PHARMACOVIGILANCE PROTOCOL FOR COVID-19 VACCINES

Directorate General of Drug Administration (DGDA)

Health Services Division
Ministry of Health and Family Welfare
Bangladesh

USAID
FROM THE AMERICAN PEOPLE

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MESSAGE FROM THE SECRETARY

Pharmacovigilance protocol for COVID-19 vaccines provides and overview of passive and Adverse event following immunization (AEFI) due to COVID-19 vaccination. Post vaccination safety surveillance is a major issue for success of vaccination as well as risk management. Directorate General of Drug Administration (DGDA) is responsible for ensuring safety, efficacy and quality of vaccines. Therefore, they have been instructed to develop "Pharmacovigilance Protocol" with the support of experts.

This Protocol will provide a guidance of reporting system which describes "what to report how to report adverse event following immunization (AEFI), how to investigate the serious adverse events (SAEs), causality assessments, signal generation and making regulatory decision". It has defined the function of district/ city corporation AEFI committee, divisional AEFI causality assessment committee and the national AEFI expert review committee. This guideline provides a comprehensive flow chart of AEFIs and SAEs. This is a very time needed document for safety issues of Covied-19 vaccine and it will help us trap safety issues of covid-19 vaccine to be administered in the country.

I would like to give my sincere thanks and gratitude to the experts who were actively involved in developing this protocol. I do believe, this protocol will help to overcome the dreadful pandemic by capturing the safety issues of Covid-19 vaccination.

Md. Abdul Mannan
Secretary, Health Services Division
Ministry of Health & Family Welfare

Directorate General of Drug Administration
Ministry of Health & Family Welfare

MESSAGE FROM THE DIRECTOR GENERAL

Directorate General of Drug Administration (DGDA) is responsible to ensure quality, safety and efficacy of medicines, vaccines, medical devices etc. It has major functions like marketing authorization & registration, regulatory inspection, pharmacovigilance (PV), market surveillance & control, clinical trial oversight, licensing of premises, lab access, and lot release of vaccines. For COVID-19 vaccine safety, post marketing surveillance and pharmacovigilance (AEFI monitoring) is needed to be organized. DGDA has developed the 'Pharmacovigilance Protocol for COVID-19 Vaccines' in consultation with expert committee.

DGDA is the National Pharmacovigilance Centre (NPC) of Bangladesh and is the 120th member country of WHO-Uppsala Monitoring Centre (UMC), Sweden, the global platform for Pharmacovigilance. DGDA has access to UMC 'VigiFlow', Vigibase & other tools for data entry and analysis.

Government of Bangladesh has taken a great initiative to immunize with COVID-19 vaccine for the people of Bangladesh to overcome the pandemic situation. For this purpose, to ensure the safety, quality & efficacy of COVID-19 vaccine MoHFW has formed a Quality Assurance committee with a notification on 11.12.2020 comprising of ten experts with Director General of Drug Administration as Chairperson. In the first meeting of this committee held on 14 December 2020 formed a working committee headed by Prof. Dr. Mahmudur Rahman, Epidemiologist, former Director, IEDCR to formulate a Pharmacovigilance Protocol for COVID-19 vaccines. Having hard work, they have developed this protocol and shared with stakeholders for their opinion &. suggestion. It has been finalized in meeting held on 12 January, 2021 of Quality assurance committee for COVID-19 vaccines.

In this protocol three level committees have been constituted to monitor and manage AEFI/SAE cases arising from the COVID-19 vaccination. The committees are District /City Corporation AEFI Committee, Divisional AEFI causality assessment committee and the National AEFI expert review committee for COVID-19 vaccine. Pharmacovigilance & COVID-19 Safety Surveillance Cell of DGDA will provide support to the National AEFI expert review committee for COVID-19 vaccine.

I expect that this protocol will help all concerned to facilitate the reporting, investigation, case management and causality assessment of AEFI/SAE cases following COVID-19 vaccination and to take necessary regulatory decision.

I appreciate all members of the working committee, USAID-MTaPS program, USP-PQM+, WHO and DGDA Pharmacovigilance team who were involved in the development of this Pharmacovigilance Protocol for COVID-19 Vaccines in Bangladesh.

