Guidance for establishing AEFI surveillance systems in countries planning to use Ebola vaccines

Draft Guidance, May 2016

Draft - Not for Implementation

This guidance is being distributed for comment purposes only.
About this guidance document

This guidance document has been adapted from the World Health Organization’s “Global manual on surveillance of adverse events following immunization”\(^1\) based on the principles outlined in the “Global vaccine safety blueprint”\(^2\).

Even though the document focuses on establishing vaccine safety systems in countries planning to use an Ebola vaccine, it would also help countries to establish minimum capacity for passive vaccine safety monitoring, as well as establishing active surveillance systems when introducing new vaccines.

**IMPORTANT:** the sections highlighted in yellow are areas where the work is still in progress and additional inputs are awaited.

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\(^2\) [http://extranet.who.int/iris/restricted/bitstream/10665/70919/1/WHO_IVB_12.07_eng.pdf?ua=1](http://extranet.who.int/iris/restricted/bitstream/10665/70919/1/WHO_IVB_12.07_eng.pdf?ua=1)
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Foreword

On 21 March 2014, the Regional Office for Africa of the World Health Organization (WHO) reported an outbreak of Ebola virus disease in Guinea. Since then, cases have been reported in five additional countries in West Africa. The outbreak of the Ebola virus disease (EVD) in West Africa is unprecedented in its scale, both in cases, fatalities and complexity. Guinea, Liberia and Sierra Leone have been severely affected by this outbreak until early 2016.

The 9th meeting of the Emergency Committee convened by the WHO Director-General under the International Health Regulations (IHR, 2005) regarding the EVD outbreak in West Africa took place on 29 March 2016. The Committee observed that, as expected, new clusters of Ebola cases continue to occur due to reintroductions of virus as it is cleared from the survivor population, though at decreasing frequency. The Committee was impressed that to date all of these clusters have been detected and responded to rapidly, limiting transmission to at most two generations of cases. As in other areas of sub-Saharan Africa where Ebola virus is present in the ecosystem, and recognizing that new clusters due to re-emergence may occur in the coming months, the Committee reinforced that these countries must maintain the capacity and readiness to prevent, detect and respond to any ongoing and/or new clusters in future. Based on the advice of the Emergency Committee, and her own assessment of the situation, the WHO Director-General terminated the Public Health Emergency of International Concern (PHEIC) regarding the Ebola virus disease outbreak in West Africa, in accordance with the IHR (2005).

The key interventions to stop Ebola transmission are:

- early isolation of patients to prevent transmission at home and in the community;
- early detection of new Ebola cases through close monitoring of contacts and isolation of contacts when they show symptoms;
- safe burial of the deceased to reduce transmission.

In addition to these control measures, two advanced candidate vaccines are currently being considered for controlling an Ebola outbreak. They include the ChAd3-ZEBOV, developed by GlaxoSmithKline (GSK) in collaboration with the US National Institute of Allergy and Infectious Diseases (NIAID), and VSV-EBOV, developed by NewLink Genetics and Merck Vaccines USA in collaboration with the Public Health Agency of Canada. Safety data from Phase I studies of both ChAd3 and rVSV vaccines indicate an acceptable safety profile in healthy adults. Ongoing Phase II/III studies will provide additional experience in adults and children; and will allow more extensive assessment of safety.

Currently, safety data is available on a small number of subjects – mostly healthy adults. There is very limited data on children and adolescents, or persons with underlying

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conditions, including immunocompromising conditions. There is also no data on their use in pregnancy.

An optimal post-licensure pharmacovigilance system, in the context of an Ebola outbreak, should be able to further characterize the safety profile of newly-developed vaccines, detect safety signals and confirm the association between suspected event(s) and the vaccine. The present pre-licensure vaccine safety trials are not large enough to detect rare and very rare adverse events following vaccination that occur below a rate of 1 per 1000 vaccinees. Since the confirmation of an adverse event/vaccine association requires large observational datasets, this can be implemented only after the vaccines are deployed on a larger scale, resulting in enhanced clarity on the individual and population risk. There may however be difficulty in reliably tracing the vaccinees. This results in challenges in detection, notification and assessment of AEFIs.

The national regulatory authorities (NRA) in the countries face challenges in licensing the vaccines due to potential uncertainties regarding their safety and efficacy, risk of vaccine failure and the risks to the immunization system.

Monitoring vaccine safety in Ebola endemic/outbreak countries is challenging as it requires good coordination between multiple stakeholders, including the National Immunization Programme (NIP), the NRA, the manufacturers and other organizations, each of whom may have specific objectives, systems and methods of collecting and managing vaccine-safety data. However, a comprehensive pharmacovigilance system is needed for proper detection and management of AEFI, and appropriate communication to maintain public trust. The AEFI reports and safety profile should also be shared between stakeholders and with the global community through the WHO United Nations Children’s Fund (UNICEF) joint reporting form (JRF) and the WHO Programme for International Drug Monitoring.

An effective and well-functioning AEFI surveillance system for Ebola vaccines will boost trust and public confidence, and will also help improve the quality of the immunization programme in the long run for routine vaccines as well. It is therefore essential that all stakeholders, like NIP, NRA, vaccine manufacturers, national clinical laboratories and health-care providers, make concerted efforts to provide documented evidence through an effective AEFI surveillance system.
Glossary

Adverse event following immunization (AEFI) Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Causal association A cause-and-effect relationship between a causative (risk) factor and an outcome. Causally associated events are also temporally associated (that is, they occur after vaccine administration); however, events that are temporally associated may not necessarily be causally associated.

Causality assessment In the context of AEFI surveillance, this is a systematic review of data about AEFI case(s) to determine the likelihood of a causal association between the event and the vaccine(s) received.

Cluster Two or more cases of the same, or similar events, related in time, geography (place) and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health facility and/or a vial of vaccine or a batch of vaccines.

Coincidental events An AEFI that is caused by something other than the vaccine product, by immunization error or immunization anxiety.

Contraindication A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/ severe febrile illness.

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Immunity

The ability of the human body to tolerate the presence of material indigenous to the human body (self) and to eliminate so-called foreign (non-self) material. This discriminatory ability provides protection from infectious diseases, since most microbes are identified as foreign by the immune system.

Immunization anxiety-related reaction

An AEFI arising from anxiety about the immunization.

Immunization error-related reaction

An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, and thus by its nature is preventable.

Immunization safety

The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse events surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.

Immunization safety surveillance

A system for ensuring immunization safety through detecting, reporting, investigating and responding to AEFI.

Injection safety

The public-health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (such as transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).

Non-serious AEFI

An event that is not serious and does not pose a potential risk to the health of the recipient. Non-serious AEFIs should also be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general.

Ring vaccination

The vaccination of all susceptible individuals in a prescribed area around an outbreak. Ring vaccination controls the outbreak by vaccinating and monitoring a ring of people around each infected individual. The idea is to form a buffer of immune individuals to prevent the spread of the disease.
Safe injection practice

Practices that ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.

Serious AEFI

An event that results in death, is life-threatening or requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.

Severe vaccine reaction

It refers to the intensity of vaccine reactions. A severe reaction refers to the high-grade intensity of its grading, such as mild, moderate and severe. Severe reactions may include both serious and non-serious reactions.

Signal (safety signal)\(^5\)

Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association between an intervention and an adverse event or set of related adverse events that is judged to be of sufficient likelihood to justify verificatory action.

Surveillance

The continuing, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.

Trigger event

A medical incident following immunization that stimulates a response, usually a case investigation.

Vaccine

A biological preparation that improves immunity to a particular disease. In addition to the antigen, it contains multiple components (excipients) and each component may have unique safety implications.

Vaccine pharmacovigilance

The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or

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<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Vaccine product-related reaction</td>
<td>An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (for example, adjuvant, preservative or stabilizer).</td>
</tr>
<tr>
<td>Vaccine quality defect-related reaction</td>
<td>An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device, as provided by the manufacturer.</td>
</tr>
<tr>
<td>Vaccination failure</td>
<td>Vaccination failure may be defined on the basis of clinical endpoints or immunological criteria where correlates or surrogate markers for disease protection exist. Primary failure (for example, lack of sero-conversion or sero-protection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to (i) failure to vaccinate, that is, an indicated vaccine was not administered appropriately for any reason, or (ii) because the vaccine did not produce its intended effect.</td>
</tr>
<tr>
<td>Vaccine reaction</td>
<td>An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.</td>
</tr>
<tr>
<td>Vaccine safety</td>
<td>The process, which maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.</td>
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# Abbreviations & acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ad26-ZEBOV</td>
<td>replication deficient human adenovirus 26 Zaire Ebolavirus vaccine</td>
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<tr>
<td>ADRs</td>
<td>adverse drug reactions</td>
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<tr>
<td>AEFI</td>
<td>adverse events following immunization</td>
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<tr>
<td>ChAd3-ZEBOV</td>
<td>replication deficient chimpanzee adenovirus 3 Zaire Ebolavirus vaccine</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>DIO</td>
<td>District Immunization Officer</td>
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<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>EVD</td>
<td>Ebola virus disease</td>
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<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
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<td>GVAP</td>
<td>Global Vaccine Action Plan</td>
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<tr>
<td>JRF</td>
<td>joint reporting form of WHO and UNICEF</td>
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<tr>
<td>MoH</td>
<td>Ministry of Health</td>
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<tr>
<td>MVA-EBOV</td>
<td>modified vaccinia Ankara Ebolavirus vaccine</td>
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<tr>
<td>NIAID</td>
<td>United States National Institute of Allergy and Infectious Disease</td>
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<tr>
<td>AD</td>
<td>auto-disposal (syringe)</td>
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<tr>
<td>VVM</td>
<td>vaccine vial monitor</td>
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<tr>
<td>OPV</td>
<td>oral polio vaccine</td>
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<tr>
<td>NIP</td>
<td>National Immunization Programme</td>
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<tr>
<td>NITAG</td>
<td>National Immunization Technical Advisory Group</td>
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<tr>
<td>NRA</td>
<td>National Regulatory Authority</td>
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<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<tr>
<td>rVSV—ZEBOV</td>
<td>recombinant replication-competent vesicular stomatitis virus Zaire Ebolavirus vaccine</td>
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<tr>
<td>SIO</td>
<td>State Immunization Officer</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<tr>
<td>VPD</td>
<td>vaccine preventable disease</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. The vaccines used for preventing Ebola, their known safety profile and the proposed immunization approaches

1.1 Vaccines for preventing Ebola

Currently, the Ebola vaccines where the early clinical trial data that have been reviewed and considered for large-scale use, include the ChAd3-EBOZ and rVSV-ZEBOV vaccines. Phase II and Phase III clinical trials for VSV-EBOV are underway in Guinea and Sierra Leone. The data from the Guinea Phase II front-line worker and the Phase III ring vaccination trials will be reviewed. A Phase II/III study in Liberia was started but, due to zero cases of EVD until recently, the trial did not move to Phase III but will provide valuable safety and immunogenicity data.

