated with immunization is small compared with the seriousness of the possible complications of the disease.
- Reactions to vaccines are normally benign, resolve spontaneously and very rarely lead to serious or chronic problems.
- Diseases preventable by immunization used to cause millions of deaths and disabilities before vaccines were introduced; this could happen again if immunization programmes are discontinued.
- Vaccine safety is a priority consideration for vaccinators; when a problem is detected, an investigation is launched to find a solution. This is what immunization safety surveillance is all about.
- An AEFI enquiry is under way, but the incident is probably due to a coincidence or a local problem (depending on the case). For the time being the vaccination programme should continue to protect the population.
- We are currently taking the necessary action.

6. Resources

WHO/EIP provides a toolkit and organizes a training workshop on communication with the media in this type of situation. For more information, contact the nearest WHO country or regional office or WHO/EIP in Geneva.

7. Questions and answers on immunization campaigns and adverse effects

7.1. Introduction

In the sections above, we stated that the media are likely to ask questions about certain aspects of the immunization programme. It is sometimes difficult to reply without prior preparation or training. There are certain techniques for answering questions.

The press greatly appreciates a list of prepared questions and answers that it can refer to. Intelligent questions and answers can save time and avoid misunderstandings on both sides.

Answering difficult questions

Below are some questions that the press will probably ask the programme directors when a serious AEFI has occurred.

«Easy/friendly» questions are not mentioned here. It is a good idea not to let the journalist dictate the direction of the exchange. Reply to each question in a way that leads naturally to what you want to say (linkage), i.e. stressing your support for immunization. Difficult questions often contain an element of truth, but one that is generally divorced from context and slanted in a particular way. We have not listed all difficult questions here; instead we have outlined a model question and answer framework that illustrates the conventional linking technique.

The linking technique

Question: Can vaccination cause abscesses?

Answer: *(Admit the element of truth)* We know that, in rare cases, vaccination can cause abscesses. *(Make the first link here)* This is why we teach staff to avoid the formation of abscess by using a sterile needle and syringe for each child. *(Now make the second link)* When, in addition, we are careful to purchase only the highest-quality vaccines approved by WHO and UNICEF, we can assure parents that our immunization programme is among the safest in the world. *(Job done!)*

Other examples of difficult questions

- Why does the government give children inferior-quality vaccines that cause adverse reactions or deaths?
- Why doesn't the Ministry of Health train health workers to avoid accidents of this kind?
- Why are vaccination injections and other medical interventions still dangerous in this country?
- Why are vaccines with dangerous side-effects that harm our children still in use?
- Why is the public not told the truth about vaccines? Is there a cover-up?
- Can vaccines transmit HIV/AIDS and hepatitis B?
- Are vaccines contaminated at the manufacturing stage?

7.2. Model pre-prepared questions and answers on general issues concerning vaccination and immunization campaigns

Question: Why are there more adverse effects during campaigns?

Answer: The declared frequency of adverse effects can seem high because:

- A large number of doses are administered within a short time;
- Awareness among health workers and the public is high and they are more likely to report adverse events;
- The occurrence of some symptoms could be a coincidence and unconnected with the vaccine, but because these symptoms appear during the campaign it is supposed that they are caused by the vaccine.

Question: Aren't injected vaccines more dangerous than those administered orally?

Answer: All vaccines administered during campaigns should meet WHO/UNICEF quality standards. There should not therefore be any difference in quality between injected and oral vaccines. But the latter, which do not require syringes or needles, can be administered by relatively untrained health workers. Injected vaccines must be administered in accordance with safe injection practices. For example, each injection must be performed using a sterile needle and syringe. If these precautions are not taken, injected vaccines can present a higher risk.

Question: Why undertake a campaign if the population is likely to experience adverse effects?

Answer: The percentage of people who experience serious adverse effects following immunization is extremely low and relatively predictable. In well-organized campaigns, the number of children with problems resulting from poor immunization techniques is close to zero. The overall frequency of serious vaccine reactions is several times lower than the risks associated with the unchecked disease (see Annex 2). Immunization therefore poses much less risk to the population than contracting the disease.

Question: What is the difference between an adverse event and an adverse reaction?

Answer: An adverse event is a medical event that simply occurs after an immunization (i.e. it has only a time relationship with immunization) and may give rise to concern about a possible link with the vaccines given. An adverse reaction implies that the medical event has been assessed as having a **causal relationship** with the vaccine(s) given (i.e. evidence shows that it is caused by the vaccine). Generally, adverse reactions can be predicted in a certain percentage of the population. They are usually mild reactions; fever or temporary pain at the injection site are typical symptoms) whose treatment involves simple remedies such as paracetamol, and there are no long-term complications. Serious or non serious adverse reactions are very rare. For example a single anaphylactic reaction may be observed for every million doses of vaccine administered.

Detailed information on vaccine safety can be downloaded from the WHO web site:

http://www.who.int/immunization_safety/aefi/en/index.html

Global Alert and Response (GAR)
www.who.int/csr