AEFI/ AESI surveillance in the context of COVID-19 vaccine introduction

- Investigation and causality assessment -

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- Preparedness
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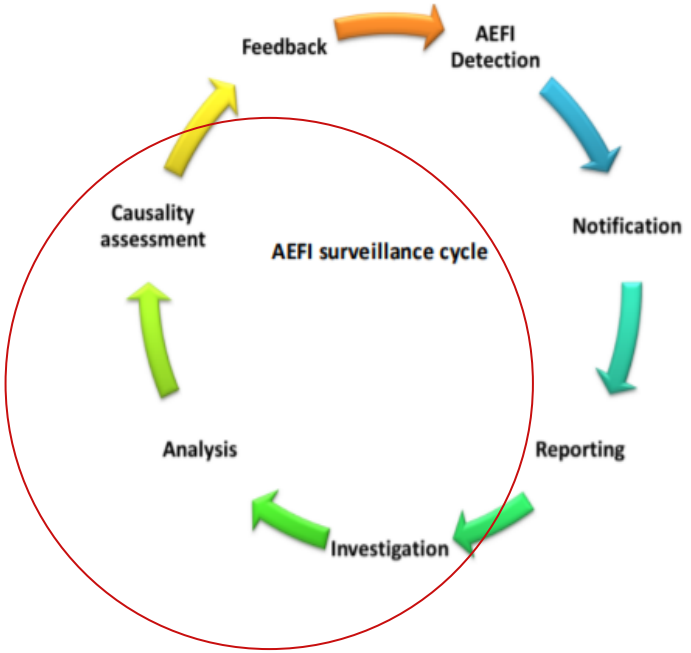
AEFI surveillance cycle



AEFI **CAUSALITY ASSESSMENT**

- General
- Case selection
- Key considerations for COVID-19 vaccine related AEFIs
- Levels and scientific basis
- Method

AESI investigation/ causality assessment

- If countries do not implement active surveillance for AESIs, all AESI-like adverse events occurring following COVID-19 immunization should be considered as **AEFIs**
- The **standard procedure for AEFI response should be adopted**

AEFI investigation - General

- Should be **timely, comprehensive and methodical**
  - Simple assessment, or
  - more rigorous scientific evaluation of the reported AEFI in order to recognize its possible cause(s)
  - Extent depends on the nature of the reported AEFI or/and the country's protocol to carry out the investigation
- Key: **Training** of relevant staff on the specific manifestations of COVID-19 vaccine-associated AEFIs.
- Important to **identify and rule out**:
  - immunization (or programme) error-related AEFIs
  - immunization stress-related responses
  - coincidental events.

Investigation of potential AEFIs - Preparedness

Decide who should conduct AEFI investigations	• Prepare investigation teams • Train the teams for AEFI investigation activities relevant to the population being vaccinated
Decide what should be investigated and when	• Develop the reporting system around these AEFIs • Timeframe
Tools and methods	• Update, print and distribute AEFI investigation tools
Ensure collection and storage of all relevant data for causality assessment	• AEFI reporting and investigation forms • clinical case record • laboratory reports • autopsy reports, etc.

AEFI investigation – Why?

- To identify the **details of vaccine(s)** administered + to determine the time interval between administration and onset of event (**time to onset**)
- To confirm the reported **diagnosis** or establish a diagnosis
- To document the **outcome** of the AEFI
- To identify the **cause** of the AEFI
- To determine whether a reported event is a **single incident** or one of a **cluster**
- To examine the **operational aspects of the programme** and detect and **prevent immunization-related errors**
- To determine whether **similar events are occurring in non-vaccinated population**

AEFI investigation – Who?

- **Profile of investigators** who carry out detailed AEFI field investigation
  - determined by the **operational structure** and the **expertise** available to the surveillance system in the country.
- **Level of investigation**
  - may vary depending on capacity at national and different sub-national levels.
  - where possible: at the level of the immunization service provider.
  - In some circumstances (*e.g.* immunization error-related events), basic preliminary investigation by local programme managers may be sufficient to identify the cause
- Each country will need to **identify adequate expertise** and **plan for responding to serious AEFIs tailored to the country's capacities**.

AEFI investigation – What?

AEFI should be investigated if it:

- appears to be a **serious event** (as defined by WHO) of known or unknown cause;
- belongs to a **cluster** of AEFI;
- is a **previously unrecognized event** associated with an old or newly introduced vaccine;
- involves an **increased number or rates of known cause**;
- is a suspected **immunization error**;
- appears on the **list of events defined for AEFI surveillance**; and
- causes **significant parental** or **public concern**.

AEFI investigation – When?

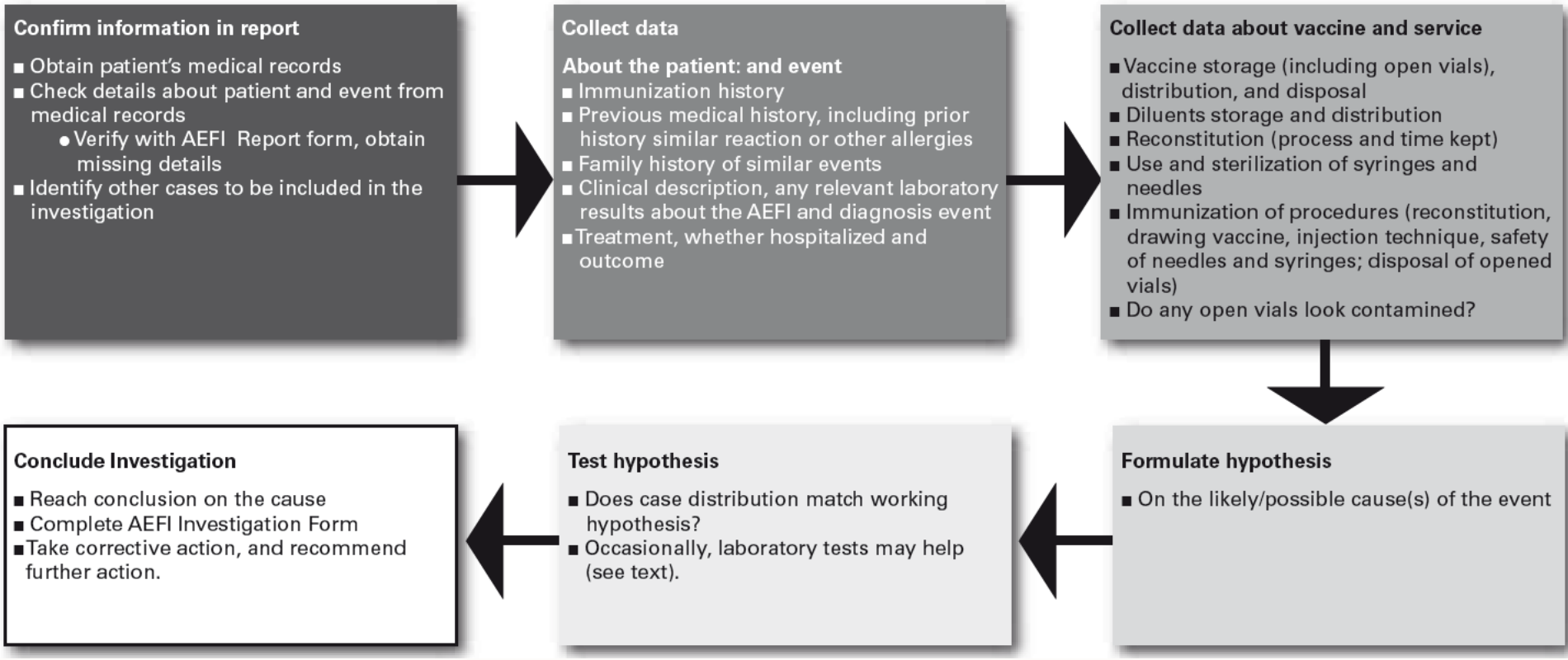
- The **urgency depends on the situation**.
  - If preliminary information suggests that field investigation is required, it should be initiated as soon as possible.

- **Standard timelines** for initiation of investigation should be defined by each country.
  - take into account capabilities and availability of personnel
  - allow for rapid responses were needed.

AEFI investigation – How?

- **Standard principles of epidemiologic investigation** apply
- Have clear working **case definitions**
  - e.g Brighton Collaboration case definitions
- Identify all cases in the community and find out the outcomes for all vaccinated subjects
- **Compare the risk of disease** between vaccinated and non-vaccinated subjects
- A **working hypothesis** is important
  - E.g., Abscess following immunization due to cold chain failure in vaccine storage
- Consider relevance/possibility for laboratory testing (not routine)

AEFI investigation overview



AEFI investigation – Tools

- COVID-19 specific AEFI investigation form

  Included in https://www.who.int/docs/default-source/covid-19-vaccines-safety-surveillance-manual/covid19vaccines_manual_aefi_20210104.pdf

Oct 2020

AEFI FOLLOWING COVID 19 VACCINATION - INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A **Basic details**

Province/State **District** **Case ID**

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

(use a separate form for each case in a cluster)

Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

OR Age at onset: __ __ *years* __ __ *months* __ __ __ *days*

OR Age group: ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years - 18 years* ☐ *> 18 years – 60 years* ☐ *> 60 years*

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

Brand name of vaccines (including manufacturer) /diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom *(hh/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)*: __ __ / __ __ / __ __ __ __ *(hh/mm)*: __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B **Relevant patient information prior to immunization**

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event?	Yes / No / Unkn	
Adverse event after any previous vaccination(s)?	Yes / No / Unkn	
History of allergy to vaccine, drug or food?	Yes / No / Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unkn	
Pre-existing acute illness (30 days) prior to vaccination?	Yes / No / Unkn	
Has the patient tested Covid19 positive prior to vaccination?	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause?	Yes / No / Unkn	
Was the patient receiving any concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy?	Yes / No / Unkn	
For adult women • Currently pregnant? Yes (weeks) _____ / No / Unknown • Currently breastfeeding? Yes / No		

For infants

The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

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:

Name and contact information of person completing these clinical details:	Designation:	Date/time

****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports, prescriptions for concomitant medication) 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

Number immunized for each antigen at session site. Attach record if available.										
	Vaccine name									
	Number of doses									

a)	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?	
b)	Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No
c)	Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes* / No / Unable to assess
d)	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
e)	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
f)	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
g)	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
h)	Number immunized from the concerned vaccine vial/ampoule	
i)	Number immunized with the concerned vaccine in the same session	
j)	Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations: _____	
k)	Could the vaccine given to this patient have a quality defect or is substandard or falsified?	Yes* / No / Unable to assess
l)	Could this event be a stress response related to immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	Yes* / No / Unable to assess
m)	Is this case a part of a cluster?	Yes* / No / Unkn
i.	If yes, how many other cases have been detected in the cluster?	
a.	Did all the cases in the cluster receive vaccine from the same vial?	Yes* / No / Unkn
b.	If no, number of vials used in the cluster (enter details separately)	

It is compulsory for you to provide explanations for these answers 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 / Unkn

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 (✓)	Status		
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same 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:

Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)	
• Correct dose and route?	Yes / No
• Time of reconstitution mentioned on the vial? (in case of freeze dried vaccines)	Yes / No
• Non-touch technique followed?	Yes / No
• Contraindications screened prior to vaccination?	Yes / No
• How many AEFI were reported from the centre that distributed the vaccine in the last 30 days?	
• Training received by the vaccinator? (If Yes, specify the date of last training _____)	Yes / No
Specific key findings/ additional observations and comments?	