Johnson & Johnson, in association with Bavarian Nordic, has developed a 2-dose vaccination approach for Ebola using different vaccines for the first and second doses. This approach is known as heterologous prime-boost. The two vaccine candidates are known as Ad26-EBOV and MVA-EBOV. Results from Phase I evaluation in humans are available.

Novavax, a biotech company in the United States of America, has developed a recombinant protein Ebola vaccine candidate based on the Guinea 2014 Ebola virus strain and has completed a Phase I human clinical trial in Australia.

An additional vaccine candidate has recently finished early stage human clinical testing in China.

The Russian Federal Ministry of Health is developing a recombinant influenza candidate Ebola vaccine, as well as other approaches. The recombinant influenza candidate was scheduled to start Phase I trials in the second half of 2015. Other products in development include an oral adenovirus platform (Vaxart), an alternative vesicular stomatitis virus candidate (Profectus Biosciences), an alternative recombinant protein (Protein Sciences), a DNA vaccine (Inovia) and a recombinant rabies vaccine (Jefferson University), among others.

1.2 Immunization strategies in the context of an Ebola outbreak

Based on review of current data WHO Strategic Advisory Group of Experts on Immunization (SAGE) made the following provisional recommendations, which are not vaccine-specific and will be reviewed and revised in light of the emerging data from different Ebola vaccines:

- Vaccination during outbreaks should be part of an integrated strategy and complement other public health measures to interrupt transmission. It does not substitute for full-time personal protective equipment use, contact tracing and other infection control measures.

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• The main objectives for vaccination are interruption of transmission and individual protection for those at high risk for infection during an outbreak.
• Health-care workers, as well as certain other categories of individuals with high likelihood of exposure to infectious body fluids, including informal health-care providers and those involved in funeral rites, are at higher risk for infection than the general population. The categories of front-line workers and other risk groups may vary between communities and should be defined locally.
• The vaccination delivery strategy will depend on the extent of the spread of disease, disease incidence at the time when vaccination is initiated, status of implementation of other control measures, effectiveness of contact tracing, and available supply of vaccine. Regular reviews of the epidemiological data should inform adjustments to the delivery strategies throughout the outbreak. Potential strategies include ring vaccination, geographic targeting of an area (mass vaccination) and vaccination of front-line workers. When more data are available, more precise recommendations on the choice of vaccination strategy will be considered.

1.3. Ebola vaccines and adverse events following immunization (AEFI)

For the sake of clarity, the following definitions introduce the reader to the details of Ebola vaccine-related adverse events following immunization (AEFI).

1.3.1 General definition

Adverse event following immunization (AEFI): this is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

1.3.2 Cause-specific definitions

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

In June 2015, the Global Advisory Committee on Vaccine Safety (GACVS) Working Group reviewed data from Phase I clinical studies of the ChAd3-EBOZ and rVSV-ZEBOV vaccines and summarized that⁷:

For the ChAd3-ZEBOV vaccines, the reported adverse events included:

- injection-site pain and fever, headache and flu-like symptoms mainly occurring within the first 24 hours after vaccination;
- fever that resolved within 24 hours;
- transient clinically non-significant reductions in lymphocyte and platelet counts that were observed within the first week following vaccination.

For the rVSV-ZEBOV vaccines the reported adverse events included:

- injection-site pain and fever, headache, malaise and flu-like symptoms mainly occurring within the first 1–3 days after vaccination;
- arthralgia, arthritis, dermatitis, rash and cutaneous vasculitis in the second week following vaccination;
- occasional vesicular lesions of the skin and oral ulcers;
- transient clinically non-significant reductions in neutrophil and lymphocyte counts within the first few days following vaccination.

**Important note: this position will be updated when further information becomes available after further trials and vaccine use.**

1.3.3.1 Fever after Ebola vaccine

In the context of Ebola vaccination, clear distinction between fever caused by the immunization and the fever as an early sign of EVD is crucial.

Typically, when an individual is infected with the Ebola virus, the infection runs its course within 14 to 21 days. The incubation period, from infection with the virus to onset of symptoms, is between two and 21 days. Humans are not infectious until they develop symptoms. First symptoms are the sudden onset of fever fatigue, muscle pain, headache and sore throat. This is followed by vomiting, diarrhoea, rash, symptoms of impaired kidney and liver function and, in some cases, both internal and external bleeding (for example, oozing from the gums, blood in the stools). Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes.

A case of Ebola has to be suspected in the case of any person, alive or dead, suffering or having suffered from a sudden onset of high fever and having had contact with a suspected, probable or confirmed Ebola case,

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any person with sudden onset of high fever and at least three of the following symptoms:

- headache
- vomiting
- anorexia/loss of appetite
- diarrhoea
- lethargy
- stomach pain
- aching muscles or joints
- difficulty swallowing
- breathing difficulties
- hiccups;

OR

any person with inexplicable bleeding,

OR

any sudden inexplicable death.

Typically, Ebola vaccine product-related fever begins within $XX$ hours and resolves within $XX$ hours of vaccination. Therefore, in the context of Ebola vaccination in outbreak conditions, it is important to document the time of vaccination on the immunization cards provided to patients and also the records maintained by the health-care workers. Antipyretic drugs, in a recommended dosage and schedule, can be given as recommended by the prescriber (or manufacturer). For example, paracetamol, at a dose of up to 15 mg per kg every 6–8 hours with a maximum of four doses in 24 hours, is useful. 

**1.3.4 Vaccine anaphylaxis**

Vaccine anaphylaxis is very rare. However, it is recommended that preparedness for emergency treatment for anaphylaxis is necessary in all clinical settings. All immunization providers need to be trained and develop competence in recognizing and managing anaphylaxis and have epinephrine (adrenaline) available. Details of identifying and responding to anaphylaxis are given in Annex 5.

Using local remedies for any serious vaccine reaction can risk the health and life of the vaccinee and is strongly discouraged. Early medical care by a qualified clinician will minimize any unwanted outcome and ensure early recovery, and may also save lives.

**1.3.5 Potential immunization error-related AEFI**

Immunization error-related reactions are preventable, and identification and correction of these errors in a timely manner are important.

In the context of the Ebola vaccination, in addition to the customary immunization error-related AEFI outlined below, there is higher potential for unique immunization errors to
occur due to the following reasons and depending on the type of Ebola vaccine used. For example:

- the type of vaccine used for the first and second dose is different for the ChAd3-ZEBOV vaccine and adequate care must be taken for providing the correct dose at the correct interval to the recipient;
- the vaccine reconstitution procedure, particularly for the rVSV-ZEBOV vaccine, is complex and has to be done meticulously by a trained person;
- the cold chain for these vaccines is unique and if the cold chain is not stringently maintained there is potential to cause vaccine failures.

Infection that can occur in cases of mass vaccination or in disaster or outbreak situations needs to be considered, particularly if there is a shortage of supplies or problems with logistics. This can be avoided with proper planning and preparedness of programme managers. Prior to the introduction of auto-disable (AD) syringes, the most common immunization error was an infection as a result of a non-sterile injection due to contamination of the vaccine or diluent vial or the injecting device (syringe and/or needle). The infection could manifest as a local reaction (for example, suppuration, abscess) or a severe systemic reaction (sepsis, toxic shock syndrome). In addition, there is a risk linking immunization with bloodborne infections.

The symptoms arising from an immunization error may help to identify the likely cause. For instance, recipients immunized with contaminated vaccine (usually the bacterium *Staphylococcus aureus*) become sick within a few hours following an injection-site reaction (local tenderness, redness and swelling) and develop systemic symptoms (vomiting, diarrhoea, high temperature, rigors and circulatory collapse). Bacteriological examination of the vial, if still available, can confirm the source and type of infection.

Ignoring contraindications may lead to serious vaccine reactions and is considered an immunization error. The immunization team should be clearly aware of such contraindications and any precautions. Any uncertainty (such as vaccinating an HIV positive or immunocompromised person) should be referred to a higher level – a programme manager or physician. However, it is equally important not to overreact to concerns of false contraindications as this may lead to missed opportunities for vaccination, reducing coverage and thereby increasing the risk of disease in both individuals and the community. Health-care workers also need a clear understanding of contraindications and precautions. Precautions are not contraindications, but a decision on whether to vaccinate requires a case-based assessment where the risk of the vaccine is balanced against the potential benefits. The use of Ebola vaccines in immunocompromised individuals is a good example of this.

To avoid/minimize immunization error, the following should be observed.

- It is both important and necessary to maintain the cold chain at all levels. It is particularly important at local level to plan beyond six hours.
- Vaccines must be reconstituted only with the diluents supplied by the manufacturer.
- **Reconstituted vaccine should be maintained in the recommended cold chain and used within six hours after reconstitution; it must be discarded at the end of each immunization session and should never be retained.**
- Other than vaccines, no other drugs or substances should be stored in the refrigerator or cold box of the immunization centre.
- Immunization workers must be adequately trained and closely supervised to ensure that proper procedures are followed.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.
- Prior to immunization, adequate attention must be given to contraindications.

### 1.3.6 Potential immunization anxiety-related AEFI

Awareness, preparedness, planning and training enable health staff to identify and manage immunization anxiety-related AEFI appropriately. Efforts should be made to minimize anxiety, especially in adolescents, during immunization. Fainting does not require any clinical management beyond placing the patient in a recumbent position. The likelihood of fainting should be anticipated when immunizing older persons. It can be reduced by minimizing stress among those awaiting injection, through short waiting times, comfortable room temperatures, preparation of the vaccine outside the recipient’s line of vision and privacy during the procedure. Sometimes, cases with hysteria may even require hospitalization and can cause public concern. Clear explanations about the immunization and a calm, confident administration will decrease the level of anxiety about the injections and thus reduce the likelihood of an occurrence. Careful observation and clinical judgement is necessary to differentiate between anaphylaxis and syncope. However, an accidental administration of a single dose of adrenaline (intramuscularly) to a vaccinee with only syncope does not harm the vaccinee. A ready reckoner to differentiate causes that mimic anaphylaxis is given in Annex 5.

