Monitoring and Evaluation of AEFI during OCV mass vaccination campaigns

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Working group on Monitoring & Evaluation
June 2014

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Introduction

An adverse event following immunization (AEFI) is a medical occurrence following immunization 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.

During mass immunization campaigns there is usually an increase (perceived or real) in AEFI. This increase is essentially attributable to three factors.

- The large number of vaccinations performed in a short period of time causes a temporary concentration of AEFI.
- The variation in vaccine administration practices between vaccination teams, arising from (1) the constraints arising from the desired high vaccination coverage objective, which seeks to vaccinate many people as quickly as possible; and (2) the temporary recruitment of additional health workers with inadequate training or without vaccination experience.
- Enhanced AEFI surveillance activities.

AEFI related to vaccination may be due to the vaccine itself (either antigenic or other components of the vaccine) or due to an error in its administration. In most cases, it is difficult to determine with certainty a causal relation between the immunization and the reaction observed.

Oral Cholera Vaccines (OCV)

There are two OCVs currently prequalified by WHO, Dukoral® ® and Shanchol™™. Dukoral® ® is a monovalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 plus additional recombinant cholera toxin B subunit and Shanchol™™ is a bivalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 and *V. cholerae* O139.

Groups for which OCV is not recommended

Both vaccines are safe with no serious adverse events having been reported. They are not recommended for use in pregnancy because of the lack of evidence to evaluate the safety and immunogenicity of OCV in pregnant women.

Dukoral® can be given to HIV-infected persons, however Shanchol™ is not recommended because of the absence of clinical data to indicate that it is safe in this group.

Dukoral® has been given to children between 1 and 2 years of age in safety and immunogenicity studies, but the protective efficacy has not been studied in this age group. Therefore Dukoral® is not recommended for children less than 2 years of age.

Shanchol™ can be administered above the age of 1 year. Data for the safety and efficacy of the vaccine in infants (less than 1 year of age) is not available.

Rationale

Most mass vaccination campaigns with OCVs so far have been pre-emptive and organized before potential upsurges in cholera transmission or outbreaks.

However, there is a lack of experience with implementing large-scale vaccination against cholera, which is why it is essential to implement monitoring and evaluation of AEFI to gather evidence about the safety of OCV and to increase our knowledge of potential AEFI caused by OCV vaccination. It is also important to gather information for specific groups which could have been vaccinated inadvertently (pregnant women, infants and immuno-compromised people), which is not possible during clinical trials.

Objectives

Overall objectives

Detect and document serious AEFI caused by OCV vaccination and take the necessary remedial actions by treating the patients, and investigating and determining the possible causes.

Specific objectives

- Estimate the proportion of AEFI among people receiving OCV
- Provide treatment/case management according to the needs
- Rapidly respond to vaccine safety concerns
- Identify vaccine lots with increased proportion or types of reported AE
- Identify risk factors in people having received vaccine for particular types of AE
- Identify rare or unexpected AEFI, which is only possible when a large population is targeted for vaccination
- Monitor trends in known AE

Definition of AEFI & OCV AEFI

Definition of AEFI

AEFI can be serious or non-serious.

- **Serious AEFI** are any unexpected medical occurrence following immunization that results in death, hospitalization or prolongation of hospitalization, or results in persistent or significant disability/incapacity, or is life-threatening.

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

OCV AEFI

The following AEFI might be reported following OCV vaccination:

Gastrointestinal: Acute watery diarrhoea (AWD), diarrhoea, vomiting/nausea, abdominal pain or cramps, stomach/abdominal gurgling (gas), dyspepsia/indigestion, oral ulcer, dryness of mouth

Respiratory: Cough, sore throat

Generic: Fever, dehydration, loss of or poor appetite, dizziness, drowsiness, fainting, sweating, rash, itching, weakness, headache, insomnia, joint pain

Other: Anaphylactic reaction, yellowing of urine, reduced sense of taste

Preparing for AEFI monitoring and evaluation

Appointment of a National Committee on AEFI

An ad-hoc national committee on AEFI should be appointed (or if available, an existing AEFI review committee can be used) and charged with setting up, monitoring and evaluating AEFI during the OCV campaign.