Major General Md. Mahbubur Rahman
Director General, Directorate General of Drug Administration

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ACRONYMS

AEFI	Adverse Events Following Immunization
AESI	Adverse Event Following Immunization of Special Interest
CHO	Chief Health Officer
COPD	Chronic Obstructive Pulmonary Disease
DGDA	Directorate General of Drug Administration
DM	Diabetes Mellitus
EPI	Expanded Programme on Immunization
HCF	Health Care Facility
HF	Health Facility
HTN	Hypertension
ICSR	Individual Case Safety Report
ID	Intradermal
IEDCR	Institute of Epidemiology, Disease Control and Research
IM	Intra-Muscular
MAH	Marketing Authorization Holder
MMO	Municipal Medical Officer
MOHFW	Ministry of Health and Family Welfare
PV	Pharmacovigilance
RMO	Resident Medical Officer
RMP	Risk Management Plan
SAE	Serious Adverse Event
UHC	Upazila Health Complex
UHFPO	Upazila Health Family Planning Officer

INTRODUCTION

Bangladesh identified the first COVID-19 case on 8th March 2020 and the first death was reported on 18th March 2020. Since its emergence in December 2019, the SARS-Cov2 virus has spread to almost every country making the COVID-19 pandemic a global health crisis. As of 09 January 2021, approximately 1.91 million people died and 88.8 million people are affected. As nobody is safe, we need to prevent this viral pandemic disease. COVID-19 vaccines will play a major role in the control of the pandemic once available. DGDA has already issued Emergency Use Authorization (EUA) in favor of Oxford-AstraZeneca vaccine manufactured by Serum Institute of India on 07th of January 2021 for import. DGDA has to ensure the safety of this COVID-19 vaccine as well as the vaccine will be registered in future. Necessary surveillance will be conducted to ensure all the safety issues related to COVID-19 vaccination. To address all the safety issues this protocol will serve as the risk management approach.

DEFINITIONS

Pharmacovigilance

"Pharmacovigilance" (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. Its aims are to enhance patient care and patient safety and to support public health programmes by providing reliable, balanced information for the effective assessment of the benefit-risk profile of medicines and vaccines. It includes Adverse events following immunization (AEFI) monitoring for vaccine.

Adverse events following immunization (AEFI)

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

Cause-specific definitions of AEFI and its implications in the COVID-19 context

- ***Vaccine product-related reaction:*** An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product. The identification of rare (occurring in 0.01% to less than 0. 1% of immunized individuals) and very rare (occurring in <0.01% of individuals) adverse events is insufficient at the time of COVID -19 vaccine licensing and more information will be needed for which AEFI surveillance has to be strengthened.
- ***Vaccine quality defect-related reaction:*** An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer. For new vaccines platforms, the knowledge of potential Vaccine quality defects might be insufficient at the time of COVID -19 vaccine licensing and more information will be needed for which AEFI and AESI surveillance must be strengthened. Moreover, the rapid scaling up vaccine

production poses additional potential risks and identification of the exact substance causing the event is needed.

- ***Immunization error-related reaction:*** An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable. It is anticipated that COVID-19 vaccines will be administered on a massive scale in a short time interval with minimum training and field preparation and larger number of Immunization error -related reactions are anticipated. Also, Staff who are not familiar with immunization may be asked to perform immunization duties. Multiple vaccines with different specifications for storage, administration, dose etc. may in be in use in a country simultaneously.
- ***Immunization anxiety-related reaction:*** An AEFI arising from anxiety about the immunization. A larger number of Immunization anxiety-related reactions are anticipated due to numerous factors including older age groups, the different vaccinating environments, the novelty of the vaccines and their administration modalities.
- ***Coincidental event:*** An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety. Because of real and potential underlying comorbidities in a large number of the vaccinees, it will become challenging to differentiate true coincidental events from COVID -19 vaccine product related reactions or drug reactions or interactions.

Similar challenges will occur in healthy individuals without comorbidities especially where a higher frequency is expected based on age, gender, geographic location or ethnic background. Knowing the population-based incidence (background rates) of pre-specified adverse events of special interest (AESI) helps to anticipate and respond to such events in order to identify those that are coincidental as opposed to vaccine product -related.

Serious AEFI

A serious AEFI is an event that results in death, hospitalization or prolongation of an existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or is life-threatening. It is currently unknown on the types and characteristics of serious AEFI that can occur particularly the rare and very rare adverse events following COVID -19 vaccines.