### 1.3.7 Potential coincidental events manifesting as AEFI

When AEFI following Ebola vaccination is investigated, it is important to take into consideration the possibility of EVD; also, malaria, typhoid fever, shigellosis, cholera, leptospirosis, plague, rickettsiosis, relapsing fever, meningitis, hepatitis and other viral haemorrhagic fevers which are endemic to a locality. Efforts should be made to exclude these coincidental conditions before the event is attributed to the vaccine. It is important that, when an AEFI is reported and investigated, all information and investigation pertaining to the clinical diagnosis is collected. Data on all reported cases should be stored in a repository (preferably electronic) so that they can be accessed when additional information becomes available through reports of similar cases or through periodic data mining. This will enable signal detection that is critical when new vaccines, such as Ebola vaccines, are introduced into the community.
1.3.8 Contraindications for vaccination

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, a vaccine is contraindicated if there is a history of anaphylaxis to a given vaccine or its components. Since the Ebola vaccines contain the following components, XX, XX and XX it is necessary to be cautious when vaccinating persons with known hypersensitivities to these components. Please refer to the summary product characteristic or package insert for the contraindication of the specific Ebola vaccine.
2. AEFI surveillance in countries using the Ebola vaccines

The surveillance of AEFI is an integral part of the National Immunization Programmes (NIP), and reinforces the safe use of all vaccines in the country while also helping to maintain public confidence. This is a key component of quality vaccination and should be done systematically (see Figure 2.1). This is done in collaboration with all stakeholders including sharing information and timely updating of the vaccine’s safety profile.

2.1 Objectives of the AEFI surveillance system in the context of Ebola vaccine use

The objectives of AEFI surveillance system in the context of Ebola vaccine use include:

- To rapidly detect and respond on time to the occurrence of an AEFI;
- to further update the safety profile of the vaccine – in the current context it implies the identification of problems not identified in the clinical trials during the use of Ebola vaccine(s) which could be related to inherent properties of the vaccine, host response, differences in population and other events of interest;
- to determine the post-licensure vaccine reaction rate and relate this to the expected vaccine reaction rates that were observed in the clinical trials;
- to identify clustering or unusually high rates of AEFI, even if they are considered mild;
- to detect defects in quality of the vaccines;
- to detect, correct and prevent immunization error-related reactions;
- to ensure that coincidental events are not mistaken for vaccine reactions;
- to identify events which may indicate a previously unknown and potential vaccine reaction (that is, a signal) and to generate new hypotheses about the causal relationship between the event and the Ebola vaccine(s);
- to maintain public confidence in the immunization programme by appropriate and timely responses to their concerns about immunization safety;
- to collaborate and share information with all stakeholders in order to generate additional information on vaccine safety.
2.2 Key components of the AEFI surveillance system

The key components of the AEFI surveillance system (Fig. 2.1) include those listed below.

1. AEFI identification: when the adverse event is first identified by the vaccine recipient.
2. AEFI notification: when the event is brought to the notice of the health-care system, either by the patient or by their relative.
3. AEFI reporting: when the first information of the event is obtained by a health-care worker (any person in the health-care system) and the information on the event is documented in an AEFI reporting form and is sent to the next level.
4. AEFI investigation: when a detailed enquiry is made and effort taken to collect adequate information so that the underlying cause of the event can be determined.
5. Analysis: when the information of all events (minor or severe) is collated and the data is processed to determine the occurrence of signals.
6. Causality assessment: when all information about a particular case, obtained after completion of the investigation, is studied in detail, deliberated by experts and the underlying cause of the event is established.

2.3 AEFI surveillance strategies proposed based on the Ebola vaccination strategy adopted by the country

2.3.1 Passive AEFI surveillance systems for the whole country (irrespective of the presence of an Ebola outbreak)

Passive AEFI surveillance systems have to be established, implemented and strengthened irrespective of the Ebola outbreak situation in a country. It is an investment that brings about long-term returns. Passive surveillance systems theoretically allow anyone in a country to report and, due to their broad coverage, they can provide the first indication of an unexpected AEFI. This can be accomplished by encouraging regular reporting of notified AEFI by health-care workers and all institutions that see patients who have received vaccines. Once the reports are received at a central level, they must be compiled and analysed to monitor possible patterns and clusters. This would be applicable whatever Ebola vaccination strategy is chosen. The main strength of passive surveillance is for early detection of unknown serious AEFI (signals).

Basic details for establishing a passive surveillance system, including establishing a national immunization safety expert committee, and how this has to be adapted in the context of Ebola vaccine deployment, is outlined in Annex 6. Countries are encouraged to review the WHO’s Global manual on surveillance of adverse events following immunization for additional information.

Passive surveillance has many limitations, including underreporting. As a result, passive surveillance is often not enough when new vaccines are being introduced. Hence, newly

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8 http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/
introduced vaccines and/or special immunization campaigns should have added layers of active surveillance and/or epidemiological studies to maximize the effectiveness of passive AEFI surveillance.

### 2.3.2 Enhanced AEFI surveillance and response after Ebola vaccine deployment

Enhanced AEFI surveillance needs to be established in situations where the Ebola vaccine is being deployed in a country due to an Ebola outbreak or the active threat of an outbreak. Establishment of such a system should be coordinated by a National Immunization Safety Expert Committee under the auspices of a National Crisis Management Committee. This is described in section 3.1.

Enhanced surveillance could be conducted as:
- stimulated passive surveillance;
- sentinel site-based active reporting.

#### 2.3.2.1 Stimulated passive AEFI surveillance

In stimulated passive AEFI surveillance, staff participating in the immunization activities, and other health workers, are trained, sensitized and followed-up by a central AEFI monitoring centre via a network of focal points. Once an AEFI is detected, an agreed protocol is used for the patient care and management. In parallel, a channel to route the transmission of reports and data is defined. A daily data review is set up to generate possible signals and identify the need for corrective actions. Thus, the stimulated passive AEFI surveillance system implies close monitoring of the detection and reporting activities.

At the time of immunization, depending upon the vaccine that is planned to be used, it is important for health workers to sensitize the recipients/parents about expected events, such as fever and pain at the injection site, rare instances of arthralgia, arthritis, etc. following immunization. Recipients and parents (of vaccinated children) should be given a vaccination card providing the details of the vaccine administered. Particular attention should be given to recording the batch numbers (of the vaccine and diluent) and the date and time of vaccination. The vaccination card should also mention the hotline number and the details of the central AEFI monitoring unit, and advise the reporting of any event that causes concern following immunization. Recipients should also be informed about simple home remedies should minor events such as pain in injection site occur; however, at the same time, they should be instructed to report severe expected events (such as febrile convulsions not responding to antipyretic drugs) or other unusual events that may occur.

#### 2.3.2.2 Sentinel site-based AEFI surveillance and reporting

A sentinel surveillance system is useful for AEFI surveillance among health-care workers receiving the Ebola vaccine. This system can also be used in strategies using geographic vaccination or ring vaccination. Selected tertiary care reporting units with a high patient
load, and with experienced well-qualified staff to identify and notify AEFI and Ebola, are ideal sentinel sites. If the sentinel sites are close by, and an AEFI is suspected, the population is advised to seek health care from these specialized sites. This method is also helpful when high-quality data are needed about AEFI and Ebola that cannot be obtained through a passive system.

The Ebola vaccine AEFI sentinel system deliberately involves only a limited network of carefully selected reporting sites – for example, a network of large secondary and/or tertiary care hospitals that are actively involved in providing comprehensive health care, including managing Ebola cases, centres offering Ebola vaccines through their facilities, etc. It may be useful to limit sentinel site-based reporting to a few sites. This could reduce the amount of data gathered and allow a more focused effort to increase reporting in the sentinel sites. An advantage of this approach is that the number of sites can be selected based on available resources so that the efforts focused on increasing reporting may be more effective. The most important disadvantage is that selection bias may be introduced, if the population of the sentinel sites differs from the general population to be vaccinated.

The following criteria should be considered in selecting a sentinel health facility:

- it should be willing to participate;
- it serves a relatively large population that has easy access to it;
- it has medical staff sufficiently specialized to identify and report AEFI cases.

At the sentinel site, it is necessary to identify a sentinel site AEFI focal person trained specifically on Ebola case detection and management, and also Ebola vaccine-related AEFI.

When the vaccine recipient is vaccinated, either at the sentinel site or in any other site:

- document the date and time of vaccination in the patient immunization card and provide contact details of the sentinel site AEFI focal person/hotline number should an AEFI occur;
- sensitize the potential vaccine recipients on the likely AEFI that could occur after vaccination;
- inform them particularly to look out for fever after vaccination and also the need to report this immediately;
- inform the vaccine recipient to report any other condition, that they suspect could be vaccine related, to the hotline at the nearest AEFI monitoring centre;
- sensitize the vaccine recipient on the need to be referred to the referral centre for further management.

There are two key considerations in the context of AEFI surveillance following Ebola vaccination. Firstly, all vaccination strategies should be linked to a sentinel site for management of AEFI should they occur. Secondly, the Ebola virus disease has high infectivity and fatality rates. Hence, for ethical reasons, the sentinel site-based active reporting should
be associated with a stimulated passive surveillance and all suspected serious cases referred to identified hospitals for adequate care. If an AEFI is detected, it is necessary to follow the same protocol as outlined in section 3.3 below. Please note that the sentinel site AEFI focal person should provide information to the central AEFI monitoring unit.

2.4 Key considerations for reporting AEFI after the use of Ebola vaccines

It needs to be stressed that health workers should report all cases that are notified to them. Table 2.1 below provides case definitions of known AEFI. All vaccination staff must be able to recognize AEFIs and report them regardless of whether they are accurately diagnosed. In the context of Ebola, one of the key aspects in the AEFI surveillance is to differentiate between a fever related to a coincidental event (such as malaria, typhoid, etc.), an Ebola vaccine component and a fever related to EVD. A validated algorithm is used for this differentiation, so any AEFI that meets the criteria to be classified as serious should be referred to the reference hospital for differentiation between a coincidental event, an AEFI and wild EVD. Once the patient has been tested negative for Ebola, they should be referred to a tertiary care hospital.