The committee should be composed of members that are not responsible for vaccination. Its responsibilities should be to:

- Ensure monitoring of OCV AEFI is part of the immunization campaign;
- Define the methods of detection, reporting and investigation of serious OCV AEFI associated with the OCV vaccination campaign;
- Prepare a case management plan
- Help draw up an estimated budget (for surveillance, investigation and treatment of serious AEFI);
- Conduct field investigations when required;
- Conduct an AEFI causality review when required;
- Investigate reports of serious AEFI to decide whether or not they are vaccine related;
- Monitor the input, management and analysis of AEFI data;
- Help take rapid remedial action if an association is found between AEFI and a specific vaccine batch;
- Rapidly deal with any rumours generated by AEFI that may jeopardize vaccination;
- Prepare a final report on monitoring and evaluation of AEFI.

A document defining the terms of reference of the AEFI Committee and its processes for functioning should be prepared ahead of the campaign. Each administrative level in the country has responsibilities and activities related to monitoring and evaluation of AEFI. The responsibilities of staff at the health facility, district and regional levels and central level should be defined for monitoring and evaluation and these responsibilities clearly communicated. The responsibilities for personnel at each level are specified in Annex 1. An organogram of the structure of the reporting system should be provided to the AEFI Committee, along with the schedule for reporting (including zero reporting).

Training

During the preparatory/training sessions for vaccination activities organized for the vaccination teams, a session on surveillance/notification of AEFI should be included in the programme covering the following topics:

- the importance of AEFI monitoring;
- the importance of careful documentation of persons, time, place and vaccine batch numbers used during the campaign to support further investigation of AEFI if required
- the procedure for detection, evaluation of AEFI (serious vs non-serious) , treatment, and reporting of AEFI

- the importance of reporting no events ('zero' reporting)
- The importance of AEFI reporting and who is responsible for AEFI at each level (including their name, title and contact details) – national, regional, district

Training should also be organised for staff at each level (national, regional, district) that are not directly involved in the vaccination activities. These will include staff in hospitals and health centres who might see patients with OCV AEFI clinical signs, or staff involved in the surveillance and reporting activities. This training should include the dates of the planned campaign as well as OCV AEFI clinical signs.

Monitoring and evaluation of AEFI

The monitoring and evaluation of AEFI is comprised of 4 steps:

1. Detection of AEFI *[Active and Passive Surveillance, Surveys)*
2. Classification of AEFI *(non-serious, serious)*
3. Investigation of serious AEFI *(establishing the link between serious AEFI and OCV)*
4. Reporting AEFI linked to OCV vaccination and analysis

1. Detection of AEFI

Passive surveillance

Passive surveillance of AEFI should be an integral part of activities carried out to monitor the campaign. It begins on day zero (the first day of vaccination) and continues for 14 days after the end of the second round of vaccination.

Vaccinators and health care professionals are responsible for detecting, treating and reporting AEFI in persons presenting with symptoms during the vaccination sessions or at health care facilities or hospitals.

Because passive surveillance might be the only tool in place to detect AEFI, all vaccinators and health care professionals should receive comprehensive training on how to detect, treat and report AEFI.

There should be one person nominated at each vaccination post with the responsibility of informing people receiving OCV about the safety of OCV, possible adverse events, and what to do if these occur within a certain timeline. During the vaccination campaign people with clinical signs that could be AEFI should return to the vaccination posts to report their signs. If the onset of symptoms is after the last day of vaccination, they should go to the nearest health facility.