Cluster

A cluster is when two or more AEFIs related in time, place and/or by vaccine occur. Vaccine may refer to a certain batch (lot), a vaccine product from a certain manufacturer or vaccine(s) protecting against a certain strain of an infective agent. When vaccines are administered on a massive scale, it is important for immunization programs to anticipate and prepare for clusters of AEFI as the chances for immunization errors and Immunization anxiety-related reactions are much higher than that of routine immunization. Coincidental events can also occur as clusters.

Signal

A signal is information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Signal detection, verification and response is a key activity that has to be specially addressed in the COVID19 context. Signals can best be identified by pooling of data from multiple sources and analyzing if the pooled data points to the occurrence of a new event that could causally related to the vaccine.

ADDRESSING AEFI IN THE CONTEXT OF COVID-19 VACCINE

Bangladesh should have an AEFI surveillance system for COVID-19 vaccine in place as described in the Global Manual on Surveillance of AEFI at the time of vaccine introduction. The AEFI surveillance cycle (Figure- 1) outlines the different steps in identification, notification, reporting, investigation, data analysis, causality assessment and feedback following all AEFI, including AEFI following Covid 19 vaccine.

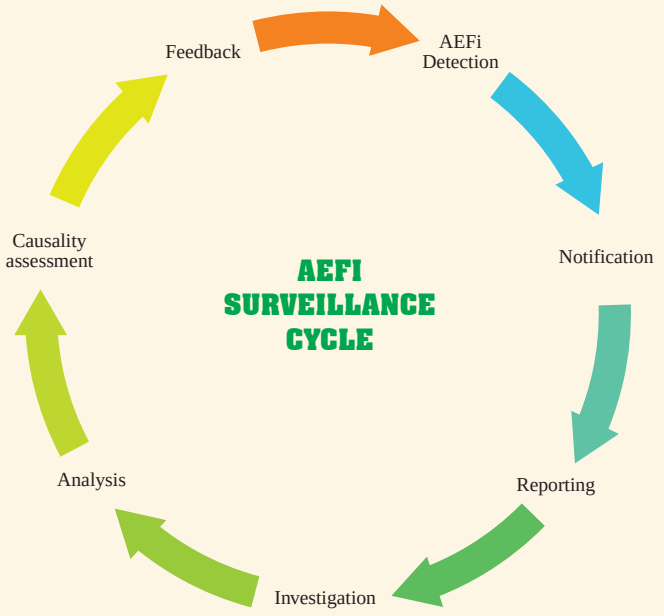


Figure- 1: The AEFI surveillance cycle

AEFI active surveillance will also be conducted in specific areas of 8 divisions. For this, one upazila from one district of 8 divisions may be selected for specific number of reports or defined period of time. This active surveillance reporting, assessment and evaluation could follow the same tools and process being used for passive surveillance. IEDCR will be responsible for active surveillance. A protocol needs to be developed for this. Active pharmacovigilance will be performed when necessary directives, protocol and fund will be available.

SCOPE OF PHARMACOVIGILANCE PROTOCOL FOR COVID-19 VACCINES

Good Pharmacovigilance practice is required for all medicinal products, medical devices including vaccines and biologics. This pharmacovigilance protocol for COVID-19 vaccines provides an overview of passive and active pharmacovigilance activities in Bangladesh related to reporting, investigation and management of AEFI arising from COVID-19 vaccines when marketing authorization or emergency use authorization will be issued by DGDA.

GOAL

Ensuring the safety of COVID-19 vaccination.

OBJECTIVES

- Timely detect and report any other adverse events including Serious Adverse Events (SAE) and Adverse Events of special interest (AESI)
- Investigation and assessment of potential risk / AEFIs
- Rapid detection, prioritization and assessment of emerging safety information derived from Spontaneous and Targeted reporting systems, observational studies and other data sources;
- Prompt evaluation of the impact of detected safety issues on the benefit-risk balance of the vaccines
- Engagement and collaboration with stakeholders including vaccines and healthcare professionals, marketing authorization holders (MAHs) and international partners;
- Prompt and effective communication of new information arising from the above activities.