Section F **Cold chain and transport** *(Complete this section by asking and/or observing practice)*	
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation:	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
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 effected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

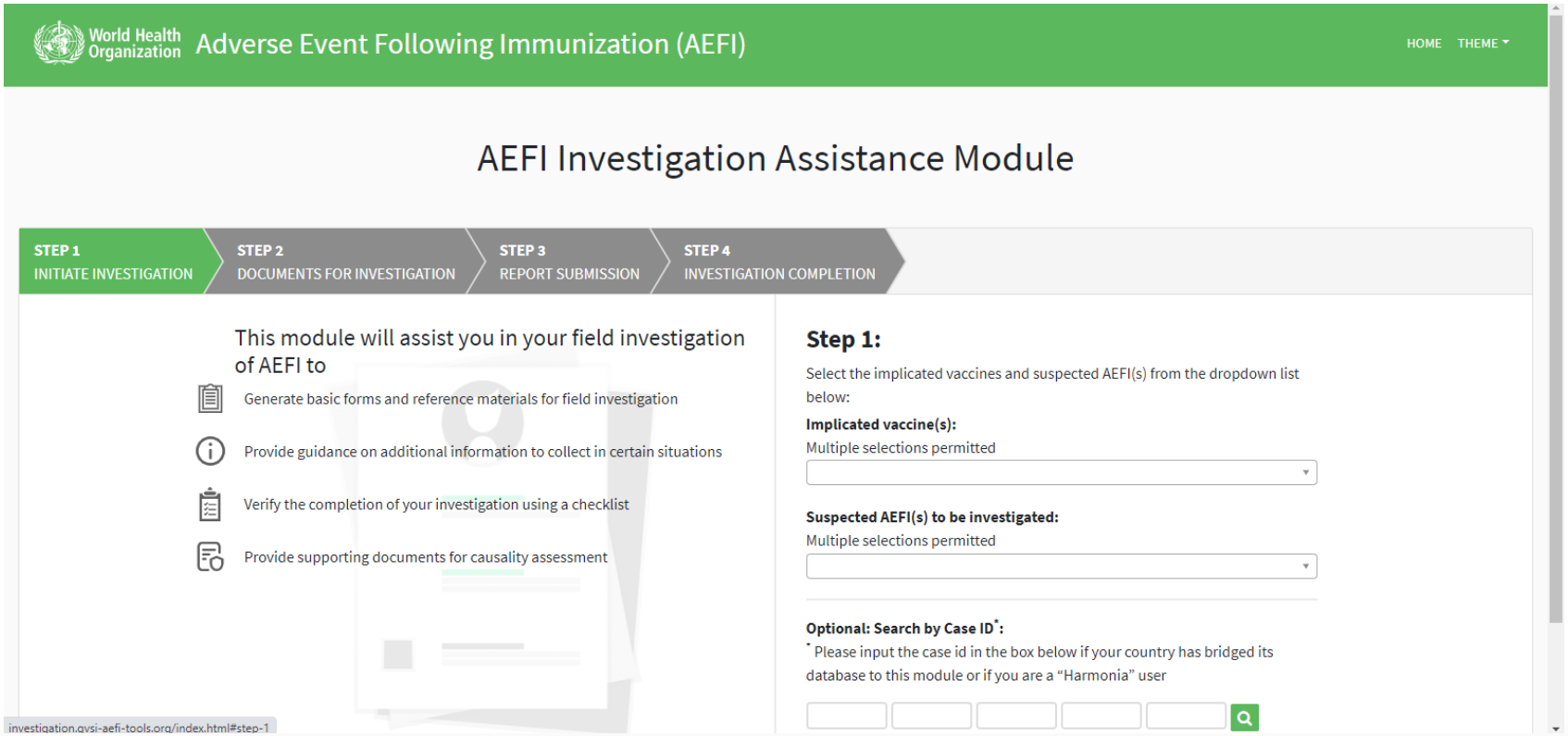
Other comments:

Section H Other findings/observations/comments

AEFI investigation – tools

- WHO AEFI investigation software

  http://investigation.gvsi-aefi-tools.org/index.html#step-1



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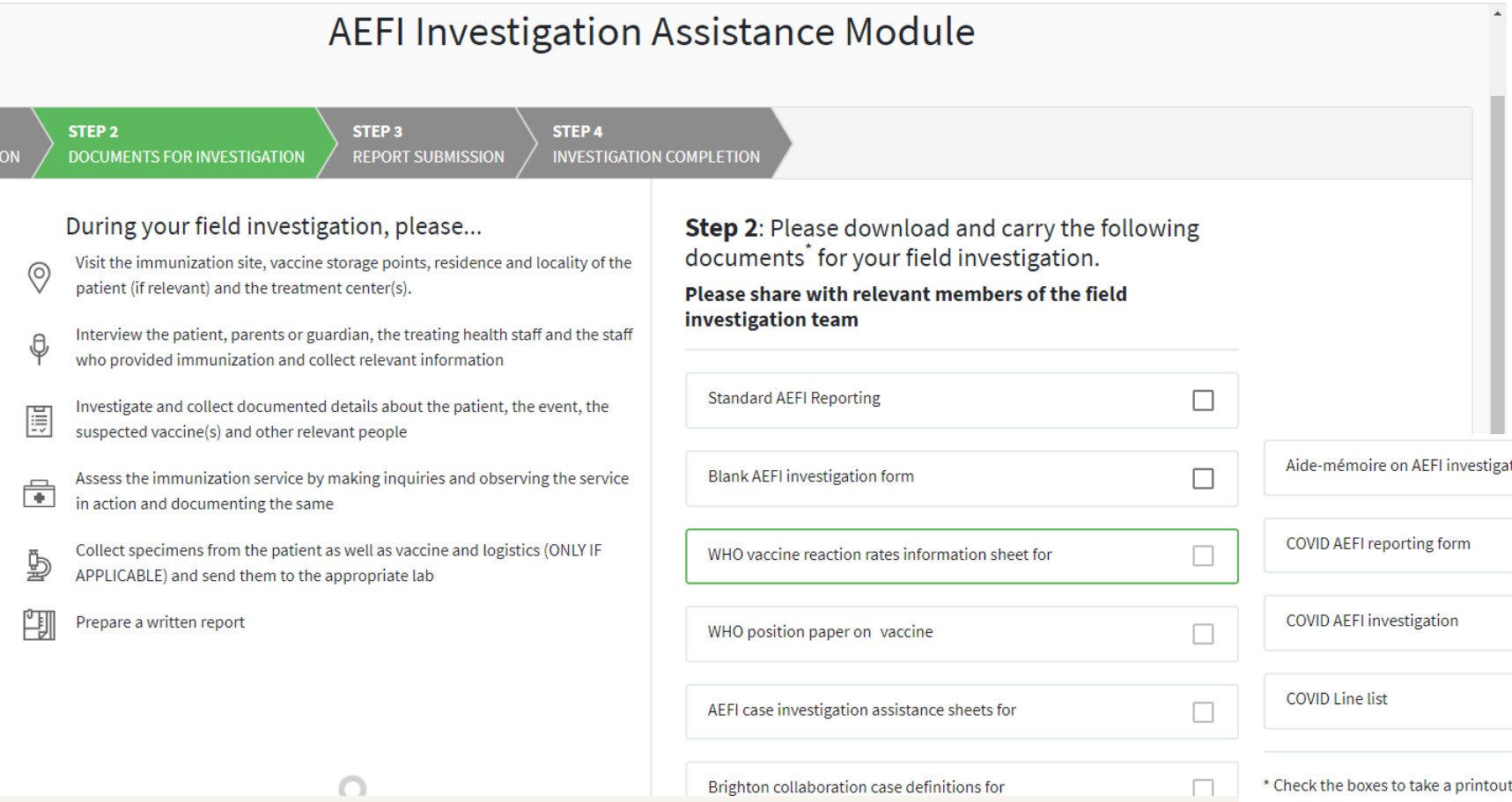

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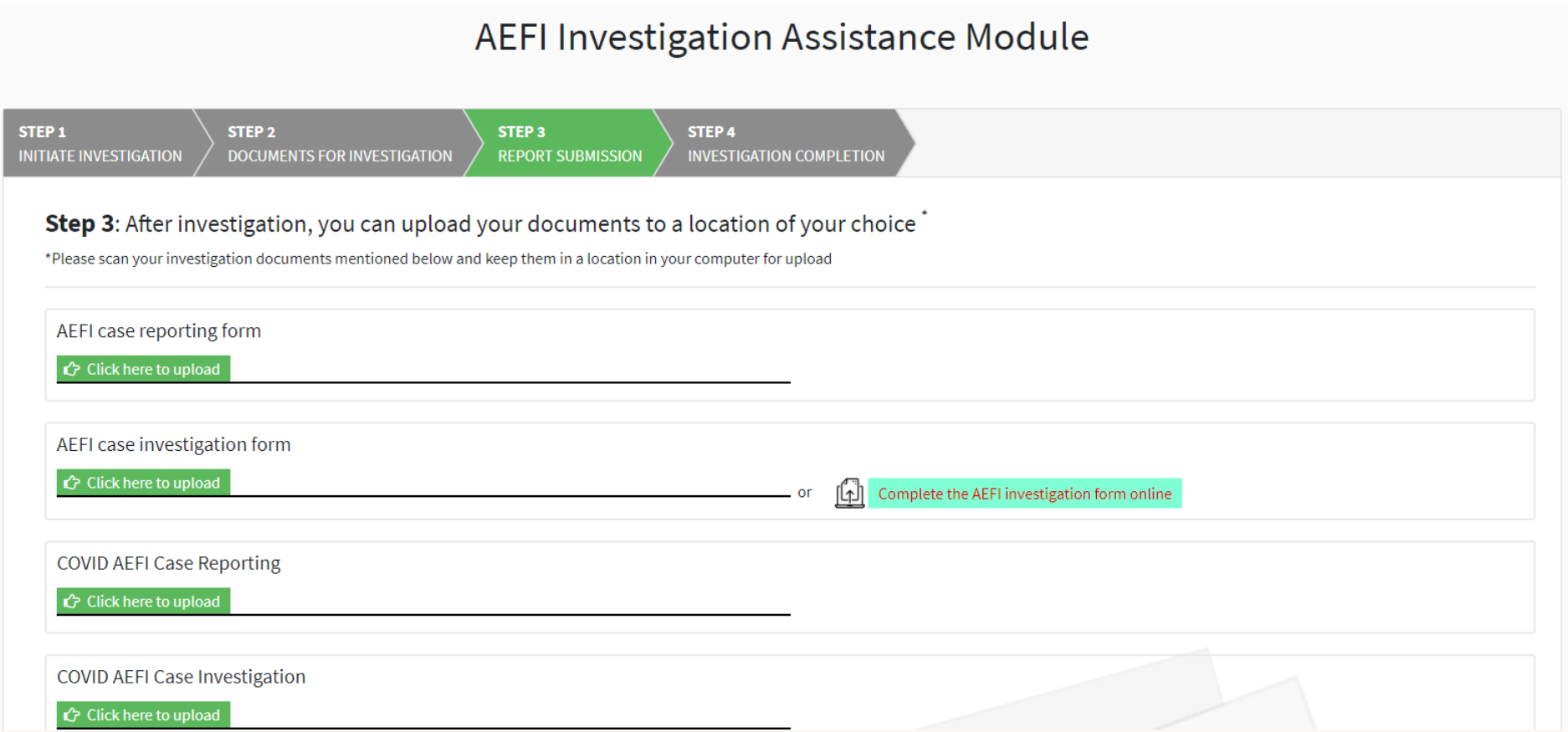