A vaccinated person presenting with unexpected symptoms (not explained by another pathology) should be treated and an assessment of his/her clinical signs must be carried out. It should be considered an AEFI case possibly linked to OCV if the following criteria are met:

- The date of onset of symptoms is within two weeks after administration of OCV
- The patient has at least one of the clinical signs listed in the section on OCV AEFI
- In the absence of another diagnosis

Each AEFI must be classified into serious or non-serious.

A reporting form must be filled out for each suspected serious or non-serious AEFI (see reporting form in Annex 2). Information on the batch number and expiry date of the vaccine administered, place and date of vaccination should be collected from the OCV vaccination card or campaign register/record.

Any AEFI considered serious should be reported immediately (within 24 hours) to the regional and central levels, and investigated to find out whether it is vaccine related.

Active surveillance to detect serious AEFI

If there are sufficient resources, active surveillance may be implemented to complement passive surveillance.

Serious AEFI are actively sought in areas where vaccination is being carried out, ideally in each health facility by examining heath facility records and/or medical files and questioning health care personnel in health care facilities.

Visits should also be made to a representative group of more elementary health facilities, selected on the basis of the reporting data submitted (for example, it might be worthwhile to select health facilities which have not reported any AEFI) and evenly distributed throughout the area covered by the vaccination campaign.

If a serious AEFI is detected, the date of onset of symptoms must be checked and if is within 2 weeks of receiving OCV and in the absence of other symptoms or medical condition, it must be reported immediately and investigated.

For practical and budgetary reasons, it will not always be possible to cover the whole of the vaccination area. In this case, selection of “referral sites” is recommended.

These sites should be chosen from among:

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

Post immunization-campaign AEFI survey

A post vaccination campaign AEFI survey may be conducted as part of the evaluation of the vaccination campaign. Detection of AEFI among the population will be based on the sample selected for the Vaccination Coverage (VC) survey.

These surveys can offset the lack of sensitivity of passive AEFI detection during the immunization campaign, as they estimate the proportion of AEFI among the vaccinated population and characterize these AEFI.

It will be possible to compare the findings of the post-campaign AEFI survey with those of passive and active detection of AEFI to assess the representativeness of the earlier results.

2. Classification

Each AEFI should be classified by the vaccinator or health care professionals examining the patient as serious or non-serious based on the following case definition:

- **Serious AEFI** are any unexpected medical occurrence following immunization that results in death, hospitalization or prolongation of hospitalization, or results in persistent or significant disability/incapacity, or is life-threatening.

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

The classification of each AEFI should be recorded on the individual reporting form (please see Annex 2).

3. Investigation of serious AEFI

Serious AEFI must be investigated as soon as possible, ideally within 24 hours of detection, to determine whether they can be linked to OCV vaccination. Specially trained health workers from the health district or central level should carry out the investigation. The information in Annex 3 should be collected for each case or cluster investigation.

The following steps are required to try and establish whether the AEFI is likely to be linked to OCV vaccination:

- **Confirming the reported diagnosis**. If the reported event does not have a valid diagnosis, the AEFI cannot be classified and additional information should be collected to arrive at a valid diagnosis. The valid diagnosis should meet a standard case definition (or a syndromic case definition). If available, it is best to adopt the Brighton Collaboration case definition for the condition, which can be accessed online (https://brightoncollaboration.org/public). Alternatively case definitions can be adapted from standard medical literature or national guidelines, or may also be adapted locally by the reviewers.
- **Confirming that the date of onset of symptoms is within 2 weeks <u>after</u> receiving OCV.** This should be based on documentary evidence rather than verbal reporting as far as possible.
- **Ruling out all other possible causes of the symptoms.** This may require laboratory testing.

Additional investigation should be carried out to try and determine if the serious AEFI has been caused by:

- Programme error - caused by an error in vaccine preparation, handling or administration
- Vaccine reaction - caused or precipitated by the vaccine when given correctly, caused by the inherent properties of the vaccine.

Annex 4 provides a list of information that can be collected to assist with the investigation.