COVID-19 AEFI REPORTING SYSTEM

All adverse events of COVID-19 vaccine will be reported by the health facilities (government and private) who will provide COVID-19 vaccination and also MAHs.

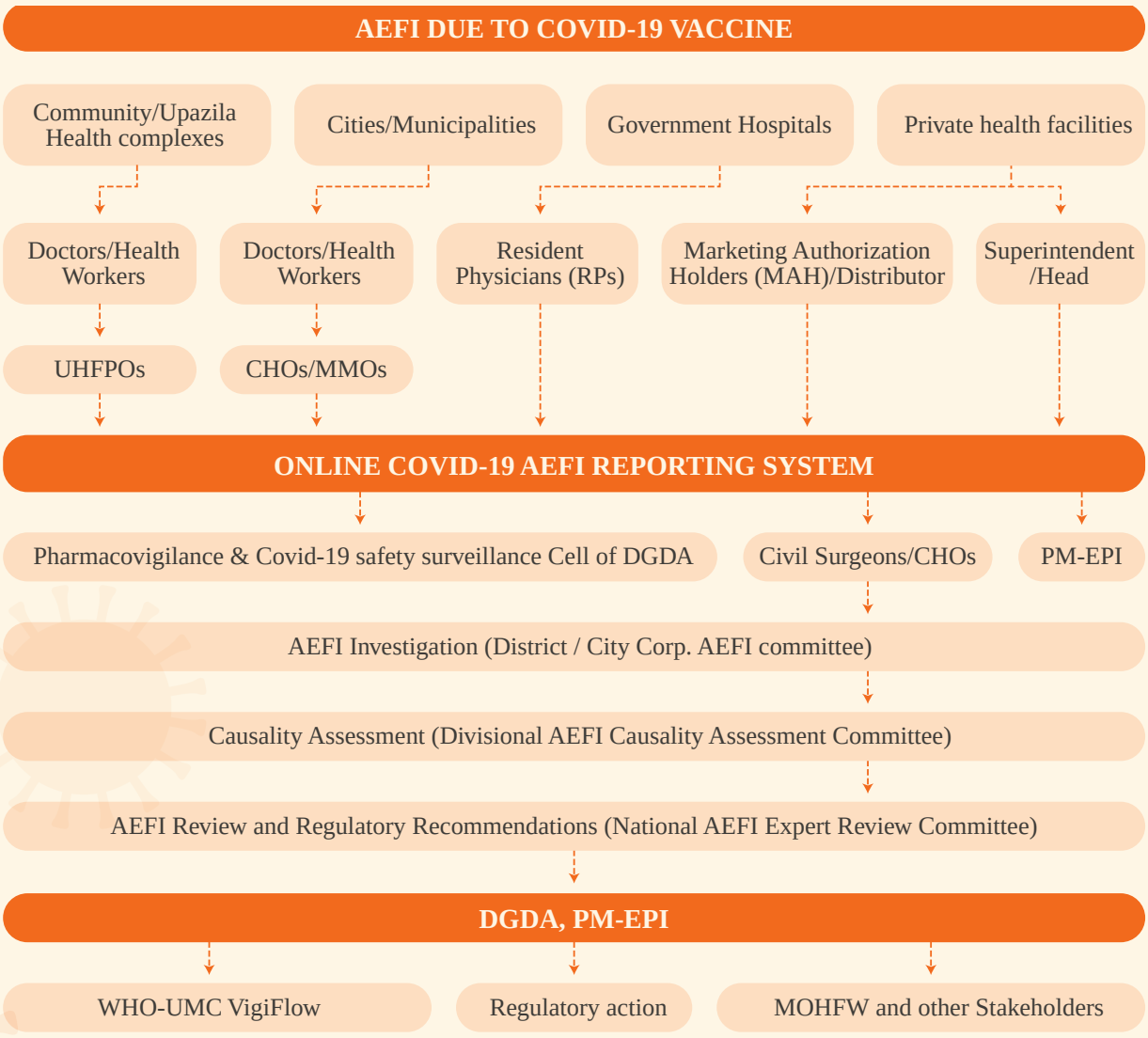
1. **Upazila health complex (UHC):** All the AEFIs in the community will be reported by the health workers to their respective Upazila Health and family planning officer (UHFPO). AEFIs those are presented to the doctors providing healthcare services in the indoor and outdoor of the UHC will also be reported to the UHFPOs. UHFPOs will ensure the reporting of AEFIs of COVID-19 vaccines within 24 hours of notification.
2. **District Hospitals:** All the AEFIs notified in the district hospitals will be reported by the civil surgeons within 24 hours of notification.
3. **Government Medical College Hospitals:** If vaccinees with AEFI come at the outdoor or emergency department or admitted in a medical college hospital must be reported by the respective treating

physician to the resident physician (RP). RPs will ensure the reporting within 24 hours of notification. In case of hospitalization the event must be reported immediately to the respective civil surgeons by phone along with usual reporting methods.