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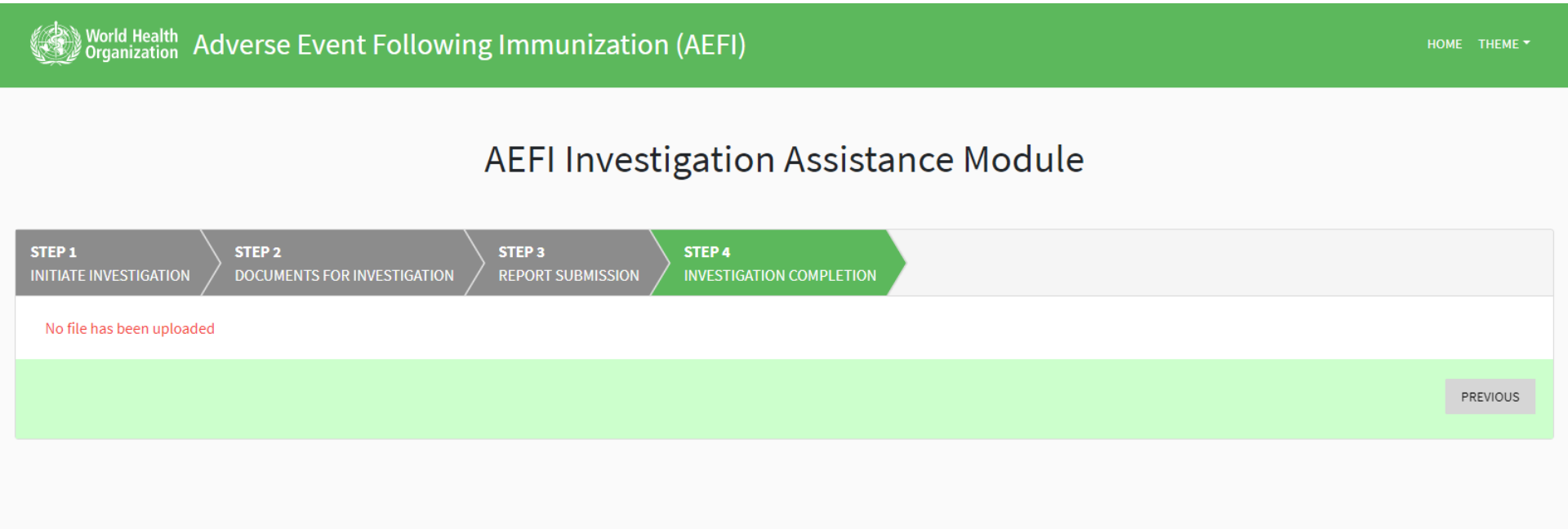


AEFI investigation – tools

- WHO AEFI investigation aide mémoire

  https://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf

World Health Organization

ADVERSE EVENT FOLLOWING IMMUNIZATION

AIDE-MÉMOIRE ON AEFI INVESTIGATION

Purpose: This aide-mémoire proposes a systematic, standardized process to investigate reported serious adverse events following immunization (AEFI) and ascertain the underlying cause of the AEFI by:

- confirming a diagnosis and timing
- identifying details of vaccine(s) administered
- documenting the outcome of the reported adverse event
- determining whether the reported event is solitary or part of a cluster
- reviewing the operational aspects of the programme

DETECTION AND REPORTING

Vaccine recipients themselves and/or parents of vaccine recipients who identify AEFI should notify the same to the health care provider. All notified AEFI cases should be documented and reported in a simple standard reporting form by the health care provider.

WHICH OF THE REPORTED AEFI SHOULD BE INVESTIGATED IN MORE DETAIL?

A detailed AEFI investigation to assess causality is necessary if:

- it is serious[i]
- it is part of a cluster[ii]
- it is part of a suspected signal[iii]
- it is a suspected immunization error[iv]
- it appears on the list of events defined for AEFI investigation or
- it causes significant parental or public concern

WHO SHOULD INVESTIGATE AEFI?

Detailed AEFI field investigation can be done based on the program's operational structure and the expertise available. A basic preliminary investigation by local programme managers may be sufficient if the cause of the reported AEFI is very clear; otherwise, investigation should be done by next/higher administrative level, by a trained/skilled person/ team, depending on the nature of event, its seriousness and impact to the programme.

WHEN TO INVESTIGATE AEFI?

If a detailed investigation is warranted, it should be initiated as soon as possible, ideally within 24 to 48 hours of the case being first reported.

CHECKLIST FOR AEFI INVESTIGATION

1. PRELIMINARY STEPS

- ☐ Develop national guidelines with case definitions for reportable AEFIs, reporting forms, investigation procedures, roles and responsibilities
- ☐ Develop resource documents and training material on reporting, management and investigation of AEFIs
- ☐ Designate and train staff to conduct an AEFI investigation using the investigation form and guidelines
- ☐ Train staff on how to collect and store specimens
- ☐ Have a functioning National AEFI Review Committee with suitable representation
- ☐ Establish procedure, criteria and designate focal persons for notifying and communicating with WHO and UNICEF (if UN- supplied vaccine) or other relevant party depending on procurement mechanism
- ☐ Identify a spokesperson for public communications

2. RECEIVING A REPORT

- ☐ Provide rapid attention to all reports received and immediate response to serious events
- ☐ Verify the information in the report, confirm the diagnosis, classify and assess the AEFI using established case definitions. Decide whether it needs further detailed investigation.
- ☐ If investigation is warranted, travel to the location of the AEFI, or delegate responsibility to another trained person

3. INVESTIGATE AND COLLECT DATA

- ☐ Obtain information from patient or relatives directly/ use available records
- ☐ Obtain information from immunization service providers and medical care service providers (hospital staff)/ use available records
- ☐ Ask about the vaccine(s) administered and other drugs potentially received
- ☐ Establish a more specific case definition if needed
- ☐ Ask about other vaccinees who may have received the same or other vaccines
- ☐ Observe the service in action
- ☐ Ask about cases in unvaccinated persons
- ☐ Formulate a hypothesis as to what may have caused the AEFI (see table below)
- ☐ Collect specimens (if indicated by investigation, but not as a routine):
  - ✓ from the patient
  - ✓ the vaccine and diluent if applicable
  - ✓ the syringes and needles

ADVERSE EVENT FOLLOWING IMMUNIZATION

World Health Organization

- ☐ Dispatch specimens to appropriate testing facility (laboratory, regulatory authority, etc.)

4. ANALYSE THE DATA

- ☐ Review epidemiological, clinical, and laboratory findings
- ☐ Share findings with national AEFI committee for expert advice
- ☐ Summarize and report findings

5. TAKE ACTION

The local response after an AEFI investigation should be based on findings (data/information) and local practices.. The highest priority is to treat patient. Suspending vaccination at the locality of the event temporarily pending investigation outcome may be necessary but is uncommon. Broader suspension of vaccination is only very rarely necessary. When taking action, it is important to

- ☐ Provide feedback to health staff
- ☐ Communicate findings and action to the parents and public – during all stages of the investigation
- ☐ Correct problem (based on the cause) by improving training, supervision and/or distribution of vaccines/injection equipment
- ☐ Replace vaccines if indicated

INVESTIGATING DEATHS AFTER IMMUNIZATION

After informing higher authorities, field investigation should be conducted by a team of clinical, laboratory and forensic experts supported by programme managers. A decision on autopsy should be taken within the local sociocultural, religious, political context. Autopsies should be done with adequate information of the circumstances of the event using standard autopsy protocols. Appropriate specimens should be collected for testing.

If an autopsy is not possible, a verbal autopsy can be carried out using established guidelines and protocols.

OUTCOME OF AEFI INVESTIGATION

On concluding the investigation, the documents and evidence collected should be compiled, a report prepared and submitted to a group of experts to determine/evaluate causality.

POSSIBLE CAUSES OF AEFI
Related to vaccine or vaccination
Vaccine product-related
Vaccine quality defect-related
Immunization error-related
Immunization anxiety-related
Coincidental adverse event

KEY RESOURCES FOR AEFI INVESTIGATION

- WHO standard AEFI reporting form http://www.who.int/vaccine_safety/REPORTING_FORM_FOR_ADVERSE_EVENTS_FOLLOWING_IMMUNIZATION.pdf?ua=1
- WHO standard AEFI investigation form http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_form_2Dec14.pdf?ua=1
- Global manual on surveillance of AEFI http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/
- User manual for the revised WHO AEFI causality assessment classification http://www.who.int/vaccine_safety/publications/gvs_aefi/en/
- Brighton Collaboration standard case definitions https://brightoncollaboration.org/public.html
- Verbal autopsy standards: ascertaining and attributing causes of death http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/index1.html

[i] An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

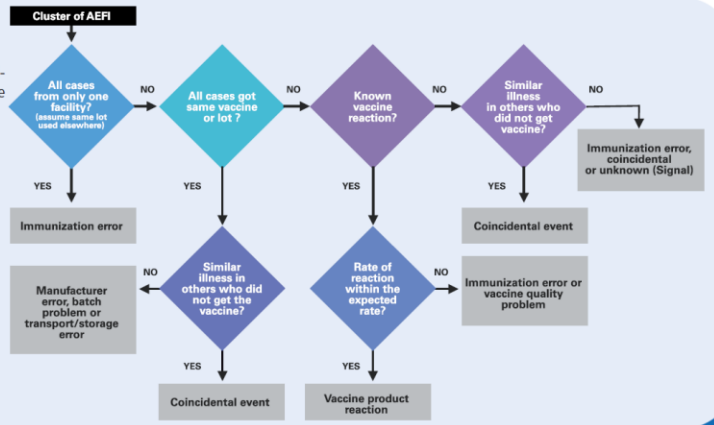
[ii] Serious AEFI include death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or is life-threatening

[iii] A cluster of AEFIs is two or more cases of the same adverse event related in time, place or vaccine administered

[iv] 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.

INVESTIGATING AEFI CLUSTERS

Suggested steps for identifying the most likely cause of a cluster of AEFI



Contact us: Essential Medicines and Health Products (EMP) Department, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland. Fax: +41 22 791 42 10
http://www.who.int/vaccine_safety/en/ E-mail: vaccsafety@who.int.