Table 2.1 Case definitions of some of the reportable adverse events after Ebola vaccination

<table>
<thead>
<tr>
<th>AEFI</th>
<th>Case definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>A clinical syndrome characterized by sudden onset (within one hour), rapid progression of signs and symptoms involving multiple (more than two) organ systems; skin – urticaria (hives), angioedema (swelling of face/body); respiratory – persistent cough, wheeze, stridor; cardiovascular – low blood pressure (hypertension) or reduced circulation (fast weak pulses); gastrointestinal – vomiting, abdominal pain.</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Acute onset of major illness characterized by depressed or altered level of consciousness and/or distinct change in behaviour lasting for one day or more.</td>
</tr>
<tr>
<td>Fever</td>
<td>The fever can be classified (based on rectal temperature) such as mild fever: 38–38.9 °C; moderate fever: 39–40.4 °C; severe fever: &gt;40.5 °C.</td>
</tr>
<tr>
<td>Injection site abscess</td>
<td>Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (such as purulent, inflammatory signs, fever, positive bacterial culture). Sterile abscess if no evidence of bacterial infection on culture. Sterile abscesses are usually due to the inherent properties of the vaccine.</td>
</tr>
<tr>
<td>Arthritis/arthralgia</td>
<td>To be added</td>
</tr>
<tr>
<td>Seizures</td>
<td>Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated &gt; 38 °C (rectal). Afebrile seizures: if temperature is normal.</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Acute onset of severe generalized illness due to bacterial infection</td>
</tr>
<tr>
<td>AEFI</td>
<td>Case definition</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
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<tr>
<td></td>
<td>and confirmed (if possible) by positive blood culture.</td>
</tr>
</tbody>
</table>
| Severe local reaction | Redness and/or swelling centred at the site of injection and one or more of the following:  
- swelling beyond the nearest joint;  
- pain, redness and swelling of more than three days and interfering with daily activities;  
- requires hospitalization.  
Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported. |

Serious AEFI: any AEFI causing:  
- death  
- hospitalization  
- disability  
- congenital anomaly  
- other severe and unusual events.  

Any additional conditions, as determined by the National Immunization Safety Expert Committee, should be included.

3. Responding to an AEFI following Ebola vaccination

The central AEFI monitoring unit coordinates the response to an AEFI, which includes the following three major components presented in Figure 3.1: notification, reporting and recording; triage and case management; and field investigation.  

Figure 3.1 Responding to an AEFI after Ebola vaccination
3.1 The national crisis management committee

The national crisis management committee is the national centre spearheading the Ebola emergency response activities in a country. The committee coordinates the preventive, promotive, curative and rehabilitative efforts undertaken by the national government. It is also involved in the national communication aspects and media management. The national crisis management committee will be represented by, for example, the national focal points from the following agencies.

1. Ministry of Health.
5. Disease surveillance and control.

3.2 The national immunization safety expert committee

The committee (represented by its chairperson at the national crisis management committee) plays a critical role in confirming the causality assessments following AEFI investigations. In the context of Ebola vaccine deployment, the roles, and also the expertise of the committee, need to be enhanced based on the local context. The details of the normative roles and functions are outlined in Annex 6.

3.3 The central AEFI monitoring unit

In the context of Ebola vaccine deployment, a central AEFI monitoring unit has to be established at the district/province or regional level depending on the area of jurisdiction decided by the national planners. The unit should have a team for vaccine safety and a focal person to lead the team. The hierarchy and reporting structure has to be decided by the local planners. The central AEFI monitoring unit has a pivotal role to coordinate the activities in the field in responding to AEFI reported after Ebola vaccination. All team members of the unit should be appropriately trained for the specialized activity they undertake. The centre has the following roles.

1. To obtain information from the field on the locales of the Ebola vaccine deployment and identify the nearest health facilities, specialized Ebola treatment centres and district, province and state focal persons as designated by the planners.
2. To maintain a hotline that is fully functional 24 hours continuously and is operated by a team that includes a trained medical person. The team should have information on all aspects of the above, as well as being capable of differentiating between a serious and a non-serious case.
3. To have provision to complete an AEFI reporting form (see Annex 1), preferably an electronic version, with information obtained by telephone.
4. To provide guidance to the patient and health-care worker on receipt of information on the AEFI to differentiate between serious and non-serious AEFI and to advise on case management (home care or referral).

5. To communicate directly with relevant levels in the hierarchy, such as the referral centre, health-care provider and specialized Ebola treatment centre, and to coordinate case triage and case management.

6. To send the electronic copy of the AEFI reporting form, for all serious AEFI cases, to all levels to initiate action.

7. To maintain a line list of all reported AEFI cases (see Annex 2) and to do data analysis and mapping periodically (daily or weekly) to identify clustering or signals.

8. To coordinate with the field investigation team and provide technical and operational expertise.

9. To collate information obtained from the field investigation (dossier) and present it to the national immunization safety expert committee (within the national crisis management committee) for causality assessment.

10. To manage the vaccine safety training and communication in the local area of jurisdiction in the context of the Ebola vaccine deployment.

3.4 Systematic approach to responding to AEFI after Ebola vaccination

AEFI surveillance systems should be tailored such that AEFI cases identified by vaccine recipients themselves and/or their relatives, health-care providers or immunization staff are brought to the notice of the health-care provider, that is, notification. All AEFI cases notified to the health-care provider should be informed to the central AEFI monitoring unit. The AEFI monitoring unit should document these using the standard reporting form (Annex 1).

The focal person in the central AEFI monitoring unit for vaccine safety should discuss (Step A, section 3.4.1) with the reporter/health-care provider and decide if the reportable AEFI should be classified as non-serious or serious (death, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect – in the context of Ebola, fever for more than 24 hours).

For any serious AEFI, the central AEFI monitoring unit should refer the patient and send the reporting form to the referral centre for case management (Step B, section 3.4.2) and alert the district to initiate AEFI investigation (Step C, section 3.4.3). At the same time, the central AEFI monitoring unit should send the reporting form to the immunization safety expert committee (part of the national crisis management committee) and other levels of the hierarchy for information and alert. Hence, the central AEFI monitoring unit and the team plays a pivotal role in coordinating the three steps for responding to an AEFI (see Figure 3.1).

The detailed steps are as follows:

- Step A: notification, reporting and recording.
• Step B: triage and case management.
• Step C: field investigation of AEFI.

3.4.1 Step A: notification, reporting and recording

Notification is the process where the patient brings the AEFI to the notice of the health-care system. Reporting is the process when details of the patient, events, vaccine and reporter is documented and recorded in a standard reporting form (Annex 1).

In the context of Ebola, notification can be made to the central AEFI monitoring unit by a patient or by a vaccinator or other health-care worker.

On notification, the central AEFI monitoring unit will initiate the reporting process by:

1. thanking the notifier for reporting the AEFI;
2. assigning a unique report identifying number (for example, EBO-COU-PRO-DIS-YR-001) where the acronyms stand for the following: EBO represents Ebola; COU the country; PRO the province or state; DIS the district; YR the year of onset and 001 the sequence of the case in that year.
3. Completing all details in the AEFI reporting form (Annex 1) with particular attention to the date and time of reporting.
4. Obtaining a detailed address with landmarks.
5. Reassuring and advising the patient to visit the nearest health-care provider.
6. When the patient visits the nearest health-care provider, the care provider there should contact the central AEFI monitoring unit to discuss and determine if the patient’s signs and symptoms indicate that the condition is to be categorized as serious or non-serious.
   • If serious, the patient is advised an examination at the referral centre to determine the cause of the illness.
   • If non serious, the patient is advised home care and provided with appropriate medications.

When an AEFI is notified by telephone directly to the central AEFI monitoring unit by a health care-worker from a health facility, the specific activities conducted at this point will include all the above steps, excluding Step 5.

Important: For all serious AEFI cases, the central AEFI monitoring unit should communicate and electronically transmit the AEFI reporting form (Annex 1) to:

• the nearest district health authority for AEFI investigation, to initiate AEFI investigation by contacting the district focal person in the locality where the patient resides, so that the focal person and a team can conduct field investigation;
• the referral centre and other levels in the hierarchy, depending on the organizational structure for information, to inform them about the patient;
• national crisis management committee for information.
3.4.2 Step B: triage and case management

All serious cases are advised to have a clinical examination at a referral hospital. The purpose of this is to differentiate if the signs and symptoms are due to:

- coincidental events such as malaria, typhoid etc.
- adverse event due to Ebola vaccine
- Ebola virus disease.

Once the patient has been tested negative to Ebola, they should be managed at the referral centre itself or, if necessary, advised treatment at a suitable specialist hospital. If Ebola is suspected, the patient should be admitted to the Ebola treatment centre (ETC).

3.4.3 Step C: field investigation of AEFI

The ultimate goal of an AEFI field investigation is to find the cause of the reported AEFI(s) and prevent recurrence. Remedial action needs to be taken promptly for immunization error-related AEFI. Even if the cause cannot be identified, or the cause of the event was due to another reason, the fact that staff had investigated the incident itself will increase public confidence in the immunization programme.

Field investigation is coordinated by the central AEFI monitoring unit and is conducted by:
visiting the patient, the care provider(s) and the hospital; interviewing relevant stakeholders (recipients, parents, health worker, treating doctor, vaccine supply focal person); conducting the investigation of the AEFI case, Initiating collection of medical reports and relevant samples as required, completing the AEFI investigation form (Annex 3) and preparing a dossier that would be helpful to the national immunization safety expert committee for causality assessment.

It is therefore necessary to:

- collect all documentation on the patient regarding the vaccination and the sequence of events leading to the AEFI (including contact tracing);
- obtain relevant information on the condition of the patient prior to the vaccination;
- identify the particulars, circumstances and procedures around the vaccine used to immunize the affected recipient;
- examine the operational aspects of the programme, even if an event seems to be vaccine product-induced or coincidental;
- determine whether a reported event was a single incident or part of a cluster and if it is a cluster, confirm that the suspected immunizations were indeed given and also the individual vaccines that were used;
- ascertain whether unimmunized people are experiencing similar medical incidents;
- collect and consolidate all the above details for each patient and prepare a dossier.
The investigator should review the available reports and first rule out immunization error-related AEFI and immunization anxiety-related AEFI. If a patient is seen in the field, the investigator should assess the patient and the local epidemiologic situation and determine if the reported AEFI case should be reviewed by the specialized Ebola treatment centre. Obtaining local or national expert assistance at this point is advisable.