4. **Municipalities and City Corporations:** All the AEFI in the city corporation and municipality area will be reported by the health workers to their respective chief health officer (CHOs) and municipality medical officers (MMOs). CHOs and MMOs will ensure the reporting within 24 hours of notification.
5. **Private health facilities:** Superintendent/Head of private health facilities will collect AEFI report from the private health facilities of upazilas/districts/municipalities/city corporations' area and will ensure reporting within 24 hours.
6. **Marketing Authorization Holder (MAH)/Distributor:** They will collect AEFI information from their distributing private health facilities and will report using online system.

All suspected AEFI of COVID-19 vaccine must be reported through DGDA's own platform http://covid19pv.dgda.gov.bd using the electronic version of the reporting form which will be available there. Also, AEFI form (pdf version) will be available on the DGDA website (www.dgda.gov.bd). AEFI reports collected by doctors/health workers from all city corporations/municipalities/other areas will be reported online by the CHOs/MMOs. AEFI reports collected by doctors/health workers from community, Upazila Health Complex (UHC) and other areas will be sent by the UHFPOs. MAHs will collect AEFI reports from their distribution health facilities and provide online entry. AEFI reports collected by superintendent/Head of private health facilities will be reported online by themselves. AEFIs presented in govt. medical college hospitals will be reported by RP (resident physicians). UHFPOs/MMOs/CHOs/RPs/Superintendent or Head of private health facilities/MAHs will upload all the received AEFI reports in the online system. Senders will also keep a record (hard copy) of AEFI reports. This report will be automatically received at PM EPI and Pharmacovogilance & COVID-19 Safety Surveillance Cell of DGDA at the same time. Civil surgeon/CHO will check the reports, arrange investigation for the Adverse Events of serious nature. During investigation they will collect relevant information using AEFI investigation report form for COVID-19 vaccine (Annex- III). Civil surgeons and CHOs will send all the AEFI investigation reports to the respective Divisional AEFI causality assessment committee. After completion of the causality assessment the reports along with assessment will be sent to DGDA and PM EPI by e-mail. Pharmacovigilance & COVID-19 Safety Surveillance Cell of DGDA will compile the reports and place before the national AEFI expert review committee for COVID-19 vaccine for review and regulatory recommendations. DGDA will take regulatory actions on the basis of recommendations, upload AEFI report information reviewed by the national AEFI expert review committee for COVID-19 vaccine to UMC vigiflow and share with relevant stakeholders including Ministry.

Reporting Flowchart



Events that should be reported

All AEFI developed due to vaccination shall be notified by the vaccinees/his or her representative/healthcare professionals using AEFI reporting form for COVID-19 vaccine (Annex-I). This reporting form will be available in DGDA's own platform http://covid19pv.dgda.gov.bd Serious AEFIs (death, hospitalization, disability, clusters, life-threatening) should be reported within 24 hours by phone to Civil surgeons/ CHOs along with online reporting. They will ensure immediate reporting of the event to PM EPI and Pharmacovigilance & COVID-19 Safety Surveillance Cell .

COVID-19 AEFI INVESTIGATIONS

Why AEFI reports should be investigated

The ultimate goal of a case investigation is to find the cause of an AEFI and to implement follow-up actions. Investigation should identify any immunization error-related or vaccine product-related reactions because these are preventable. If coincidental events are recognized, proving them will be important to maintain public confidence in the immunization programme.