4. Reporting and analysis

Reporting of AEFI

If associated with immunization, the AEFI will appear within two weeks after the end of each vaccination round. Therefore reporting of AEFI should start on the first day of the first round of the vaccination campaign and continue for two weeks after completion of the second round of vaccination.

It is recommended that each health centre or "reporting unit" send to district health authorities all completed individual reporting forms (see Annex 2) of AEFI suspected to be linked to OCV vaccination, two weeks after the second round of vaccination. There should be a "zero events" notification if no AEFI have been detected or reported from vaccination sites.

When a serious AEFI is detected it must be treated and reported immediately (by telephone, email, or fax) to the district, regional and central level. Serious AEFI should be followed, managed appropriately by qualified healthcare staff and their outcome reported to the central level.

The results of the investigation into the link with OCV vaccination should be reported at the central level as soon as these become available including the method(s) for ruling out other possible causes of serious AEFI, and the results of laboratory tests carried out.

AEFI in patients that have received OCV inadvertently

If the following groups of people were administered OCV and present with AEFI (serious or non-serious) in the two weeks following vaccination with OCV, they should be followed up until they are fully recovered to ensure any additional AEFIs are detected and treated rapidly. The outcome of these patients (serious AEFI or non-serious AEFI) should be recorded and presented in the analysis .

- Pregnant women (both the mother and baby must be followed up).
- Immuno-compromised people that received Shanchol™™Shanchol™inadvertently
- Children aged less than 2 administered Dukoral® ® inadvertently, and infants (aged less than 1 year) administered Shanchol™™Shanchol™ inadvertently.

Analysis of AEFI

Data collected in AEFI surveillance activities should be entered at the central level. The data analysis should give the indicators detailed in Annex 5. This analysis should be completed 3 weeks after the second round of OCV vaccination. The national committee on AEFI should discuss and validate the results and draw conclusions of any investigation(s) in terms of diagnosis and putative causal link with the vaccination. A copy of the analysis should be sent to ICGsecretariat@who.int.

Annexes

Annex 1. Responsibilities at the health facility, district and regional levels

Central level

The following responsibilities should be designated at the central level.

- The national committee should be proactively involved in setting up surveillance of AEFI and be ready to respond to any reports of serious events to
    - direct necessary investigations, and
    - make a causality review of serious AEFI;
- national epidemiological surveillance officials must monitor AEFI reporting and organize input and analysis of reported data.

Regional health authority level

A focal point for AEFI surveillance should be designated within the regional health authority, responsible for:

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

District health authority level

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

Health facility level

If AEFI are reported to the vaccination team, they should coordinate with the clinician at the local health facility to refer the affected person(s) for appropriate management. The clinician is responsible for:

- case management
- analysing medical data on serious or non-serious AEFI cases recorded on reporting forms or transmitted by health care personnel who reported the case;
- forwarding as quickly as possible clinical details on suspected serious AEFI to the district health authority and national committee; and
- participating in the investigation of any serious AEFI in the district and at the vaccination site.

Annex 2. Individual notification report of AEFI

VACCINATION SITE:

District name (in CAPITAL letters): ----------

Vaccination date (dd/mm/yyyy): ----------

Vaccination site: ----------

Vaccine batch number: ----------

First name and Last name of the person filling the form: ----------

IDENTIFICATION OF THE PERSON SUFFERING THE ADVERSE EVENTS

First Name: ----------

Last Name: ----------

Sex: Male [ ] Female [ ]

If woman, pregnant? Yes [ ] No [ ] Do not know [ ]
n.b OCV is not recommended for use in pregnancy because of the lack of evidence to evaluate the safety and immunogicity of OCV in pregnant women.

Is the person immune-compromised? Yes [ ] No [ ] Do not know [ ]
n.b Dukoral® can be given to HIV-infected persons, however Shanchol™ is not recommended because of the absence of clinical data to indicate that it is safe. Administration may be considered after a benefit- risk evaluation.