giz Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH

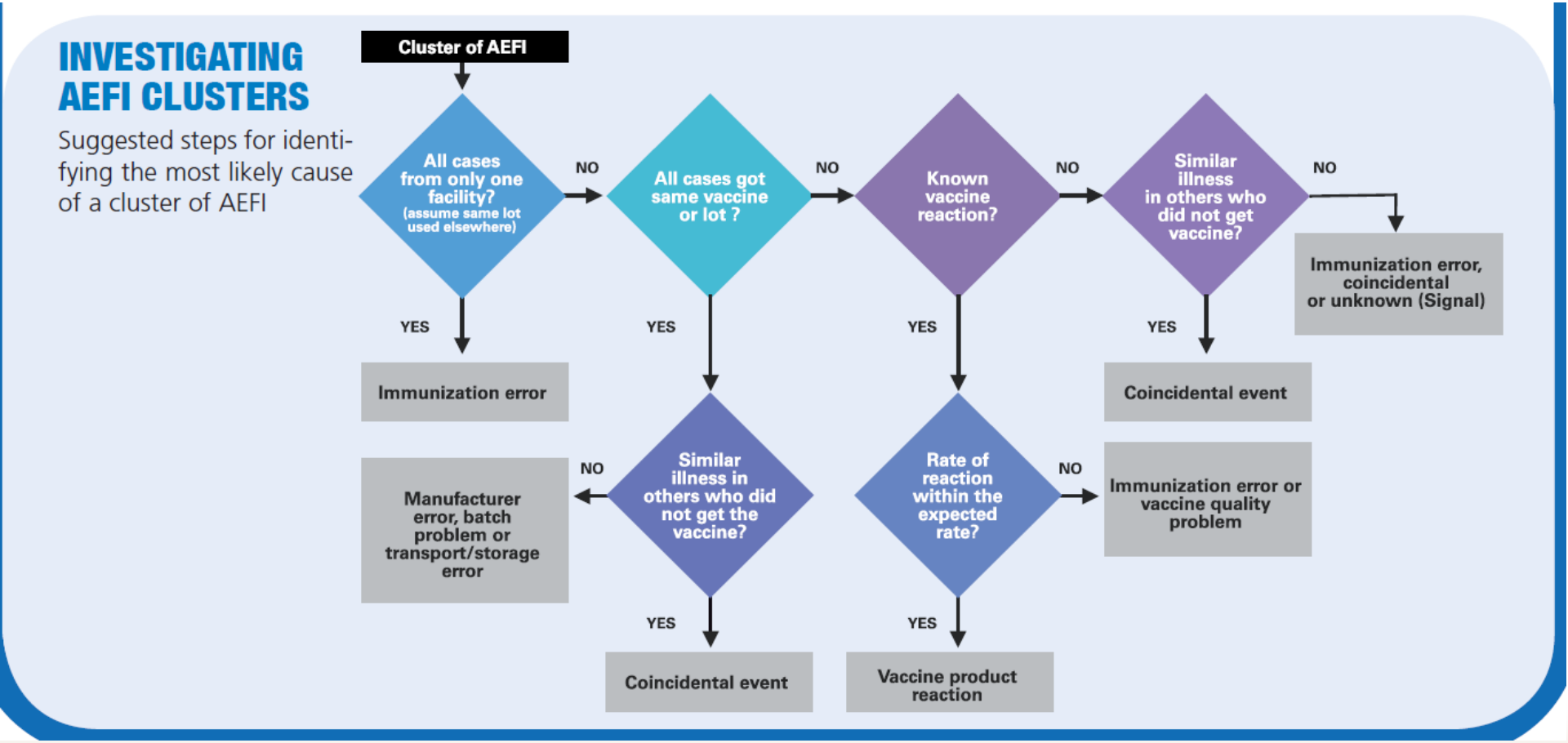
AEFI investigation – clusters

- **Definition** of cluster
  - **Two or more cases** of the **same AE** related in time, place or vaccine administration
- When vaccines are administered on a massive scale: important for immunization programmes to **anticipate** and **prepare for clusters** of AEFI
- **Clusters can be detected** by gathering details such as:
  - detailed data on each patient
  - programme-related data (storage, handling, etc)
  - immunization practices and healthcare workers practices
- **Cluster investigation**
  1. establish a case definition for the AEFI and related circumstances
  2. identify all cases that meet the case definition
  3. promptly characterize all known cases and research similar ones

AEFI investigation – clusters (cont´d)

- Identify **common exposures among the cases** by reviewing:
  - all data on vaccines used (name, lot number, etc)
  - data on other people in the area (including non-exposed)
  - any potentially coincident factors in the community
- Consider and investigate any **potential causes** such as:
  - vaccine quality defects
  - immunization error-related AEFI
  - immunization anxiety-related reactions
- Due to novelty of the COVID-19 vaccines, the different technologies and conservation methods, it's important to identify quickly potential signals related to their use.

AEFI investigation – clusters (cont´d)



https://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf

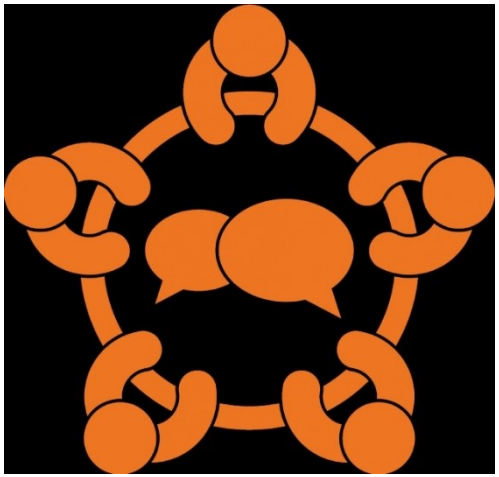
AEFI investigation – Deaths

- **All administrative levels should be notified of the death**
  - includes the national immunization programme.
- An **autopsy is preferred** and is **recommended following all deaths suspected to be caused by vaccine or immunization**.
- A **field investigation** of a death following immunization is often essential to **exclude any coincidental causes of an AEFI**.
  - conducted **without delay** as the death can cause significant community concern.
  - carried out by a **team of clinical, laboratory** and **forensic experts**.

AEFI investigation – communication

- The **findings of the investigation** should be shared with:
  - the immunization service provider
  - the authorities at the national level

Please share your experience with those investigation tools, if any



AEFI causality assessment - General

- Causality assessment
  - **= systematic review of data about an AEFI case**
  - aims to determine the **likelihood of a causal association** between the event and the vaccine(s)
  - critical part of AEFI monitoring to **ensure scientific evaluation of potential COVID-19 vaccine-related AEFI** and to **enhance confidence in the immunization programme**.
- Countries preparedness
  - **All countries must establish a process for causality assessment prior to the introduction of COVID-19 vaccines** - with a functional expert group for causality assessment either at national, subnational, or regional levels.
    - Not sufficient local ressources? Collaborate with neighbouring countries if possible

AEFI causality assessment - General

- AEFI causality assessment committee
  - experts from different medical disciplines.
- Committees aimed at identifying signals
  - additional expertise from statisticians and epidemiologists.
- All committees must be independent
- Causality assessment for AESI cases that have history of COVID-19 vaccination: method used for AEFI

AEFI causality assessment – Case selection

AEFI cases reported from passive surveillance systems are selected for causality assessment with focus on the following situations:

- serious AEFIs in vaccinated patients that
  - result in **death**
  - are **life-threatening**
  - require inpatient **hospitalization** or prolongation of existing hospitalization
  - result in **persistent or significant disability/incapacity**
  - result in a **congenital anomaly/birth defect**
- occurrence of events with an **unexpected high rate or unusual severity**
- **signals** generated as a result of individual or clustered cases
- **significant events of unexplained cause, occurring up to 1 year after COVID-19 vaccination** (not listed in the product information)
- events causing **significant parental, family or community concerns**.

AEFI causality assessment – case selection (con't)

Other AEFIs that may require causality assessment:

- AEFI that may have been caused by **immunization error** (*e.g.* bacterial abscess, severe local reaction, high fever, sepsis, toxic shock syndrome, etc);
- **significant events of unexplained cause occurring within 30 days after a vaccination** (and not listed in the product label);
- events that are causing **significant parental or community concern** and where a formal case assessment can provide a **detailed, more reassuring explanation to the parents and/or community** (e.g. febrile seizures).

AEFI causality assessment – case selection (con't)

Cases selected should have a **completed AEFI investigation dossier** containing:

- AEFI form
- case investigation form
- clinical case record
- laboratory report
- details of field investigation
- autopsy report where applicable

AEFI causality assessment – key considerations for COVID-19 vaccine related AEFIs

- Evidence for causes other than COVID-19 vaccines:
  - Prior **knowledge on background rates** of AEFIs are essential to determine if the event is associated or not with the vaccine.
- Known causal association between COVID-19 vaccines and vaccination:
  - **Information available from clinical trials**, information **published on vaccine platforms** and **brand specific AEFI rates** will be useful for the assessment.
  - In addition, **risk management plans** and **PSURs** provided by the vaccine manufacturers and MAHs will be useful.
- Novel administration technologies and handling requirements:
  - Administration of some COVID-19 vaccines will require **specific skills for storage conditions and handling of new technology**. This could increase the risk of immunization-related errors.

AEFI causality assessment – key considerations for COVID-19 vaccine related AEFIs (cont´d)

- Diverse age groups:
  - The use of COVID-19 vaccines for the immunization of adults and adolescents and in mass campaigns could increase the risk of reporting of **immunization anxiety** or **immunization stress-related responses**.
- Other qualifying factors for classification:
  - These could include **previous history of a similar event, background rates of pre-existing, present and past health conditions, medications,** etc.
- Vaccine-enhanced COVID-19 disease:
  - **risk to develop COVID-19-like disease or its complications**. Also a potential risk of individuals that have received COVID-19 vaccination could **develop severe COVID-19 disease when exposed to wild-type COVID-19 virus**. At present, there is no evidence that either of these risks exist for COVID-19 vaccines, but they cannot be excluded

AEFI causality assessment – levels and scientific basis

Causality assessment should be done at different levels:

- population level: necessary to test if there is a causal association between the use of a vaccine and a particular AEFI in the population
- Individual AEFI report: determine if an AEFI in a specific individual is causally related to the use of the vaccine
- Investigation of signals

AEFI causality assessment – levels and scientific basis (cont´d)

Population level

The aim is to answer the question **"Can the given vaccine cause a particular adverse event?"** (*i.e.* "Can it?").

Population level assessments are done through epidemiological studies. Several criteria are relevant to establishing causality but only the first criterion is absolutely essential:

- **Temporal relationship** i.e the vaccine exposure must precede the onset of the event.
- **Strength of association**: The association should meet statistical significance to demonstrate that it was not simply a chance occurrence.

AEFI causality assessment – levels and scientific basis (cont´d)

- **Dose-response relationship**: Evidence that increasing exposure increases the risk of the event supports the suggestion of a causal relationship. However, one should keep in mind that, in the case of vaccines, dose and frequency tend to be fixed.
- **Consistency of evidence:** Similar or the same results generated by studies using different methods in different settings support a causal relationship.
- **Specificity**: The vaccine is the only cause of the event that can be shown.
- **Biological plausibility and coherence**: The association between the vaccine and the adverse event should be plausible and should be consistent with current knowledge of the biology of the vaccine and the adverse event.

AEFI causality assessment – levels and scientific basis (cont´d)

Individual level

The aim is to address the question **"Did the vaccine given to a particular individual cause the particular event reported?"** (i.e. "Did it?").

Usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report.

However, it is **important to try assessing this relationship** in order to identify a possible new vaccine product-related reaction, as well as to determine if the event is preventable or remedial - such as a product-related quality defect or immunization error.

AEFI causality assessment – levels and scientific basis (cont´d)

Investigation of signals

The assessment of whether a particular vaccine is likely to cause a particular AEFI takes into account all evidence:

- individual AEFI cases
- surveillance data and, where applicable
- cluster investigations as well as nonclinical data.