The purposes of investigating an AEFI case are the following:

- To identify the details of vaccine(s) administered and to determine the timing between administration of the vaccine and the onset of the event
- To confirm the reported diagnosis or establish a diagnosis
- To document the outcome of the reported adverse event
- To identify the cause of the AEFI
- To determine whether a reported event is a single incident or one of a cluster and, if it is part of a cluster, where the suspected immunizations were given and what vaccines were used
- To examine the operational aspects of the programme and to prevent immunization-related errors
- To determine whether similar events are occurring in individuals who have not
- received the same vaccine

If the cause is determined to be an immunization error, problem should be corrected quickly. If an AEFI is found to be coincidental, then the community can be reassured about the safety of the vaccine and the immunization programme. The act of investigating AEFI increases the confidence of the community in the health care system and the immunization programme in particular.

Which AEFI reports should be investigated?

Not all AEFI reports need investigation. The following AEFIs must be investigated:

- serious AEFI event (death, hospitalization, disability, life-threatening)
- belongs to a cluster of AEFI
- is a previously unrecognized event associated with an existing or newly introduced vaccine
- involves an increased number or rates of known cause
- is a suspected immunization error
- causes significant parental/guardian or public concern

Cluster of AEFI

A cluster is defined as two or more cases of the same or similar events, related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health facility, and/or a vial of vaccine or a batch of vaccine. For e.g. two or more cases of abscess occurring following one immunization session in a village; repeated abscess cases following immunization by same vaccinator.

When to investigate AEFI?

AEFIs investigation procedure should start as soon as possible, ideally within 24 hours of notification.

Who should investigate AEFI?

The District/City Corporation AEFI Committee shall be responsible for AEFI investigation in the respective districts/city corporations.

How to investigate AEFI?

After receiving the information of a serious AEFI the local manager (UHFPO/MMO/ZMO/AHO/HO will immediately inform respective CS/CHO and the Member Secretary of the District/City Corporation AEFI committee about the AEFI. The Member Secretary will initiate the investigation with identified members of the AEFI committee as approved by CS/CHO within 24 hours of notification.

The concerned local Manager (UHFPO/MMO/AHO /ZMO/ HO/CHO) should begin an enquiry immediately and collect preliminary data about the patient, vaccine/s administered (e.g. brand name of vaccine, name of the manufacturer, Batch/lot number, expiry date) immunization session in question and the condition of the other vaccinees. He will also find out where these lots of vaccines were distributed to identify cluster of events.

During investigation the team should be prepared to visit

1. the immunization sites
2. vaccine storage points
3. residence and locality of the patients
4. the treatment centres/hospitals/clinic (if applicable).

The investigators will interview the patients/guardians, the treating health staff/clinicians and the staff who administered the vaccine to collect relevant information. Those who received vaccine on the same session should also be interviewed if necessary.

Steps of AEFI Investigation for COVID-19 vaccine is attached as **Annex-II.**
AEFI investigation report form for COVID-19 vaccine is attached as **Annex-III.**

District / City Corporation AEFI Committee for COVID-19 vaccine

Composition of the District AEFI Committee for COVID-19 vaccine
1. Civil Surgeon (Chairperson)
2. Asst. Director/Superintendent of Drugs. DGDA
3. Medicine Specialist/Medicine sub-specialist
4. Medical Officer- Disease Control (MO-DC)

5.	RMO (District Sadar Hospital)
6.	EPI Superintendent
7.	Upazila Health & Family Planning Officer (UHFPO of concerned upazila)
8.	Deputy Civil Surgeon/MO-CS (Member secretary)

Composition of the City Corporation AEFI committee for COVID-19 vaccine	
1.	Chief Health Officer (CHO) (Chairperson)
2.	Zonal Medical Officer/Assistant Health Officer (of concerned zone)
3.	Medicine Specialist/Medicine sub-specialist
4.	EPI Supervisor
5.	Local Asst. Director /Superintendent of Drugs, DGDA
6.	Health Officer/ Medical Officer City Corporation (Member Secretary)

Note: In absence of CHO, Health Officer (HO) will be chairperson of the committee and Asst. Health Officer will be the member secretary.