If the district immunization authorities feel that the investigation can be done locally, they can visit the patient and locality and initiate the detailed investigation, along with appropriate members of the local health-care team. If, however, assistance with the investigation is required from the province/state or national level, additional assistance should be solicited. National investigations should be led by a team from the national immunization safety expert committee, supported by the NIP and the NRA. During field investigations, the AEFI investigation form (Annex 3) should be used as a guide to collect suitable information. Additional information, apart from the investigation form, should be collected if the circumstances warrant.

A detailed investigation is mandatory if the event is a serious AEFI (death, hospitalization, significant disability, life threatening, or congenital anomaly/ birth defect)

- or is part of a cluster,
- or a part of a group of events above expected rate/severity,
- or a suspected signal.

Generally, before the AEFI is attributed to any vaccine product-related problems, the investigator should rule out any potential immunization errors. Therefore, the investigation should first try to rule out immunization errors related to the storage, handling, reconstitution or administration of vaccines.

Attention can then focus on other events. Details of some coincidental events can be determined, by reviewing hospital admissions for similar conditions during the same period, and verifying their vaccination status. A quick review of the morbidity pattern of similar conditions in the previous years can also indicate if the event is a part of a similar pattern observed in previous years. The medical literature can also help, as the estimated background incidence of various conditions may be available in the published domain.

Once the investigation is initiated, the central AEFI monitoring unit should inform the AEFI focal person in the national crisis management committee, and other levels in the hierarchy, on the status and progress of the investigation. This is necessary as a national or sub-national level officer should be the spokesperson of the government to the media and the
public about the investigation. The completed case investigation form (Annex 3) along with the supporting documents such as the medical report, vaccine quality report, logistic samples quality report, laboratory reports, for example, cerebrospinal fluid (CSF), serum (or other biological products) should be sent to the focal person at the national crisis management committee to be presented to the national immunization safety expert committee the day following the patient release. A progress report should be made on a daily basis.

It is important to remember that in case state (province) or national assistance is requested for an investigation, more accurate information can be obtained by a single coordinated investigation than a piecemeal investigation. Table 3.1 below summarizes the key steps in an AEFI investigation.

When the national AEFI focal point receives the documents of the AEFI case, it is essential to review it in the context of other reported AEFI received from all parts of the country, particularly in the same period of time, to see if this report may constitute a signal. This can be done by appending data into a national AEFI linelist (Annex 2) with information from the reporting form, and reviewing the data or conducting analyses as needed. If similar cases were reported earlier, it is essential to determine if an epidemiological linkage, or other pattern can be identified, if there is one.

Investigator(s) may use the *WHO Aide memoire on AEFI investigation* as a guide\(^9\).

**Table 3.1 Steps in an AEFI investigation**

<table>
<thead>
<tr>
<th>Step</th>
<th>Actions</th>
</tr>
</thead>
</table>
| 1. Confirm information in report | ☐ Obtain patient’s medical file (or other clinical record)  
☐ Check details about patient and event from medical file and document the information  
☐ Obtain any details missing from AEFI Report Form |
| 2. Investigate and collect data about the patient: | ☐ Immunization history  
☐ Previous medical history, including prior history of similar reaction or other allergies  
☐ Family history of similar events |
| About the event: | History, clinical description, any relevant laboratory results about the AEFI and diagnosis of the event  
Treatment, whether hospitalized and outcome |
| About the suspected vaccine(s): | Conditions under which the vaccine was shipped, its present storage condition, state of vaccine vial monitor and temperature record of refrigerator  
Storage condition of vaccine at all levels before it arrived at health facility  
Vaccine vial monitor |

\(^9\) Available at www.who.int.immunization_safety/en.
3.4.4 Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administered. Apart from checking on these three factors, the investigator should look for AEFI occurring in similar age groups and populations with genetic predisposition or disease.

In the context of Ebola vaccination, currently there is very limited data on the safety profile of the vaccines in sub populations of different persons with different genetic, cultural, nutritional or geographic backgrounds. Also, there is no data available on the safety of the vaccine in children and adolescents, and persons with underlying conditions, including immunocompromised conditions. Therefore, identification of AEFI clusters is critical for identifying new unreported events and signal detection. Knowledge of the background
Cluster investigation begins by establishing a case definition for the AEFI, and related circumstances, and by identifying all cases that meet the case definition. The investigator should demarcate the cluster and identify common exposure factors within the cluster.

Cluster identification (that is, cases with common characteristics) is achieved by gathering details (when and where) of vaccines administered. This is done by collecting and recording:
- detailed data about each patient;
- programme-related data (storage and handling, etc.);
- immunization practices and the relevant health workers’ practices.

Common exposures, among the cases, can be identified by reviewing:
- all data on vaccine(s) used (name, lot number, etc.);
- data on other people in the area (also non-exposed);
- any potentially coincident factors in the community.

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. Generally, the key considerations will be to investigate the possibility of an immunization error vaccine or a quality defect. The possibility of immunization error must be considered when events cluster in one setting without a similar change in frequency in other settings using the same vaccine. On the other hand, if an increased frequency of events is reported from multiple settings, the possibility of a vaccine product-related or quality defect-related event must be considered more strongly.
If all cases received vaccines from the same health worker/facility and there are no other cases, an immunization error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine or the respective lot is likely. If the event is a known vaccine reaction but is found to occur at an increased rate, an immunization error or a vaccine problem are likely causes. Finally, if cases in the unvaccinated population are occurring at about the same rate/proportion as among the vaccinated, from the same area, in the same age group, the adverse event was probably coincidental (see Figure 3.2).

### 3.4.5 Approach to AEFI investigation in hospitals

It is essential that the treating physician be interviewed for all serious AEFI cases. All clinical details, including the signs and symptoms and the patient’s management (treatment and laboratory tests) should be discussed. If possible, copies of relevant documents such as clinical records, laboratory results and progress notes, should be obtained. If patients are admitted in hospital at the time of investigation, they should be visited and evaluated. If the patient has died and an autopsy conducted, the forensic pathologist should be interviewed and, if possible, autopsy records collected.

Hospital records should also be scrutinized to determine if other patients have been admitted with similar manifestations. If historical records are available, admission patterns of similar conditions should be assessed.
4. Laboratory testing of specimens

Laboratories have an important role in AEFI case diagnosis and case management. They also have a key role in testing the quality of the samples of vaccines and the logistics used.

Laboratory tests and other complementary examinations for the purpose of AEFI case diagnosis and case management, conducted on the patient (for example, blood, urine, radiology, ECG, etc.), are based on the provisional case diagnosis and recommendations of the treating physician. These tests are considered routine and should be performed in clinical laboratories. The results of the tests are important to confirm the case diagnosis and arrive at the valid diagnosis for assessing causality.

Under normal circumstances, laboratory testing of samples of vaccines and logistics are rarely necessary. In the context of Ebola vaccines, laboratory testing of vaccines and logistics are at times required to confirm or rule out if the vaccine or vaccination is the suspected cause.

The laboratory testing of specimens includes testing of human specimens, vaccines and logistics.

4.1 Human specimens

It is difficult to generalize about what specimens will be required in a given situation, as it will depend on the clinical symptoms and signs of the patient, and the clinical decisions made by the treating physician in charge of the case. It is necessary to record the type, date and time of collection of each and every sample collected. Documents of clinical investigations and medical records related to the incident will support correct laboratory investigations. It is advisable to consult the treating physician(s) to make a decision on samples to be tested.

For biochemical, histo-pathological and microbiological examination, specimens should be handled in a local laboratory or, if this is not possible, they may be forwarded to the nearest suitable laboratory where facilities are available to carry out requested laboratory tests.

In case of death believed to be due to an AEFI suspected after Ebola vaccination, if the treating physician specifically requests, an autopsy may be performed as soon as possible (within 72 hours) to avoid tissue lysis. Extreme care must be taken when handling the tissues if Ebola is suspected as a cause of death. Further details on conducting post-mortems are available in the WHO guidance document Clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker10.

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10 Available at http://apps.who.int/iris/bitstream/10665/130883/2/WHO_HSE_PED_AIP_14.05.pdf?ua=1.
4.2 Vaccines and logistics

The investigation may require that the vaccine and logistics be tested along with the human specimens. Since the Ebola vaccines have not been extensively used, a quality check can be undertaken on the vaccines, diluents and syringes. The appropriate specimen should be collected in the correct quantity required for the investigation. Laboratory specimens should be stored and transported as recommended and accompanied by clear supporting documents, reasons for specimen collection and any additional information required by the expert committee. In case laboratory investigation is required, an AEFI laboratory request form (Annex 4) should be completed and sent with each specimen collected.

- Laboratory testing is not a routine requirement but may be a part of an investigation.
- Laboratory testing is costly and is recommended only when it is necessary.
- However, securing samples (vaccine vials, syringes, blood, etc.) and storing them correctly, is important, because later investigation may require them. Therefore, proper storage and transport of suspected samples is recommended.
5. Brief overview of AEFI causality assessment
This section is a short introduction and practical overview of the purpose, process and classification of AEFI cases after causality assessment. A comprehensive guide and background to causality assessment has been published by WHO.\(^\text{11}\)

Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood that the event might have been caused by the vaccine/s received. Causality assessment does not necessarily establish whether or not a definite relationship exists, but generally ascertains a degree of association between the reported adverse events and the vaccine/vaccination. Nevertheless, causality assessment is a critical part of AEFI monitoring and enhances confidence in the national immunization programme.

Causality assessment is important for:
- identifying vaccine-related problems;
- identifying immunization error-related problems;
- excluding coincidental events;
- detecting signals for potential follow-up, testing of hypothesis and research;
- validating pre-licensure safety data with comparison of post-marketing surveillance safety data.

5.1 Case selection for causality assessment
In the context of Ebola vaccination, causality assessment should be done for:
- serious AEFI – mandatory
- clusters
- events above expected rate/severity
- evaluation of signals
- other AEFI (if required) as decided by reviewing team/committee, including:
  - if immunization error is suspected;
  - significant events of unexplained cause within 30 days of vaccination;
  - events causing significant parental or community concern.

5.2 Preparation for causality assessment
Prior to causality assessment:
- the AEFI case investigation should have been completed;
- a dossier with all details of the case, such as case report form, case investigation form (Annex 3), completed clinical case record, laboratory reports, autopsy report, details of field investigations, etc., should be available at the time of assessment.
- There must be a valid diagnosis, which is the extent to which the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease is defined.