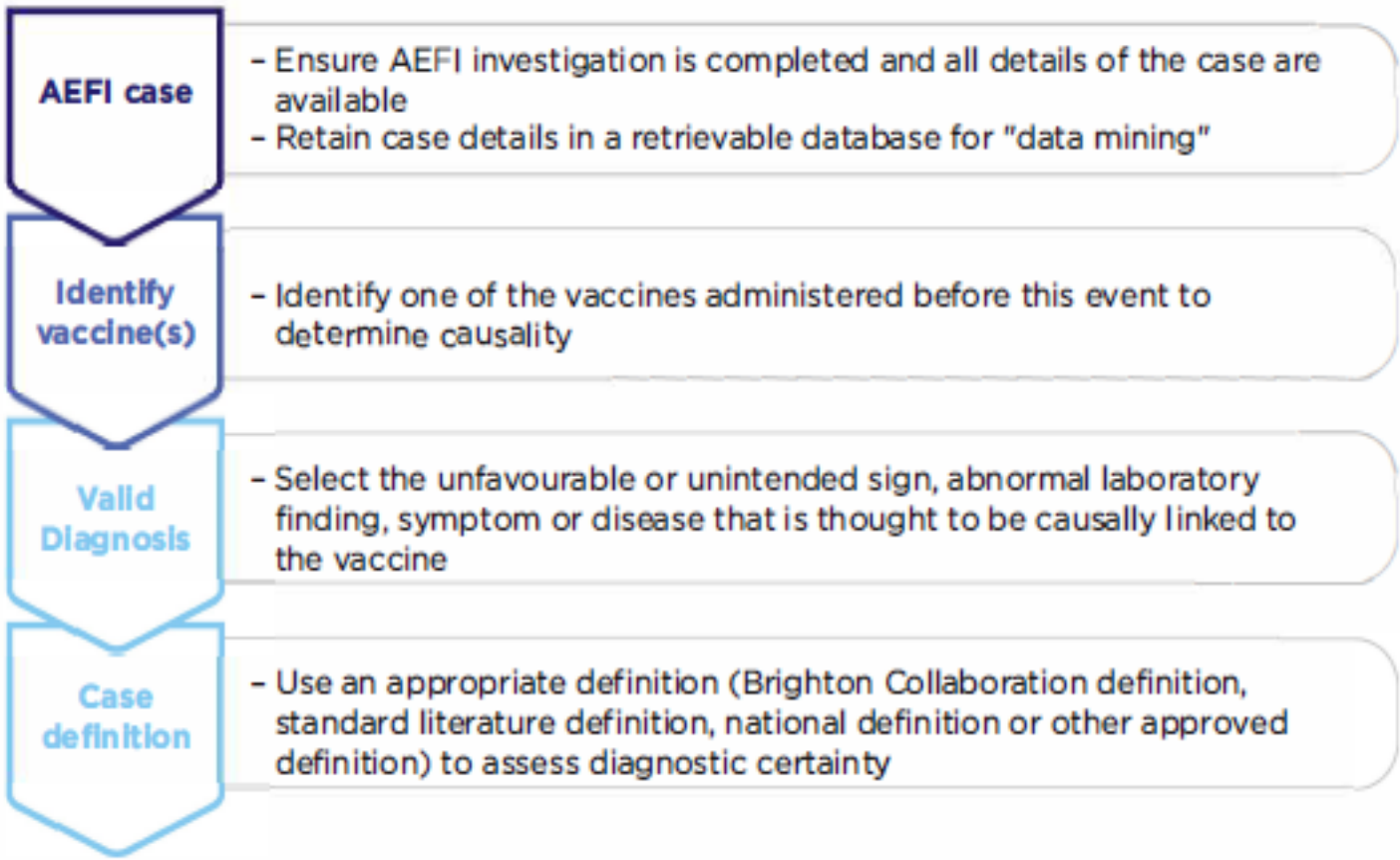
AEFI causality assessment - Steps for causality assessment of an individual AEFI

There are four steps in causality assessment.

- Step 1. Eligibility: to determine if the AEFI case satisfies the minimum criteria for causality assessment
- Step 2. Checklist: to systematically review the relevant and available information to address possible causal aspects of the AEFI
- Step 3. Algorithm: to obtain direction as to the causality with the information gathered in the checklist.
- Step 4. Classification: to categorize the AEFI's association to the vaccine/vaccination on the basis of the direction determined in the algorithm.

AEFI causality assessment – Method

Eligibility:



!

- Define the “causality question”
  - e.g., “Has the COVID-19 vaccine A caused anaphylaxis?”

AEFI causality assessment – Method

Step 1 (Eligibility)

Patient ID/Name :	*DoB/Age:*	*Sex: Male/Female*
Name one of the vaccines administered before this event	What is the Valid Diagnosis?	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine / vaccination caused _____ (The event for review in step 2 - valid diagnosis)

Is this case eligible for causality assessment? Yes/No; If, "Yes", proceed to step 2

AEFI causality assessment – Method (cont´d)

Checklist

The checklist contains elements to guide the reviewers as they collate the evidence for a case review.

The checklist can be found in the WHO updated manual on causality assessment of AEFI and focuses on:

- Evidences of other causes
- Known association with vaccine or vaccination (product, product quality, immunization error, immunization anxiety)
- Time to onset
- Other qualifying factors

AE causality software: http://gvsi-aefi-tools.org/

	Y	N	UK	NA	Remarks
I. Is there strong evidence for other causes?					
1. In this patient, does the medical history, clinical examination and/or investigations, confirm another cause for the event?	☐	☐	☐	☐	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product					
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	☐	☐	☐	☐	
2. Is there a biological plausibility that this vaccine could cause such an event?	☐	☐	☐	☐	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	☐	☐	☐	☐	
Vaccine quality					
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	☐	☐	☐	☐	
Immunization error					
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐	☐	☐	☐	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐	☐	☐	☐	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐	☐	☐	☐	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐	☐	☐	☐	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐	☐	☐	☐	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐	☐	☐	☐	

	Y	N	UK	NA	Remarks
Immunization anxiety (Immunization stress related responses - ISRR)					
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc)?	☐	☐	☐	☐	
II (time): Was the event in section II within the time window of increased risk (i.e. 'Yes" response to questions from II 1 to II 11 above)					
12. In this patient, did the event occur within a plausible time window after vaccine administration?	☐	☐	☐	☐	
III. Is there strong evidence against a causal association?					
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) **against** a causal association between the vaccine and the event?	☐	☐	☐	☐	
IV. Other qualifying factors for classification					
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	☐	☐	☐	☐	
2. In this patient, did such an event occur in the past independent of vaccination?	☐	☐	☐	☐	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐	☐	☐	☐	
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	☐	☐	☐	☐	
5. Was this patient taking any medication prior to the vaccination?	☐	☐	☐	☐	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☐	☐	☐	☐	

Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable.

Adverse Event Following Immunization (AEFI)

Home Language

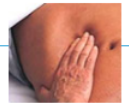
AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.

The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

This AEFI causality assessment is performed as per the WHO's revised causality assessment methodology which can be accessed at

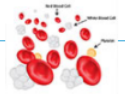
SYMPTOM

e.g. Cough, Rash, Pain Etc



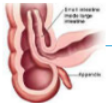
SIGN

e.g. Icterus, Hepatomegaly Etc



LAB FINDING

e.g. Thrombocytopenia, ECG Changes Etc



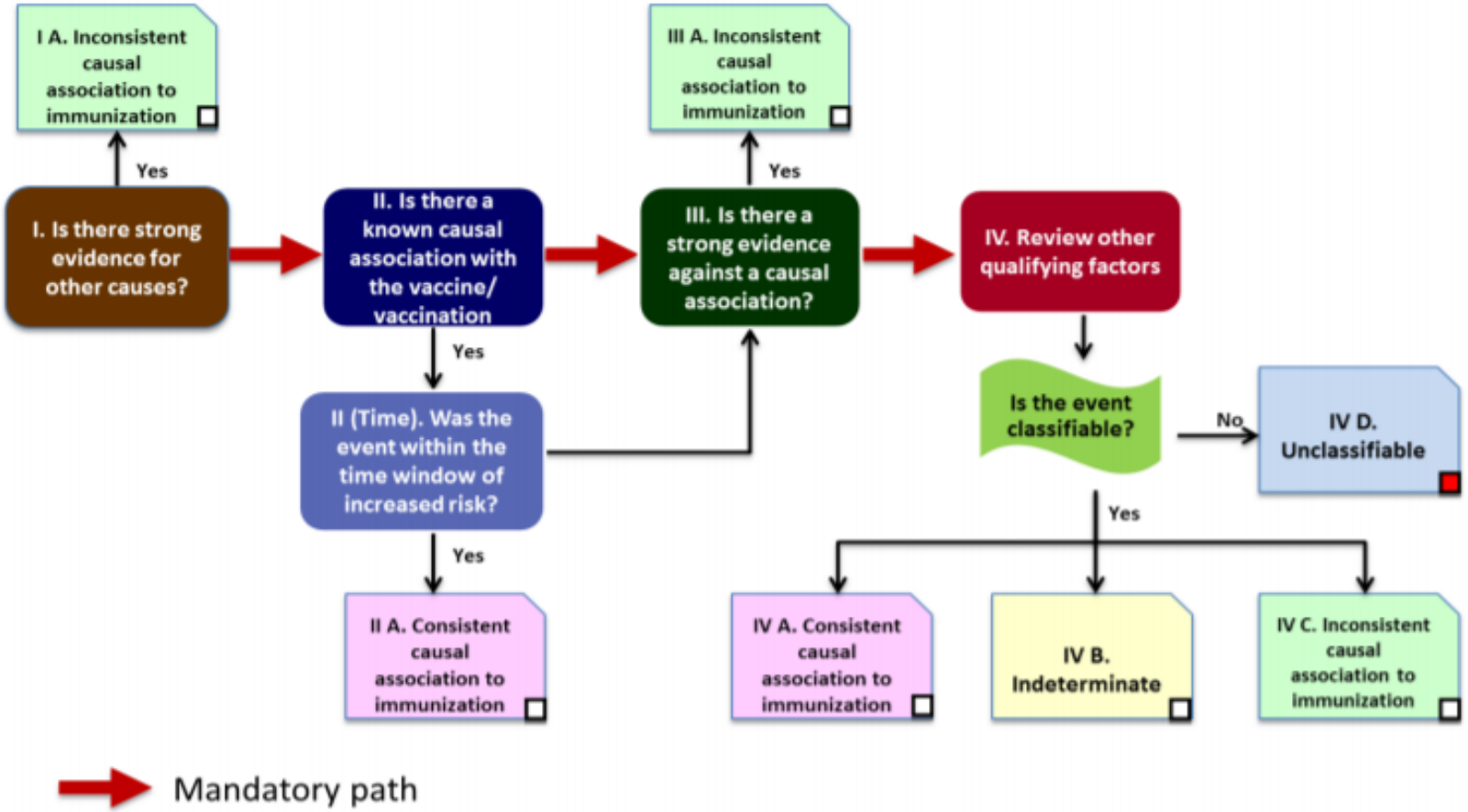
DISEASE

e.g. Intussusception, Meningitis Etc

Click here to access causality

AEFI causality assessment – Method (cont´d)

Algorithm



AEFI causality assessment – Method (cont´d)

Classification

Classification is critical as it provides direction to follow-up actions

Cases with adequate information for causality can be classified as follows:

A: Consistent causal association to immunization

- A.1: vaccine-product related reaction
- A.2: vaccine quality defect related reaction
- A.3: immunization error-related reaction
- A.4: immunization anxiety-related reaction

AEFI causality assessment – Method (cont´d)

Classification

B: Indeterminate

- B1. Temporal relationship is consistent but there is insufficient definitive evidence that vaccine caused the event (it may be a new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.
- B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization (i.e. it may be vaccine-associated as well as coincidental and it is not possible clearly to favour one or the other).

AEFI causality assessment – Method (cont´d)

Classification

C: Inconsistent causal association to immunization (coincidental)

This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine.

AEFI investigation – tools

- WHO AEFI invescausality assessment aide mémoire
- https://www.who.int/vaccine_safety/initiative/investigation/New_aide_mem_causal_assmt.pdf

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ADVERSE EVENT FOLLOWING IMMUNIZATION

AIDE-MÉMOIRE ON CAUSALITY ASSESSMENT

Purpose: This aide-mémoire serves as a guide to a systematic, standardized process of assessing whether serious adverse events following immunization (AEFI[1]) are causally linked to vaccines/immunization or not.

Definition: AEFI causality assessment determines if a causal relationship exists between a vaccine (and/or vaccination) and an adverse event.

Rationale: Safety requirements for vaccines are stricter than those for drugs since vaccines are biological products that are more prone to lot variation and instability, they are used in healthy populations and the target groups are vulnerable. Vaccines therefore require a causality assessment process that responds in a timely manner and with scientific rigour to AEFI.

WHO SHOULD ASSESS AEFI CAUSALITY?

Ideally an AEFI review committee should be in place backed by written terms of reference. It should consist of independent experts who have no conflicts of interest. As far as possible, the experts should cover a broad range of expertise: infectious diseases, epidemiology, microbiology, pathology, immunology, neurology, forensics and vaccine programming. The committee should be supported by a secretariat (usually the national regulatory authority [NRA] and the immunization programme) that can provide supporting evidence and investigation findings to enable causality to be determined.