Date of birth (dd/mm/yyyy): ---------- **Age (if date of birth not known)**: ----------years

MEDICAL HISTORY

Does the person have a history of allergy? Yes [ ] No [ ] Do not know [ ]

If "yes ", please specify which type of allergy ----------

AEFI OBSERVED

Date of onset of symptoms (dd/mm/yyyyy): ----------

Number of days between receipt of vaccine and onset of symptoms: ---------- **days**

CLINICAL SIGNS

Please specify by ticking the appropriate box whether the clinical sign is present or not **AND** whether it is serious or not

Clinical sign(s)	Presence		Seriousness of symptom(s)	
	Present	Not present	Serious	Non- serious
Acute watery diarrhoea (AWD)				
Vomiting				
Nausea				
Abdominal pain				
Fever				
Other Diarrhoea				
Acute gastritis				
Cough and cold				
Anaphylactic reaction				

*** Anaphylactic reaction: (Cardiovascular collapse (e.g altered consciousness, low blood pressure, weakness or absence of peripheral pulse, cold extremities) may be accompanied by bronchospasm, laryngospasm, laryngeal edema or all of these symptoms with respiratory insufficiency that manifests immediately after the vaccination**

Other clinical sign(s) No [ ] Yes [ ] if yes, please specify below which and if serious or not

n.b. Other clinical signs might be: loss or poor appetite, dehydration, headache, dizziness, drowsiness, insomnia, fainting, reduced sense of taste, abdominal cramps, stomach/abdominal gurgling (gas), sore throat, dyspepsia, sweating, rash, joint pain, itching, weakness, dryness of mouth, oral ulcer, yellowing of urine.

PATIENT OUTCOME

Full recovery Yes [ ] No [ ] Do not know [ ]

Death Yes [ ] No [ ] Do not know [ ]

Hospitalisation Yes [ ] No [ ] Do not know [ ]

Managed by (Name, function and facility): ----------

Annex 3. Data to be collected for each serious AEFI case or cluster investigation

Patient:

- demographic data about patient, including a unique case number and contact information;
- history of patient's present illness - symptoms, when they appeared and their duration, treatment, outcome; diagnosis;
- history of patient's past illnesses - reactions to previous doses, drug allergies, pre-existing neurological or gastrointestinal disorders, current medications;
- OCV immunization history - vaccine, number of doses received, date, and place of last immunization or immunizations;
- laboratory results about blood, stool, or other samples, if appropriate.

OCV administered to the patient:

- Location where OCV was administered/vaccination site
- Lot number
- Expiry date
- Manufacturer
- When and from where vaccine was sent
- Laboratory results about vaccine, if appropriate

Programme-related data.

Common practices in storing and handling vaccines, and vaccine administration at the sites where OCV was administered.

Other people in the area:

- Number of people who received immunizations with vaccine from the same lot or in the same immunization session, or both, and the number of these who fell ill and their symptoms
- Number of unimmunized people or people immunized with other lots (from the same or a different manufacturer) who fell ill with similar symptoms