\(^{11}\) Available at http://www.who.int/vaccine_safety/publications/gvs_aefi/en/
With inadequate or incomplete case information, an adequate causality assessment (see Figure 5.1) cannot be performed or, if attempted, the AEFI may be deemed unclassifiable or not assessable due to lack of information. On the other hand, even with complete information, the AEFI may be categorized as indeterminate due to the lack of clear evidence of a causal link, or conflicting external evidence or other inconsistencies. Nevertheless, these assessments should be recorded because the reporting of more cases may lead to a stronger signal and a plausible hypothesis, or a sounder refutation of any link.

**Figure 5.1 Final classification of cases after determining causality**

![Figure 5.1 Final classification of cases after determining causality](image)

*B1: Potential signal and maybe considered for investigation

### 5.3 Causality assessment team

Causality assessment in a country is done by a national reviewing team/committee (national immunization safety expert committee) that is independent, is free of real or perceived government or industry conflicts of interest, and that has a broad range of expertise in the areas of infectious diseases, epidemiology, microbiology, pathology, immunology, neurology and the vaccine programme.

The committee has written terms of reference. The details are provided in Annex 6. An existing committee that was used previously for AEFI causality assessment will be the best option available.

To summarize, causality assessment of AEFI needs high levels of expertise and should only be done by an expert committee at national level. An assessment will usually not prove or disprove an association between an adverse event and the immunization, but is meant to assist in determining the level of certainty of such an association. A definite causal association, or absence of association, often cannot be established for an individual event.
6. Action and response to AEFI

Responding to AEFI following Ebola vaccine may involve immediate short-term activities and/or long-term follow-up activities. Follow-up activities should be based upon the findings of investigations, causality assessments and recommendations by the investigation/expert committees (see Table 6.1 below).

Proper and early treatment should be provided to patients regardless of the diagnosis. Case management and referral will vary depending on the seriousness. Mild symptoms, such as mild fever and pain, need to be carefully reviewed and the algorithm applied and the cases managed. If recipients or parents return to seek medical attention, these cases should be documented and reported in the standard form. In case patients need hospitalization, a clear system for referral should be in place.

In the context of Ebola vaccines, if there is information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between the vaccine and an adverse event or set of adverse events, a signal should be suspected and further studies will have to be conducted.

Table 6.1 Summary of actions to be taken upon completion of the investigation/causality assessment

<table>
<thead>
<tr>
<th>Type of AEFI</th>
<th>Follow-up action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signal</strong></td>
<td>The details of such AEFI cases should be maintained in a national database. This can help later to identify a signal suggesting a new potential causal association, or a new aspect of a known association, between a vaccine and an event or set of related events.</td>
</tr>
<tr>
<td></td>
<td>• Contact the WHO <a href="mailto:vaccsalert@who.int">vaccsalert@who.int</a> and inform them about the suspected signal for further verification.</td>
</tr>
<tr>
<td></td>
<td>• Inform the manufacturer.</td>
</tr>
<tr>
<td><strong>Known vaccine related reaction</strong></td>
<td>If there is a higher reaction rate than expected from a specific vaccine or lot, obtain information from the manufacturer and consult with the WHO country office to consider:</td>
</tr>
<tr>
<td></td>
<td>• withdrawing that lot;</td>
</tr>
<tr>
<td></td>
<td>• investigating with the manufacturer.</td>
</tr>
<tr>
<td><strong>Immunization error related</strong></td>
<td>Correct the cause of the error. This may mean one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>• changing logistics for supplying the vaccine;</td>
</tr>
<tr>
<td></td>
<td>• changing procedures at the health facility;</td>
</tr>
<tr>
<td></td>
<td>• training of health workers;</td>
</tr>
<tr>
<td></td>
<td>• intensifying supervision.</td>
</tr>
<tr>
<td></td>
<td>Whatever action is taken, it is important to review at a later date to check that the immunization error-related events have been corrected.</td>
</tr>
<tr>
<td><strong>Coincidental</strong></td>
<td>The main objective is to present the evidence showing that there is no</td>
</tr>
</tbody>
</table>

38
indication that the AEFI is a vaccine-related reaction or immunization-related error and, that the most likely explanation is a temporal association between the event and vaccine/vaccination. In the context of Ebola, this communication can be challenging, particularly as it is a new vaccine.

Sometimes, it may be useful to enlist further expert investigation to ensure that the event was truly coincidental. The potential for coincidental events to harm the immunization programme through false attribution is immense.

| Immunization anxiety related | Review the procedures for immunization and ensure that future vaccinations take place in an ambient and safe environment. |

If AEFI causality is not established – depending on the nature of the event, its extent and whether it is ongoing – a further investigation or epidemiological study may be warranted. However, it must be accepted that, in some cases, the relationship to vaccine will never be clear.

**Communication and training are two important follow-up actions that have long-term implications.**
Annex 1. AEFI reporting form

AEFI Report ID Number: EBO-COU-PRO-DIS-YR-001

---

### Reporting Form for Adverse Events Following Immunization (AEFI)

**Patient full name:** Nen of Kin  
**Patient’s full Address:**  
**Telephone:**  
**Sex:** M □ F  
**Date of birth (DD/MM/YYYY):** ___ ___ / ___ ___ / ___ ___  
**OR: Age at onset:** □ Years □ Months □ Days  
**Reporter’s Name:**  
**Designation, Department & address:**  
**District/ Province:**  
**Reporting Institution:**  
**Telephone & e-mail:**  
**Today’s date (DD/MM/YYYY):** ___ ___ / ___ ___

---

### Health facility (or vaccination centre) name:

---

### Vaccine

<table>
<thead>
<tr>
<th><em>Name</em></th>
<th><em>Date of vaccination</em></th>
<th><em>Time of vaccination</em></th>
<th><em>Dose (1st, 2nd, etc.)</em></th>
<th><em>Batch/Lot number</em></th>
<th>Expiry date</th>
<th><em>Batch/Lot number</em></th>
<th>Expiry date</th>
<th>Time of reconsultation</th>
</tr>
</thead>
</table>

|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |

---

### Adverse event(s):

- Severe local reaction □ > 3 days □ beyond nearest joint
- Seizures □
- Abscess □
- Sepsis □
- Encephalopathy □
- Tonic-Clonic seizure □
- Seizures □
- Tense abdominal distension □
- Incontinence □
- Enteritis □
- Convulsion □
- Pertussis □
- Other (specify) □
- Other (specify) □

**Descriptive AEFI (Signs and symptoms):**

---

**Treatment provided:** Yes □ No □  
**Serious Yes □ No □**  
**Death Yes □ No □**  
**Life Threatening Yes □ No □**  
**Disability Yes □ No □**  
**Hospitlization Yes □ No □**  
**Congenital anomaly Yes □ No □**

---

### Treatment provided: Yes/No

**Outcome:**

- Recovered □
- Recovered with sequelae □
- Not Recovered □
- Unknown □

**If died, date of death (DD/MM/YYYY):** ___ ___ / ___ ___ / ___ ___

**Antepartum death:** Yes □ No □

**Neonatal death:** Yes □ No □

**Premedical history:**

**Medical history:** (including history of similar reaction or other allergies), concurrent medication and other relevant information (e.g., other cases). *Use additional sheet if needed:*

---

### First decision making level to complete:

**Investigation needed:** Yes □ No □  
**If yes, date investigation planned (DD/MM/YYYY):** ___ ___ / ___ ___ / ___ ___

---

### National level to complete:

**Date report received at national level (DD/MM/YYYY):** ___ ___ / ___ ___ / ___ ___

**AEFI worldwide unique ID:**

---

### Comments:

*Compulsory field*
### Annex 2. AEFI linelist

<table>
<thead>
<tr>
<th>Name/ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Village/Town/District</td>
</tr>
<tr>
<td>Date of birth (dd/mm/yyyy) and age</td>
</tr>
<tr>
<td>Date of immunization(dd/mm/yyyy)</td>
</tr>
<tr>
<td>Reaction type (code)</td>
</tr>
<tr>
<td>Outcome (Recovering/ Recovered/disabled/Died)</td>
</tr>
<tr>
<td>Suspect vaccine (name and dose, e.g. Penta-2)</td>
</tr>
<tr>
<td>Vaccine batch/Lot number</td>
</tr>
<tr>
<td>Diluent batch number</td>
</tr>
<tr>
<td>Onset time interval (hours, days, weeks)</td>
</tr>
<tr>
<td>Date reporting (dd/mm/yyyy)</td>
</tr>
<tr>
<td>Investigated? (If yes, date)</td>
</tr>
<tr>
<td>Cause (code)</td>
</tr>
</tbody>
</table>

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

**Coding for cause of AEFI:**

|----------------------|--------------------------------|---------------------------------|------------------|-----------------|--------------------------------------|
Annex 3. AEFI investigation form

<table>
<thead>
<tr>
<th>Section A</th>
<th>Basic details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Province/State</strong></td>
<td><strong>District</strong></td>
</tr>
</tbody>
</table>

Place of vaccination (✓): [ ] Govt. health facility [ ] Private health facility [ ] Other (specify) __________

Vaccination in (✓): [ ] Campaign [ ] Routine [ ] Other (specify) ________

Address of vaccination site:

Name of Reporting Officer: ____________________________

Date of investigation: ______/_____/______

Date of filling this form: ______/_____/______

Designation/Position: ____________________________

This report is: [ ] First [ ] Interim [ ] Final

Telephone # landline (with code): ____________________________

Mobile: ____________________________

E-mail: ____________________________

Patient Name: ____________________________

Sex: [ ] M [ ] F

Date of birth (DD/MM/YYYY): ______/_____/______

OR Age at onset: ______ years ______ months ______ days

OR Age group: [ ] < 1 year [ ] 1-5 years [ ] > 5 years

Patient’s full address with landmarks (Street name, house number, locality, phone number etc.):

<table>
<thead>
<tr>
<th>Name of vaccine/different received by patient</th>
<th>Date of vaccination</th>
<th>Time of vaccination</th>
<th>Dose (e.g. 1st, 2nd, etc.)</th>
<th>Batch/Lot number</th>
<th>Expiry date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type of site (✓) [ ] Fixed [ ] Mobile [ ] Outreach [ ] Other ________

Date of first key symptom (DD/MM/YYYY): ______/_____/______

Time of first symptom (h/mm): ______/______

Date of hospitalization (DD/MM/YYYY): ______/_____/______

Date first reported to the health authority (DD/MM/YYYY): ______/_____/______

Status on the date of investigation: [ ] Died [ ] Disabled [ ] Recovering [ ] Recovered completely [ ] Unknown