WHAT ARE PREREQUISITES FOR AEFI CAUSALITY ASSESSMENT?

- AEFI case investigation should be completed. Premature assessments may mislead classification.
- All relevant information should be available, including documents of investigation, laboratory and postmortem findings (if applicable).
- Valid diagnosis (unfavourable or unintended sign, abnormal laboratory finding, symptom or disease) for the AEFI must be defined, be well-founded and correspond accurately to the event being assessed.
- Information that could bias results (patient name, hospital name, etc.) should be anonymized.

POSSIBLE CAUSES OF AEFI

Related to vaccine or vaccination

- Vaccine product-related
- Vaccine quality defect-related
- Immunization error-related
- Immunization anxiety-related

Coincidental adverse event

AT WHAT LEVELS IS AEFI CAUSALITY ASSESSED?

AEFI causality assessment could be performed:

- **At population level** (is there a causal association between usage of a vaccine and a particular AEFI in the population?)
- **For an individual** (is the adverse event in the individual patient causally linked to the vaccine/vaccination?)

CONSIDERATIONS FOR ASSESSING CAUSALITY OF A SOLITARY AEFI:

- **Temporal relationship:** is it certain that the vaccination preceded the adverse event?
- **Alternate explanations:** is the event coincidental, i.e. is it due to something other than the vaccine product, immunization error or immunization anxiety?
- **Proof of association:** is there clinical or laboratory proof that the vaccine caused the event?
- **Prior evidence:** has a similar AEFI been previously reported in studies/literature or other sources?
- **Population-based evidence:** does the rate of event occurrence exceed the expected rate of the event in the population? (Refer to WHO information sheets on observed rates of known vaccine reactions.)
- **Biological plausibility:** can the association be explained by the natural history, biological mechanisms of the disease, laboratory evidence or animal studies? However this is not an important consideration.

WHICH AEFI TO SELECT FOR CAUSALITY ASSESSMENT?

All reported AEFI require verification of diagnosis, coding, review, information collation and storage. Causality assessment needs to be done for:

- **Serious AEFI** (i.e. events that are life-threatening or lead to death, hospitalization, significant disability or congenital anomaly)
- **Clusters of AEFI** (the cause for each case in the cluster should be determined separately). Line-listing of data may identify patterns that could constitute a signal
- Occurrence of **events above the expected rate** or of **unusual severity**

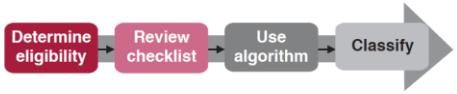
World Health Organization

ADVERSE EVENT FOLLOWING IMMUNIZATION

- **Signals** resulting from single or cluster cases
- Other AEFI as decided by the review committee or an investigation team such as **immunization errors**, significant **events of unexplained cause** occurring within 30 days after a vaccination (not listed in the product label), or events causing **significant parental or community concern.**

WHAT ARE THE STEPS[2] OF A CAUSALITY ASSESSMENT?

- Determine the eligibility of the case
- Review the checklist to ensure that all possible causes are considered
- Use algorithm to determine trend of causality
- Classify causality.



HOW ARE CASES CLASSIFIED AT THE END OF THE ASSESSEMENT?

I. Case with adequate information

A. Consistent with causal association to immunization

- **A1. Vaccine product-related**
- **A2. Vaccine quality defect-related**
- **A3. Immunization error-related**
- **A4. Immunization anxiety-related**

B. Indeterminate

- **B1 Consistent temporal relationship but insufficient definitive evidence for vaccine causing the event**
- **B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization**

C. Inconsistent with causal association to immunization (coincidental)

Underlying or emerging condition(s) or condition(s) caused by exposure to something other than vaccine

II. Case without adequate information

It is categorized as "unclassifiable" since it requires additional information to determine causality (the available information on such cases should be archived in a repository or an electronic database and classified when additional information becomes available)

WHAT ARE THE ACTIONS AFTER CAUSALITY ASSESSMENT?

They include providing feedback, training, modifying systems, refining tools, research, etc. to avoid and/or minimize recurrences. Based on outcomes of assessment, the following need to be considered:

A. Consistent with causal association to immunization

A1 Vaccine product-related reaction: Follow protocols adopted by each country.

A Vaccine quality defect-related reaction: Inform the NRA, manufacturer and relevant stakeholders. Take decision on existing vaccine stock.

A3 Immunization error-related reaction: Training and capacity-building are critical to avoid recurrences.

A4 Immunization anxiety-related reaction: Vaccinating in an ambient and safe environment.

B. Indeterminate

B1 The temporal relationship is consistent but there is insufficient evidence for vaccine causing the event: A national database of such AEFI cases could help to identify signals.

B2 Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization: If additional information becomes available, the classification can move into more definitive categories; if not, they are to be archived.

C. Inconsistent with causal association to immunization (coincidental)

Confirm diagnosis; information on why the case is classified as coincidental to be provided to the patients, relatives, care provider and community.

KEY RESOURCES FOR CAUSALITY ASSESSMENT

Causality assessment of an AEFI - User manual for the revised WHO classification
http://www.who.int/vaccine_safety/publications/gvs_aefi/en/

WHO vaccine reaction rates information sheets
http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

Brighton Collaboration
https://brightoncollaboration.org/public.html

[1] AEFI definition: 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. http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf

[2] For detailed description of the steps, please refer to the Causality assessment of an AEFI - User manual for the revised WHO classification shown in key resources

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ADVERSE EVENT FOLLOWING IMMUNIZATION

Step 1 (Eligibility)

Name of the patient	Name of one or more vaccines administered before this event	What is the Valid Diagnosis? (The case diagnosis of the AEFI)	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine/vaccination caused _____ ?(The event for review in step 2)

Step 2 (Event Checklist) [✓ check all boxes that apply]

I. Is there strong evidence for other causes?	Y	N	UK	NA	Remarks
Does clinical examination, or laboratory tests on the patient, confirm another cause?	☐	☐	☐	☐	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product(s)					
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐	☐	☐	☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐	☐	☐	☐	
Immunization error					
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐	☐	☐	☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐	☐	☐	☐	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	☐	☐	☐	☐	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐	☐	☐	☐	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐	☐	☐	☐	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐	☐	☐	☐	
Immunization anxiety					
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	☐	☐	☐	☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?					
Did the event occur within an appropriate time window after vaccine administration?	☐	☐	☐	☐	
III. Is there strong evidence against a causal association?					
Is there strong evidence against a causal association?	☐	☐	☐	☐	
IV. Other qualifying factors for classification					
Could the event occur independently of vaccination (background rate)?	☐	☐	☐	☐	
Could the event be a manifestation of another health condition?	☐	☐	☐	☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐	☐	☐	☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐	☐	☐	☐	
Was there acute illness prior to the event?	☐	☐	☐	☐	
Did the event occur in the past independently of vaccination?	☐	☐	☐	☐	
Was the patient taking any medication prior to vaccination?	☐	☐	☐	☐	
Is there a biological plausibility that the vaccine could cause the event?	☐	☐	☐	☐	

Y: Yes. N: No. UK: Unknown. NA: Not applicable.

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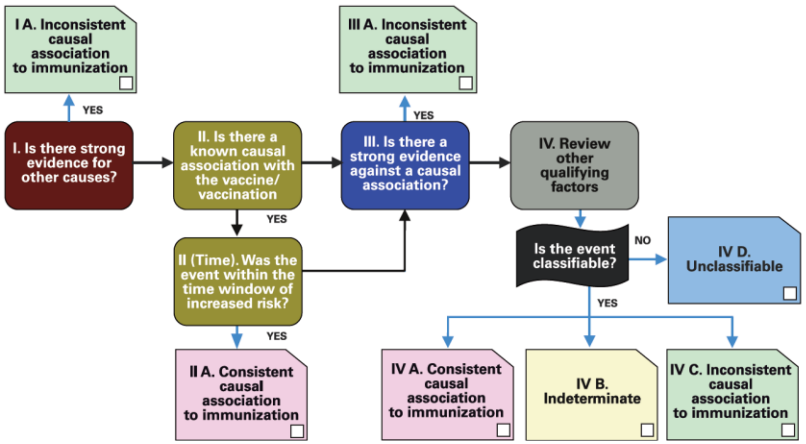
ADVERSE EVENT FOLLOWING IMMUNIZATION

STEP 3: (ALGORITHM) REVIEW ALL STEPS AND ✓ ALL THE APPROPRIATE BOXES



Notes for Step 3:

STEP 4: (CLASSIFICATION) ✓ ALL BOXES THAT APPLY

	A. Consistent causal association to immunization	B. Indeterminate	C. Inconsistent causal association to immunization
Adequate information available	☐ A1. Vaccine product-related reaction (As per published literature) ☐ A2. Vaccine quality defect-related reaction ☐ A3. Imminization error-related reaction ☐ A4. Immunization anxiety-related reaction	☐ *B1. Temporary relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event) ☐ B2. Qualifying factors result in conflicting trends of consistency and inconstistency with causal association to immunization	☐ C. Coincidental Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine
Adequate information not available	Unclassifiable ☐ Specify the additional information required for classification		

*B1: Potential signal and maybe considered for investigation

Summarize the classification logic

With available evidence, we could conclude that the classification is _____ because:

FEEDBACK AND CORRECTIVE ACTION RECOMMENDED:

References

- WHO Global manual on Surveillance on Adverse Events Following Immunization

https://www.who.int/vaccine_safety/publications/Global_Manual_revised_12102015.pdf?ua=1

- WHO Causality assessment of an adverse event following immunization (AEFI) – updated user manual for the revised WHO classification

https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf?sequence=1&isAllowed=y

- WHO COVID-19 Vaccines: Safety Surveillance Manual

https://apps.who.int/iris/bitstream/handle/10665/338400/9789240018280-eng.pdf?sequence=1&isAllowed=y