Annex 4. Information to be collected during the investigation

Information	Source
1. Information to be obtained in all cases	
Proof of vaccination and details of vaccine administered	(Manufacturer, batch number, expiry dates of vaccine and diluent) . Vaccination card . Pharmacy record (to check which lots were dispatched to which site)
Age, sex and contact address	Vaccination card/patient or relative/friend
State of health at time of vaccination	Patient, relative/friend (or vaccinator)
Past history of similar reactions (description)	Patient or relative/friend
Clinical course/results of clinical examination/patient's state of health at time of investigation/diagnosis at time of investigation (specific clinical and laboratory tests can be carried out depending on the AEFI suspected and the likely cause)	Patient or relative/friend, medical file, health worker
Results of laboratory tests conducted prior to and during the investigation	Health worker/medical file/test laboratory
Similar reaction among patient's relatives or friends or in the same geographical area (description)	Patient or relative/friend and neighbouring health centres/hospital
2. Information to be obtained where vaccine reaction is suspected	
Preservation/management of the cold chain	Depending on the vaccination facility/post, obtain temperature readings from the various vaccine storage sites; Cold chain indicators of unused vaccines stored at the same sites
Method used to keep track and dispose of opened vaccine vials	Vaccination team leader
Number of vaccines from the same batch, storage facilities and vaccination posts concerned	Immunization campaign supervisory teams, person responsible for logistical operations/vaccine supply
Whether the vaccine may have caused the problem (number of doses administered from the same batch of vaccine)	Vaccination teams that used the vaccine from the same batch/record sheet
Result of quality control tests on a vial of vaccine with the same batch numbers as those administered to the patient	Laboratory with capacity to perform quality control tests. From designated AEFI manager at the district level responsible for arranging testing of Specimen/vial of vaccine with the same batch numbers as those administered to the patient
Any known allergy	Patient or relative
3. Information to be obtained where programme error is suspected	
Vaccination post and team (team members) concerned	Vaccination post (card)
Other material and items stored in the vaccine	Vaccination team and supervisory team

storage refrigerator	
Vaccination post	Vaccination card and AEFI case
Vaccinator's qualifications and training to administer the vaccine in question	Vaccination team leader
Method of ensuring that opened vials are accounted for and disposed of	Vaccination team leader
Number of OCV vaccine doses administered to the case in question	AEFI case or relative/friend or vaccinator
Other similar AEFI in the same geographical area	AEFI case or relative/friend and surrounding population; District-level AEFI surveillance data
Other similar AEFI in patients vaccinated by the same team	Health centres and hospitals close to the sites where the vaccination teams in question worked; District-level AEFI surveillance data
Other similar AEFI in patients vaccinated with the same batch	Health centres and hospitals close to vaccination sites that used the same batch of vaccine; District-level AEFI surveillance data

Annex 5. AEFI indicators for evaluation of OCV campaigns

1. **Type of surveillance**: Active [ ] Passive [ ] Survey [ ]

2. **Number of doses delivered (in round 1 and 2):** ----------

3. **Total number of AEFI reported during the vaccination campaign and in the 2 weeks after each round:** ---------

4. **Number of AEFI and severity of AEFI:**

	Number of adverse events	
	Serious	**Non-serious**
Acute watery diarrhoea (AWD)		
Vomiting		
Nausea		
Abdominal pain		
Fever		
Other diarrhoea		
Cough and cold		
Acute gastritis		
Anaphylactic reaction		
Other clinical signs (please specify below if any)		
(please specify)		
(please specify)		
(please specify)		
(please specify)		
(please specify)		
(please specify)		

5. **Of the total number of AEFI, numberamong patients with a history of allergy:** ----------

6. **Of the total number of AEFI, number among pregnant women:** ----------

   n.b Pregnant women would have been inadvertently vaccinated. OCV is not recommended for use in pregnancy because of the lack of evidence to evaluate the safety and immunogenicity of OCV in pregnant women.

7. **Of the total number of AEFI, number among immuno-compromised patients**: ----------

   n.b These persons would have been inadvertently vaccinated if the OCV used is Shanchol™. Dukoral® can be given to HIV-infected persons, however Shanchol™ is not recommended because of the absence of clinical data to indicate that it is safe. Administration may be considered after a benefit-risk evaluation.

8. Number of persons with AEFI by age group and sex:

Age	Serious		Non- serious	
	Male	**Female**	**Male**	**Female**
<1*				
1-4				
5 to 14				
15+				

***n.b** These children would have been inadvertently vaccinated

9. Number of persons with serious AEFI by Outcome:

Outcome	Numbers
Dead	
Fully recovered	
Hospitalized	
Outcome unknown	