If died, date and time of death (DD/MM/YYYY): ______/_____/______

(h/mm): ______/______

Autopsy done? (✓) [ ] Yes (date): ______/_____/______

Time: ______/_____/______

Attach report (if available):

**Section B**

Relevant patient information prior to immunization

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Remarks (if yes provide details)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history of similar event</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Adverse event after previous vaccination(s)</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>History of allergy to vaccine, drug or food</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Pre-existing illness (30 days) / congenital disorder</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>History of hospitalization in last 30 days with cause</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Patient currently on concomitant medication? (if yes, name the drug, indication, doses &amp; treatment dates)</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Family history of any disease (relevant to AEFI) or allergy</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>For adult women</td>
<td>Currently pregnant? Yes (weeks) <strong><strong><strong>/</strong></strong><em>/</em></strong>___ / No / Unknown</td>
<td>Currently breastfeeding? Yes / No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For infants:

<table>
<thead>
<tr>
<th>The birth was</th>
<th>Full-term</th>
<th>Pre-term</th>
<th>Post-term</th>
<th>Birth weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery procedure was</td>
<td>Normal</td>
<td>Caesarean</td>
<td>Assisted (forceps, vacuum etc.)</td>
<td>With complication (specify)</td>
</tr>
</tbody>
</table>
Section C  Details of first examination** of serious AEFI case

Source of information (✔ all that apply): □ Examination by the investigator □ Documents □ Verbal autopsy
□ Other
If from verbal autopsy, please mention source __________________________

Name of the person who first examined/treated the patient __________________________
Name of other persons treating the patient: _______________________________________
Other sources who provided information (specify): _________________________________

Signs and symptoms in chronological order from the time of vaccination:

<table>
<thead>
<tr>
<th>Name and contact information of person completing these clinical details:</th>
<th>Designation:</th>
<th>Date/time</th>
</tr>
</thead>
</table>

**Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.
- If patient has received medical care – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below.
- If patient has not received medical care – obtain history, examine the patient and write down your findings below (add additional sheets if necessary).

Provisional / Final diagnosis:
### Section D
Details of vaccines provided at the site linked to AEFI on the corresponding day

<table>
<thead>
<tr>
<th>Number immunized for each antigen at session site</th>
<th>Vaccine name</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Number of doses</th>
</tr>
</thead>
</table>

- **When was the patient immunized?** (✓ the ☐ below and respond to ALL questions)
  - [ ] Within the first vaccinations of the session
  - [ ] Within the last vaccinations of the session
  - [ ] Unknown

- **In case of multidose vials, was the vaccine given**
  - within the first few doses of the vial administered?
  - within the last doses of the vial administered?
  - unknown

- **Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?**
  - Yes*/No

- **Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?**
  - Yes*/No / Unable to assess

- **Based on your investigation, do you feel that the vaccine’s physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?**
  - Yes*/No / Unable to assess

- **Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?**
  - Yes*/No / Unable to assess

- **Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?**
  - Yes*/No / Unable to assess

- **Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?**
  - Yes*/No / Unable to assess

- **Number immunized from the concerned vaccine vial/amploue**

- **Number immunized with the concerned vaccine in the same session**

- **Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations:**

- **Is this case a part of a cluster?**
  - Yes*/No / Unknown

  - a. Did all the cases in the cluster receive vaccine from the same vial?
    - Yes*/No / Unknown

  - b. If no, number of vials used in the cluster (enter details separately)

---

### Section E
Immunization practices at the place(s) where concerned vaccine was used

(Complete this section by asking and/or observing practice)

- **Syringes and needles used:**
  - Are AD syringes used for immunization? Yes*/No / Unknown
  - If no, specify the type of syringes used: [ ] Glass [ ] Disposable [ ] Recycled disposable [ ] Other

  - Specific key findings/additional observations and comments:

- **Reconstitution:** (complete only if applicable, ✓ NA if not applicable)
  - **Reconstitution procedure (✓)**
    - Same reconstitution syringe used for multiple vials of same vaccine?
      - Yes* / No / NA
    - Separate reconstitution syringe used for reconstituting different vaccines?
      - Yes* / No / NA
    - Separate reconstitution syringe for each vaccine vial?
      - Yes* / No / NA
    - Separate reconstitution syringe for each vaccination?
      - Yes* / No / NA

  - **Are the vaccines and diluents used the same as those recommended by the manufacturer?**
    - Yes* / No / NA

  - Specific key findings/additional observations and comments:
### Section F  
**Cold chain and transport**  
*(Complete this section by asking and/or observing practice)*

<table>
<thead>
<tr>
<th>Last vaccine storage point:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Is the temperature of the vaccine storage refrigerator monitored?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>▪ If “yes”, was there any deviation outside of 2–8°C after the vaccine was placed inside?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>▪ If “yes”, provide details of monitoring separately.</td>
<td></td>
</tr>
<tr>
<td>• Was the correct procedure for storing vaccines, diluents and syringes followed?</td>
<td>Yes / No / Unknown</td>
</tr>
<tr>
<td>• Were any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?</td>
<td>Yes / No / Unknown</td>
</tr>
<tr>
<td>• Were any partially used reconstituted vaccines in the refrigerator?</td>
<td>Yes / No / Unknown</td>
</tr>
<tr>
<td>• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?</td>
<td>Yes / No / Unknown</td>
</tr>
<tr>
<td>• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?</td>
<td>Yes / No / Unknown</td>
</tr>
</tbody>
</table>

**Specific key findings/additional observations and comments:**

**Vaccine transportation:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Type of vaccine carrier used</td>
<td></td>
</tr>
<tr>
<td>• Was the vaccine carrier sent to the site on the same day as vaccination?</td>
<td>Yes / No / Unknown</td>
</tr>
<tr>
<td>• Was the vaccine carrier returned from the site on the same day as vaccination?</td>
<td>Yes / No / Unknown</td>
</tr>
<tr>
<td>• Was a conditioned ice-pack used?</td>
<td>Yes / No / Unknown</td>
</tr>
</tbody>
</table>

**Specific key findings/additional observations and comments:**

### Section G  
**Community investigation (Please visit locality and interview parents/others)**

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality?  
*Yes / No / Unknown*  
If yes, describe:

If yes, how many events/episodes?

Of those affected, how many are

- Vaccinated: _______________________
- Not vaccinated: ___________________
- Unknown: _______________________

**Other comments:**

### Section H  
**Other findings/observations/comments**
# Annex 4. AEFI laboratory request form

**AEFI – LABORATORY REQUEST FORM (LRF)**

* (To be completed by XXX. LRF should be accompanied by specimens)

(For Serious Adverse Events Following Immunization)

<table>
<thead>
<tr>
<th>Province</th>
<th>Case ID</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>District</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sub District</th>
</tr>
</thead>
</table>

AEFI category (Encircle): Death / Hospitalized / Cluster / Disability

<table>
<thead>
<tr>
<th>Name of person sending the specimen:</th>
<th>Date of filling LRF:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Designation:</th>
</tr>
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<table>
<thead>
<tr>
<th>Phone Number:</th>
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<table>
<thead>
<tr>
<th>Case Name</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>Age (in months)</th>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
</table>

Complete address of the patient with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No., etc.)*

<table>
<thead>
<tr>
<th>PHONE -</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of vaccination</th>
<th>Date of onset</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of collection of specimen</th>
<th>Time of collection of</th>
</tr>
</thead>
</table>

| H H M M ( AM PM ) |
|--------------------|----------------------|

46
Precise description of samples:

a) For vaccine/diluents specimens: (to be transported in reverse cold chain)

<table>
<thead>
<tr>
<th>Mention vaccine/diluent</th>
<th>Quantity Sent</th>
<th>Name of Manufacturer (BLOCK Capitals)</th>
<th>Batch No.</th>
<th>Manufacturing Date</th>
<th>Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

b) For logistics or device specimens: (AD, reconstitution, disposable syringes)

<table>
<thead>
<tr>
<th>Mention Logistics</th>
<th>Quantity Sent</th>
<th>Name of Manufacturer (BLOCK Capitals)</th>
<th>Batch No.</th>
<th>Manufacturing Date</th>
<th>Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

c) For biological product specimen: (CSF, blood, urine, etc.)

2. Test requested:

3. Preliminary clinical diagnosis (working hypotheses):

4. Name & complete address of officials to whom laboratory results should be sent:

<table>
<thead>
<tr>
<th>Send to</th>
<th>Complete address</th>
<th>Phone/Fax</th>
<th>Mobile</th>
<th>Email-ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>National level</td>
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<tr>
<td>Province/state level</td>
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<tr>
<td>District level</td>
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<tr>
<td>Others (specify)</td>
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**To be completed by laboratory officials after receiving the specimen**

<table>
<thead>
<tr>
<th>Date of receipt of specimen at laboratory</th>
<th>D</th>
<th>D</th>
<th>M</th>
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<th>Y</th>
<th>Y</th>
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<tr>
<td>Name of person receiving specimen(s) at laboratory:</td>
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<tr>
<td>Condition of specimen upon receipt at laboratory (encircle):</td>
<td>Good</td>
<td>Poor</td>
<td>Unknown</td>
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<td>Comments by pathologist, virologist or bacteriologist:</td>
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<tr>
<th>Date specimen results sent from this laboratory:</th>
<th>D</th>
<th>D</th>
<th>M</th>
<th>M</th>
<th>Y</th>
<th>Y</th>
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<tr>
<td>Name of laboratory professional:</td>
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<td>Signature:</td>
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Annex 5. Anaphylaxis and similar conditions

Sudden and severe events occurring post-vaccination, especially syncope, are frequently reported as anaphylaxis. However, anaphylaxis following vaccination is very rare and the risk (in general) is 1–2 cases per million vaccine doses.

The onset of anaphylaxis can occur after several minutes (> 5 minutes) but rarely up to two hours following vaccination. The progression of symptoms is rapid and usually involves multiple body systems, almost always with skin involvement (generalized erythema and/or urticaria), as well as signs of upper and/or lower respiratory tract obstruction and/or circulatory collapse. In young children (though anaphylaxis occurs at any age) limpness, pallor or loss of consciousness may reflect hypotension. In general, the more rapid the onset, the more severe is the reaction.