Take home messages

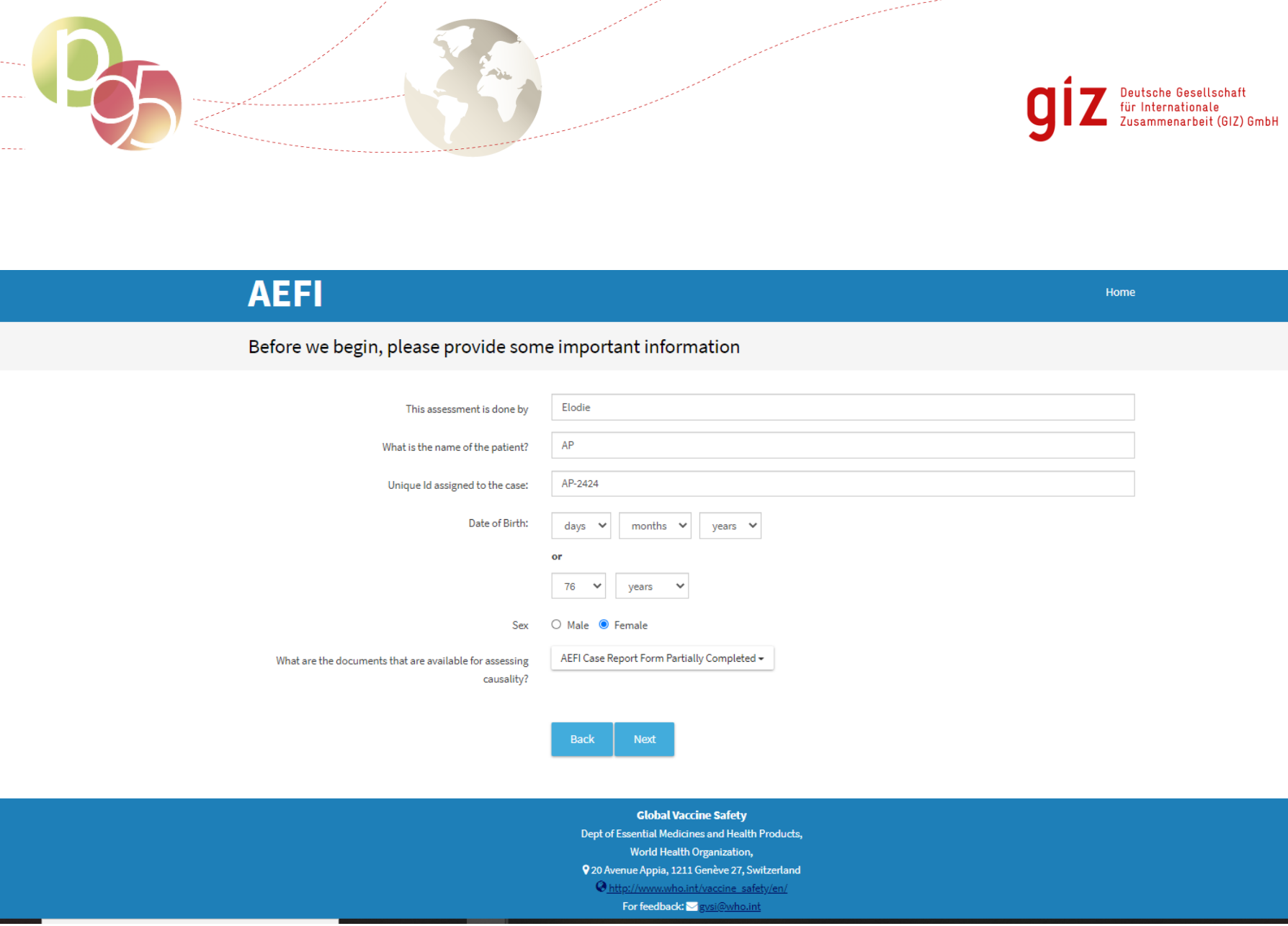
- Train staff responsible for investigation and causality assessment
- Use tools available and ensure users are familiar with these tools
- A good investigation will streamline the process of causality assessment
- A good causality assessment will help identifying new potential risks


QUESTIONS

Case study

Causality assessment - Example 1: Anaphylaxis

- A 76-year-old female subject (AP – 2424) was vaccinated with a COVID-19 vaccine (Comirnaty).
- The subject's medical history included a shellfish allergy. No relevant concomitant medications were reported
- The subject received the first dose on 30 Dec 2020 and second dose on 29 Jan 2021.
- On 15 Mar 2021 at 8am, the subject had rash, dizziness and chest tightness. She was admitted to hospital with a diagnosis of anaphylaxis.
- On questioning further, she had consumed food at a restaurant the night previously and was also found to have insect bites on the back of her legs.
- Treatment medication for the reported event included: corticosteroids, IV fluids, oxygen via face mask, and antihistamines.


AEFI
Home
Before we begin, please provide some important information
This assessment is done by
Elodie
What is the name of the patient?
AP
Unique Id assigned to the case:
AP-2424
Date of Birth:
days
months
years
or
76
years
Sex
Male
Female
What are the documents that are available for assessing causality?
AEFI Case Report Form Partially Completed
Back
Next
Global Vaccine Safety
Dept of Essential Medicines and Health Products,
World Health Organization,
20 Avenue Appia, 1211 Genève 27, Switzerland
http://www.who.int/vaccine_safety/en/
For feedback: gvsi@who.int

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Please certify the available information and its quality

I hereby certify that the available documents used for determining the cause of this AEFI include

☑ AEFI Case report form Partially completed

The quality of these documents provided to me for causality assessment is *

○ Perfect ○ Excellent ○ Very good ○ Good ◉ Average ○ Poor ○ Very Poor ○ ineligible to classify

*** Perfect ➡100% of required information available; Excellent ➡95-99% of required information available; Very good ➡90-94% of required information available; Good ➡85-89% of required information available; Average ➡ 80-84% of required information available; Poor ➡ 75-79% of required information available; Very Poor ➡<75% of required information availablel; Unable to classify – Information inadequate.**

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***This can be subjective**

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http://www.who.int/vaccine_safety/en/
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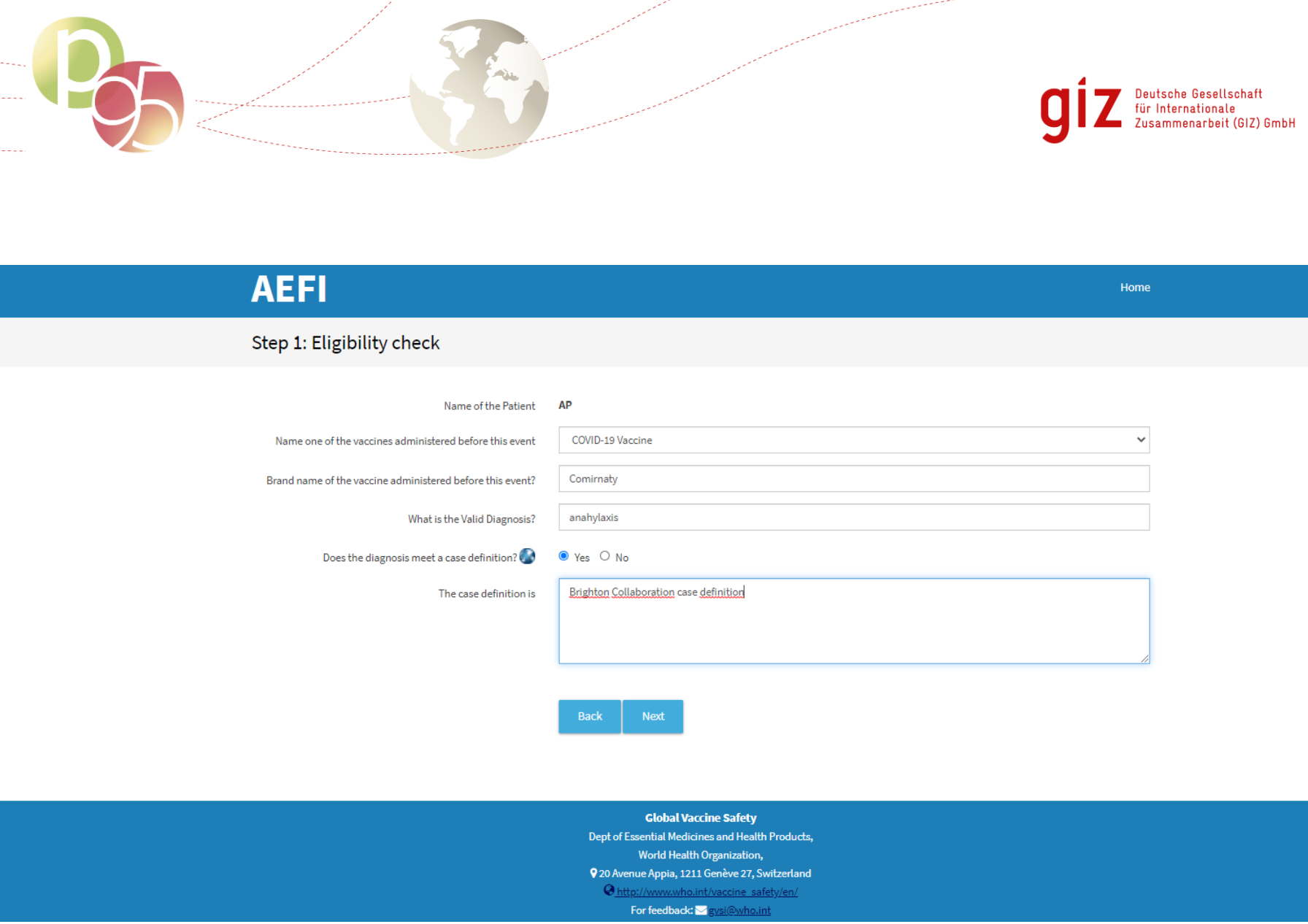
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Step 1: Eligibility check
Name of the Patient
AP
Name one of the vaccines administered before this event
COVID-19 Vaccine
Brand name of the vaccine administered before this event?
Comirnaty
What is the Valid Diagnosis?
anahylaxis
Does the diagnosis meet a case definition?
Yes
No
The case definition is
Brighton Collaboration case definition
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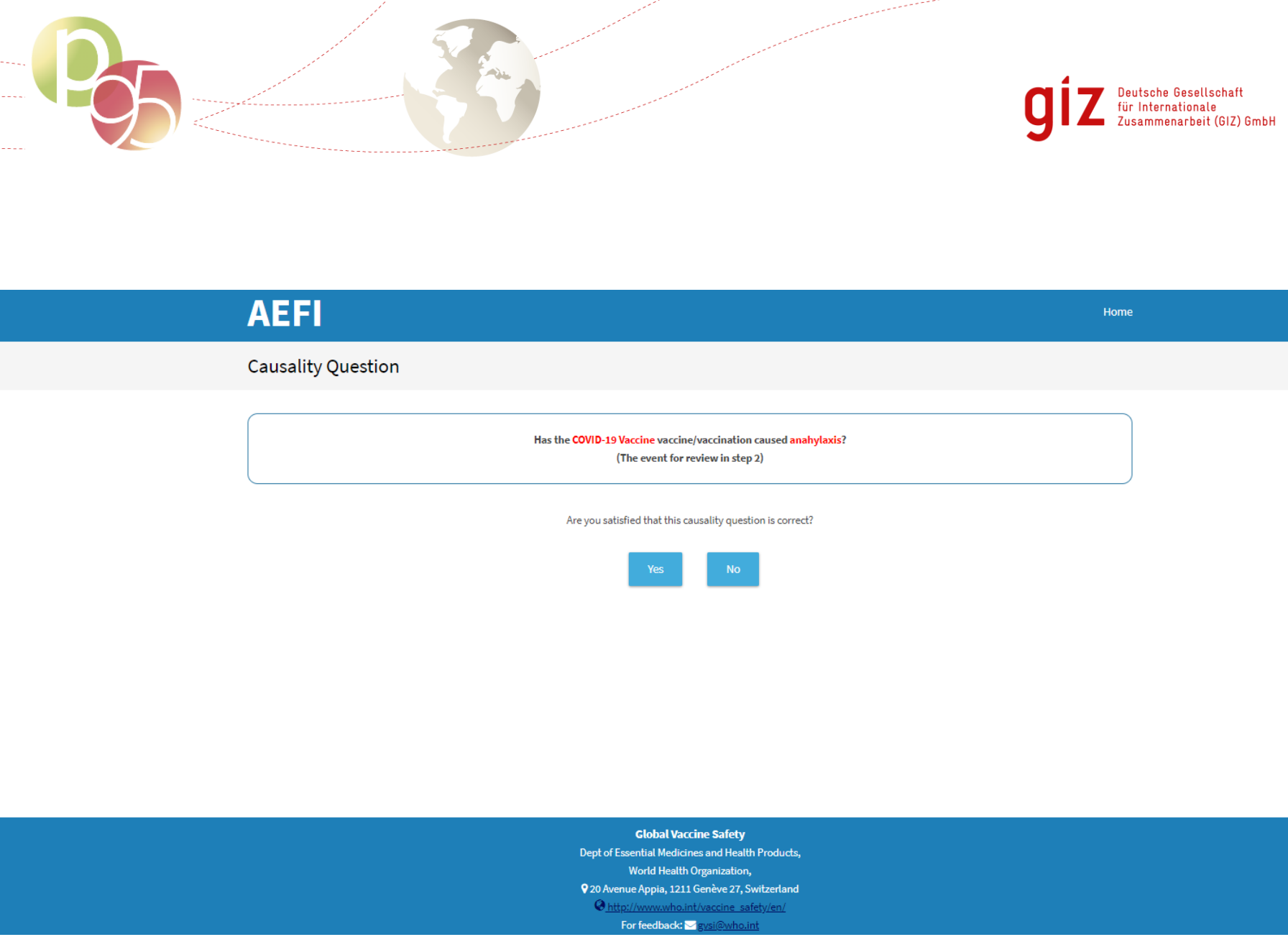
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Causality Question
Has the COVID-19 Vaccine vaccine/vaccination caused anahylaxis?
(The event for review in step 2)
Are you satisfied that this causality question is correct?
Yes
No
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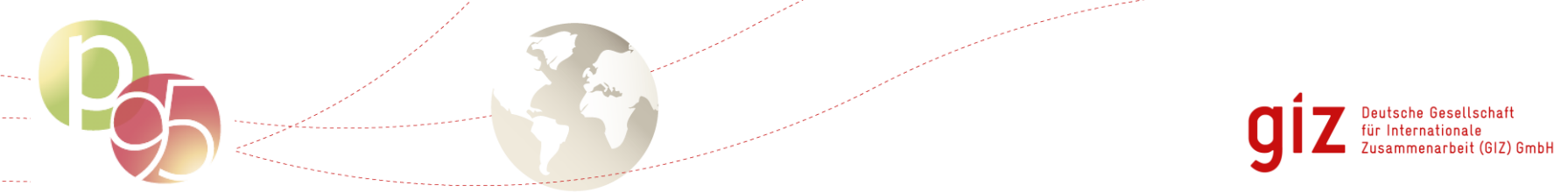
Step 2: EVENT CHECKLIST