Events happen without warning, so emergency equipment must be immediately at hand whenever immunizations are given. All vaccinators must be familiar with the practical steps necessary to save life following anaphylaxis. Each vaccinating centre must have an emergency kit with adrenaline. The expiry date of the adrenaline should be written on the outside of the emergency kit and the whole kit should be checked three or four times a year. It is important to note that health-care workers may misdiagnose syncope attack as anaphylaxis and may administer adrenaline as a part of the emergency care. If the correct dose of adrenaline, according to age and weight, is administered via the intramuscular route, no harm is likely to occur. However, an overdose, by administering intravenous or intracardiac adrenaline, or by repeated administration, may cause harm.

For all cases of suspected anaphylaxis, it is important that all symptoms and signs are well documented by health-care providers. As anaphylaxis is very rare, other causes of sudden and severe symptoms post-immunization that are more common than anaphylaxis, need to be considered. Table 2.7 lists conditions which may be mistaken for anaphylaxis.

Table 2.7 Conditions that may be mistaken for anaphylaxis post-immunization

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Onset: symptoms and signs</th>
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<tbody>
<tr>
<td>Vasovagal event</td>
<td>Symptoms are usually immediate (&lt; 5 minutes) and commence during the injection process.</td>
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<td>No skin rash, bradycardia or tachycardia, no respiratory involvement, spontaneous resolution when prone.</td>
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<tr>
<td>Hypotonic-hyporesponsive</td>
<td>Onset 2–6 hours post-immunization, sudden pallor, hypotonia and unresponsiveness, usually in an infant.</td>
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<tr>
<td>episode</td>
<td>No skin rash, respiratory or cardiovascular compromise.</td>
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<tr>
<td>Seizure</td>
<td>Onset usually at least 6–8 hours post-vaccination with a killed vaccine. Sudden unresponsiveness usually with</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Tonic-clonic movement, usually febrile, no cardiovascular compromise, no respiratory compromise unless apnea or aspiration.</td>
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<tr>
<td>Aspiration of oral vaccine, e.g. oral polio vaccine (OPV) or rotaviral vaccine</td>
<td>Immediate respiratory symptoms (cough, gagging, stridor or wheeze) during administration, usually in infant. No skin rash or cardiovascular compromise.</td>
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<tr>
<td>Somatic conversion symptoms</td>
<td>Immediate or delayed respiratory symptoms, syncope, neurological symptoms without objective respiratory or neurological signs.</td>
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<tr>
<td>Severe coincidental diseases</td>
<td>Usually due to coincidental – unrecognized congenital heart disease or occult infections. May have respiratory or cardiovascular compromise but there are usually symptoms, signs or investigations to indicate alternate cause.</td>
</tr>
<tr>
<td>Immunization-error related</td>
<td>Immediate toxic drug reaction with symptoms and signs due to drug toxicity. Reported with immunization-related errors which have resulted from inadvertent administration of a muscle relaxant or insulin.</td>
</tr>
</tbody>
</table>
Annex 6. Outline of a national passive AEFI surveillance system (irrespective of the presence of an Ebola outbreak) and preparing for Ebola vaccine safety

A passive surveillance system relies on the cooperation of health-care providers — laboratories, hospitals, health facilities and private practitioners — to report the occurrence of any adverse event following immunization through the national notification channel. Once the data have been received, they must be compiled and analysed to monitor possible patterns and clusters.

Passive surveillance is less expensive than other surveillance strategies and covers wide areas (whole countries or provinces). However, it can be difficult to ensure completeness and timeliness of data. The passive surveillance systems can be enhanced in a number of ways, depending on the completeness and quality of data required, the financial constraints and the availability of specialist skills and services.

The basic components of an AEFI surveillance system include case definitions, standardized forms, clear routes of reporting, data entry and quality control and analysis and feedback.

When establishing a system, the national programme should define the purpose, what is intended to be monitored (serious adverse events, all events, all vaccines, only new vaccines, etc.) and define who will identify the AEFI and collect information. It should also define who and where to report, the timelines, who and how to process data, and analyse and define the outputs of the system and periodicity of monitoring. A sample system for countries with two administrative and three administrative levels is illustrated in Figure 6.1 below.

**Important:** The flowcharts – describing the routing, timeline and action – are hypothetical, will vary from country-to-country and should be discussed in detail at the national level with all stakeholders and developed after arriving at a consensus.

In the context of EVD, the country has to take a decision on how to enhance the roles and performance of the existing surveillance system that will be most suited. This will involve discussion with stakeholders, such as the Ministry of Health, National Immunization Programme, National Regulatory Authority, national AEFI experts committee, immunization technical advisory group, State/Province immunization authorities, district immunization authority, etc.
The diagram illustrates the AEFI Reporting, Routing, Timeline and Actions process for countries with two administrative and three administrative levels. It outlines the flow from the Health Care Worker (Primary or Hospital) to the National Immunization Officer (NIP) and ultimately to the Ministry of Health (MoH) and National AEFI Committee.

**District**
- Immediate report in reporting form (Annex 1)
- For completed reporting form (Annex 1) 24 Hours (fax/ e mail)
- For investigation form (Annex 3) 7 days (Hard copy with supporting doc)

**National**
- NIP (JRF)
  - Copy of Vigilflow report
- NRA
- MoH

**AEFI Reporting – Routing, Timeline and Actions**
- Health Care Worker
  - Complete AEFI reporting form (Annex 1)
- District Immunization officer
  - For completed reporting form 24 Hours (e mail)
  - For investigation form 7 days (Hard copy with supporting doc)
- State Immunization Officer
  - For completed reporting form 24 Hours (e mail of receipt)
  - For investigation form 7 days (Hard copy with supporting doc) of receipt
- National NIP (JRF)
  - Copy of Vigilflow report
  - National AEFI Committee

**Levels, responsibilities, routing, timelines and forms**
- Sample for countries with 2 reporting levels
- Sample for countries with 3 reporting levels

Figure 6.1 A sample system for countries with two administrative and three administrative levels
The national immunization safety expert committee

The committee plays a critical role in confirming the causality assessments following AEFI investigations. In the context of Ebola vaccine deployment, the roles and also the expertise need to be enhanced.

The committee should include a wide range of specialists, such as paediatrics, neurology, general medicine, forensic medicine, pathology, microbiology, immunology and epidemiology. Medical experts should be invited for the review of specific events. The committee needs to be independent and have support from, and work in close communication with, both the immunization programme and the NRA.

The following generic terms of reference may be adapted by the national immunization safety expert committee:

- assessing potential causal links between AEFI and a vaccine;
- monitoring reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events;
- reviewing all reported serious AEFI presented for expert opinion, making arrangements to investigate further to establish causality and making the necessary recommendations to rectify problems;
- making final decisions on causality assessment following inconclusive investigations and ensuring quality control of the immunization surveillance system;
- communicating with other national and international experts, when required, to establish causality and to resolve vaccine quality issues;
- advising the National Immunization Programme and NRA on AEFI-related issues when requested by these institutions;
- advising the Ministry of Health (MoH) on vaccine and immunization safety-related matters when requested by the ministry.

Complete independence from government and all industry-associated experts may not always be possible to achieve, since it would mean excluding much potential expertise. Therefore, the committee should discuss how conflicts of interest/competing interests should be declared and decide which conflicts of interest may hinder an individual expert from taking part in the causality assessment of a specific event for a given vaccine, and which conflicts will not.

It is important to emphasize that employees of vaccine manufacturing companies cannot be members of the expert committee, as they will have conflicts of interest that could undermine the credibility and acceptance of the committee’s conclusions. However, the committee may choose to question company representatives if the industry is potentially the best source for certain information. For example, the committee might invite the
industry to describe a specific production process in one of their meetings, that is, of other national stakeholders.

**Role of other national stakeholders**

The NRA and the national immunization safety expert committee play a key role in supporting the immunization programme for AEFI investigation and causality assessment. They also provide recommendations to the National Immunization Technical Advisory Group (NITAG), the MoH and NIP on vaccines based on their causality assessment findings. The NRA and the NIP together constitute the national AEFI Secretariat and together they coordinate and provide technical/logistical support to conduct the meetings of the national immunization safety committee.

NIP is responsible for providing all feedback to the relevant stakeholders at the state and district level within seven days of causality assessment or potential signals determined by data review/analysis at the national level. The data collected has to be reported by the NIP to the global database through the WHO UNICEF JRF. The NIP is also responsible for following up on the actions recommended at the national level and state level (for example, change in logistics, cold chain, training after programme errors, etc.) and ensuring that they are implemented.

The NRA or the national pharmacovigilance centre is responsible for sharing the information with the global community by uploading the information onto the global pharmacovigilance database, VigiBase® – maintained by the Uppsala Monitoring Centre under the WHO International Drug Monitoring Programme – using information available in the completed case investigation form (Annex 3). A copy of the uploaded case details in VigiBase® should be provided to the NIP on a monthly basis.
Annex 7. Monitoring and evaluating the performance of the AEFI surveillance system

The AEFI surveillance system performance in any country (irrespective of the EVD status) needs to be regularly reviewed at all levels to ensure that the system is sensitive enough to identify and respond to AEFI rapidly. The standard overall indicator proposed to determine the quality of AEFI surveillance is AEFI reporting ratio per 100,000 surviving infants per year.\(^{12}\) This is calculated as

\[
\frac{\text{AEFI reporting ratio per 100,000 surviving infants per year}}{} = \frac{\text{Number of AEFI cases reported from a country per year}}{\text{Total number of surviving infants in the country per year}} \times 100,000
\]

Notes: The target proposed is at least 10 reports per 100,000 surviving infants per year. Some of the other key indicators that help to monitor the performance of the system include:

- timeliness and completeness of AEFI reporting.
  - Percentage of AEFI cases reported on time (< 24 hours of notification) to the national level.
  - Percentage of serious AEFI cases investigated on time (< 24 hours of onset) using standard formats.
- Number (%) of serious AEFI cases where final classification, including causality assessment by AEFI committee, is completed within 30 days of receipt of all documentation from districts.
- Number (%) of serious AEFI cases reviewed by national immunization safety expert committee following receipt of reported AEFI cases from region at national level.
- Response to AEFI by the programme, particularly those related to programme error.

\(^{12}\) An estimate of Surviving Infants can be calculated by subtracting the number of children who die before they reach their first birthday from the number of children born during that year. Number of children dying during the first year of their life can be estimated by dividing the number of births by 1000 times the infant mortality rate (IMR), where the infant mortality rate is expressed as number of infant deaths per 1000 live births.