Clear Contents

	Y	N	UK	NA	Remark
I. Is there strong evidence for other causes?					
	Y	N	UK	NA	
1) In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the anahylaxis	☐	☐	☑	☐	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product(s)					
	Y	N	UK	NA	
1) Is there evidence in published peer reviewed literature that this COVID-19 Vaccine vaccine may cause such an anahylaxis if administered correctly?	☑	☐	☐	☐	Anaphylaxis is an identified risk
2) Is there a biological plausibility that this COVID-19 Vaccine vaccine could cause such an anahylaxis?	☑	☐	☐	☐	Anaphylaxis is an identified risk
3) In this patient, did a specific test demonstrate the causal role of the COVID-19 Vaccine vaccine ?	☐	☑	☐	☐	
Vaccine quality					
	Y	N	UK	NA	
4) Could the COVID-19 Vaccine vaccine given to this patient have a quality defect or is substandard or falsified?	☐	☑	☐	☐	
Immunization error					
	Y	N	UK	NA	
5) In this patient, was there an error in prescribing or non-adherence to recommendations for use of the COVID-19 Vaccine vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐	☑	☐	☐	

	Y	N	UK	NA	
Immunization error					
5) In this patient, was there an error in prescribing or non-adherence to recommendations for use of the COVID-19 Vaccine vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐	☑	☐	☐	
6) In this patient, was the COVID-19 Vaccine vaccine (or diluent) administered in an unsterile manner?	☐	☑	☐	☐	
7) In this patient, was the COVID-19 Vaccine vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐	☑	☐	☐	
8) When this patient was vaccinated, was there an error in COVID-19 Vaccine vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐	☑	☐	☐	
9) In this patient, was there an error in COVID-19 Vaccine vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐	☑	☐	☐	
10) In this patient, was the COVID-19 Vaccine vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐	☑	☐	☐	
Immunization anxiety					
	Y	N	UK	NA	
11) In this patient, could this anahylaxis be a stress response related to immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological	☐	☑	☐	☐	
II (time): Was the event in section II (questions above from II 1 to II 11) within the time window of increased risk					
	Y	N	UK	NA	
12) In this patient, did the anahylaxis occur within a plausible time window after vaccine administration?	☐	☑	☐	☐	4 months after vaccination
III. Is there strong evidence against a causal association?					
	Y	N	UK	NA	
1) Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the COVID-19 Vaccine and the anahylaxis?	☐	☑	☐	☐	
IV. Other qualifying factors for classification					
	Y	N	UK	NA	



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III. Is there strong evidence against a causal association?

	Y	N	UK	NA	
1) Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the COVID-19 Vaccine and the anahylaxis?	☐	☑	☐	☐	

IV. Other qualifying factors for classification

	Y	N	UK	NA	
1) In this patient, did such an anahylaxis occur in the past after administration of a similar COVID-19 Vaccine vaccine?	☐	☑	☐	☐	No reaction after the 1st dose
2) In this patient did such an anahylaxis occur in the past independent of vaccination?	☐	☐	☑	☐	shellfish allergy
3) Could the current anahylaxis have occurred in this patient without vaccination (background rate)?	☑	☐	☐	☐	Many other causes of anaphylaxis
4) Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the anahylaxis?	☑	☐	☐	☐	Food allergy
5) Was this patient taking any medication prior to the vaccination?	☐	☑	☐	☐	
6) Was this patient exposed to a potential factor (other than vaccine) prior to the anahylaxis (e.g. allergen, drug, herbal product etc.)?	☑	☐	☐	☐	consumed food at a restaurant the night previously and was also found to have insect bites on the back of her legs

Y - Yes N - No UK - Unknown NA - Not applicable

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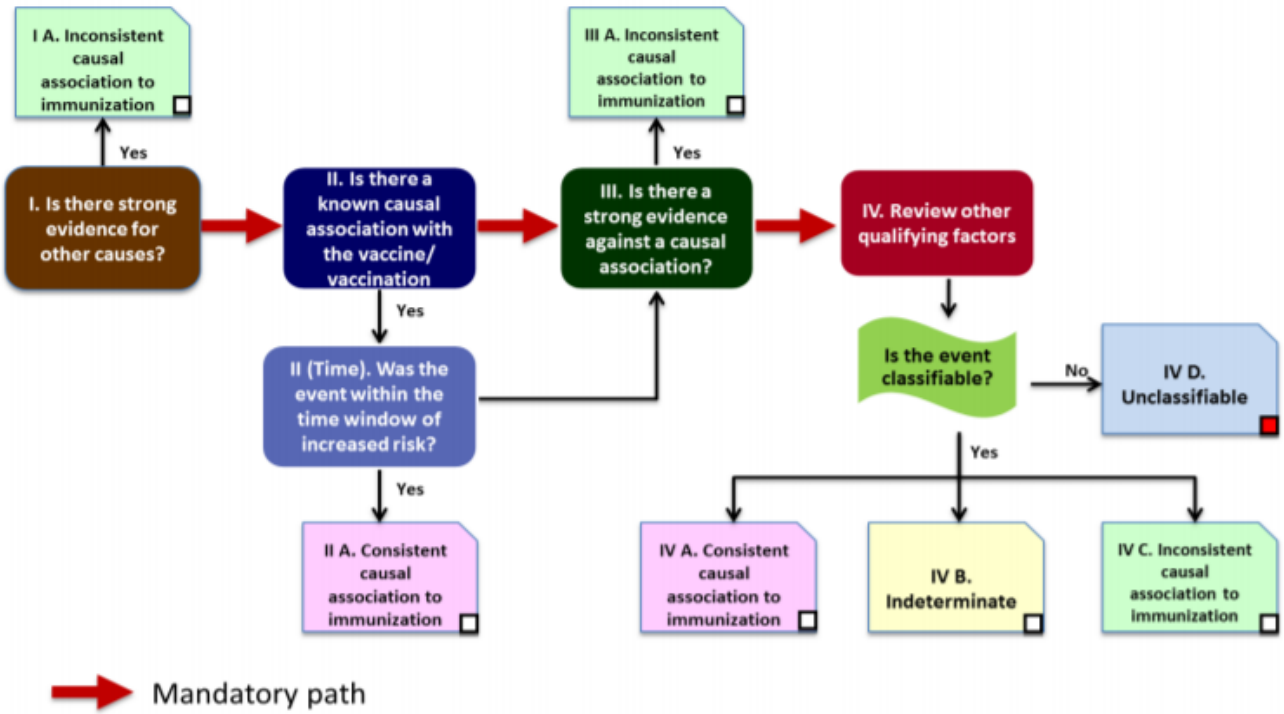
Step3: Algorithm



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The AEFI in **AP** with id number **AP-2424** who received **COVID-19 Vaccine** vaccine of brand **Comirnaty** was diagnosed to have **anahylaxis** has been classified.

The classification and its logic are as follows

The **anahylaxis** after **COVID-19 Vaccine** vaccines was evaluated using information provided by **AEFI Case report form Partially completed** using documentation that is considered **Average**
The **anahylaxis** is likely to be **C.Coincidental Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine** this is because **1) Many other causes of anaphylaxis, 2) consumed food at a restaurant the night previously and was also found to have insect bites on the back of her legs, 4) Food allergy**
Other considerations include
This assessment is done by: **Elodie**

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Causality assessment - Example 2: Bells Palsy

- A healthy 12 year-old female patient was administered a known authorised vaccine as part of routine vaccination schedule on the 18 October 2016 (at 9:30 am) .
- The subject was not taking any concomitant medications.
- On 20 October 2016 (at 10:30 am), she was seen by a neurologist for left sided facial paralysis.
- No Further information available.

Causality assessment - Example 2: Bells Palsy

Causality Assessment:

1. Biologic Plausibility?
2. Recognised Association with product class
3. Temporal Plausibility
4. Alternative etiology
5. Dechallenge
6. Rechallenge

Causality assessment - Example 2: Bells Palsy

Causality assessment:

1. Biologic Plausibility? – Yes
2. Recognised Association with product class - Yes
3. Temporal Plausibility – Yes
4. Alternative etiology – No
5. Dechallenge – Not Applicable
6. Rechallenge – Not Applicable

Conclusion – **Related** due to temporal and biological plausibility.

Causality assessment - Example 2: Bells Palsy

Follow-up received:

The Neurology consultation notes were received by the clinic which stated that the patient was seen two weeks prior with a diagnosis of Bells palsy and was being treated with dexamethasone. In the follow-up appointment on the 20 October 2016 the neurologist noted that the event had resolved and that there was no worsening of the condition following vaccination.

Conclusion: **Not related** due to this being a pre-existing condition with no worsening following vaccination.

Causality assessment - Example 3: Rash/urticaria

- A 12 year-old male subject received the first dose of a vaccine as part of routine vaccination schedule.
- Four hours after the vaccination, the grandmother noticed an erythematous rash over the trunks, upper legs and arms, and brought the child to the clinic.
- She stated that as it had been a hot day, the child had been playing in the forest without a shirt on 1 hour prior to the rash onset and he was allergic to poison ivy plant.
- He was treated with antihistamines and the rash resolved.
- After 6 months, the subject received a second dose of the same vaccine. After 2 hours the subject complained of itchiness and was taken to the primary care clinic. On examination he had a widespread erythematous/urticarial rash. Vital signs and oxygen saturation was normal. He was treated with antihistamines, dexamethasone and observed for 2 hours before being discharged home.

Causality assessment - Example 3: Rash/urticaria

Causality Assessment:

1. Biological Plausibility?
2. Recognised Association with product or class?
3. Temporal Plausibility?
4. Alternative Aetiology?
5. Dechallenge
6. Re-challenge

Causality assessment - Example 3: Rash/urticaria

Causality Assessment:

1. Biological Plausibility? – Yes
2. Recognised Association with product or class? - Yes
3. Temporal Plausibility? – Yes
4. Alternative Aetiology? - Yes (for the first episode of rash)
5. Dechallenge – Not applicable
6. Re-challenge – Yes

Conclusion: **Related** based on biological plausibility, temporal plausibility and positive rechallenge.

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Thank you