Terms of References for District / City Corporation AEFI Committee

- Investigate serious AEFI cases including clusters and AEFI causing significant community concern. Initiate preliminary investigation within 24 hours of notification and provide an initial report within 48 hours to PM-EPI and DGDA. Complete final investigation within 7 days and send reports to Divisional AEFI causality assessment committee.
- Not all committee members need to be part of the investigation. Member Secretary will initiate investigation with the members as advised by the chairperson. Later on, expert opinion can be sought from other members as per need.
- The investigation team will submit the investigation report to the Divisional AEFI Causality Assessment Committee for COVID-19 vaccine for causality assessment. Also send a copy to PM-EPI and Pharmacovigilance & COVID-19 Safety Surveillance Cell.
- Analyze and review AEFI data on daily basis for SAE leading to fatalities by individual committee during the first 3 months of COVID-19 vaccines introduction. Later on, the committee can have meetings weekly. The committee can have meetings earlier also as per need.
- Review media reports / reports from other sources and conduct investigation if needed.
- Chairperson of the committee or any person of his/her nominated member will act as spokesperson for media communication.
- Ensure AEFI reporting from the Govt/ private facilities under his/her districts /city corporation/ Municipality and Upazilla.

- Communicate and share the conclusions and results of investigation with health workers and the community, where needed.
- The committee will review the functionality of AEFI surveillance in the district/city corporation/ Municipality/Upazilla.
- Any other responsibility in context to vaccine safety that the committee would like to add.
- After completion of investigation, reports will be scanned and sent to Divisional AEFI causality assessment committee in the following day by email.
- The chairperson of the committee can co-opt members for AEFI investigation, if needed.

COVID-19 AEFI CAUSALITY ASSESSMENT

Causality assessment is the systematic review and evaluation of available data about an AEFI to determine the likelihood of a causal association between the event(s) and the vaccine received. This step is critical for any country to ensure the scientific evaluation of potential COVID-19 vaccine-related AEFIs.

As per proposal of the working committee for assuring safety of COVID-19 vaccine, DGDA formed a Divisional AEFI causality assessment committee for COVID-19 vaccine prior to the introduction of COVID -19 vaccines.

The Causality assessment of an adverse event following immunization (AEFI), user manual for the revised WHO AEFI causality assessment classification outlines the scientific basis for causality assessment and performing the assessment in a four-step process (Link of the manual *https://www.who.int/vaccine_safety/publications/CausalityAssessmentAEFI_EN.pdf?ua=1*). The same causality assessment principles and process will be applied for the assessment of COVID -19 vaccine-related AEFIs.

Causality assessment has four steps, as follows:

Step 1 Eligibility. The first step aims to determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.

Step 2 Checklist. The second step involves systematically reviewing the relevant and available information to address possible causal aspects of the AEFI.

Step 3 Algorithm. The third step obtains a trend as to the causality with the information gathered in the checklist.

Step 4 Classification. The fourth step categorizes the AEFI's association to the vaccine or vaccination on the basis of the trend determined in the algorithm.

The worksheet used for the causality assessment of an individual AEFI case is presented in Annex-IV. This can be used by the reviewers to arrive at a decision on causality. WHO has developed an e-tool that will help assessors perform an AEFI causality assessment both online (on computers) and both online and offline modes on tablets and iPads. Details are available at *http://www.who.int/vaccine_safety/causality-assessment-software-EN/en/*.

Steps of Causality Assessment of AEFI for COVID-19 Vaccine is attached as ***Annex-IV***

Divisional AEFI Causality Assessment Committee for COVID-19 vaccine

AEFI causality assessment will be done by Divisional AEFI causality assessment committee. Medical college hospitals of divisional districts will form a divisional causality assessment committee.

Composition of Divisional AEFI causality assessment committee
1. Director of Govt. Medical College Hospital (Chairperson)
2. Divisional Director Health, DGHS (Co-chairperson)
3. Respiratory disease specialist
4. Neurologist
5. Medicine Specialist
6. Pharmacologist
7. Dermatologist
8. Gynecologist
9. Microbiologist/ Virologist
10. Nephrologist
11. Epidemiologist/ public health specialist
12. Cardiologist
13. Endocrinologist
14. Civil Surgeon-Member Secretary

Note:

1. *In absence of chairperson, co-chairperson will preside over the committee meeting.*
2. *In absence of both chairperson and co-chairperson, the chairperson will nominate any member of the committee to chair the meeting.*
3. *The Divisional AEFI Causality Assessment committee can be extended up to district level as per need.*

Terms of reference for Divisional AEFI Causality Assessment Committee

- The committee will conduct desk review of the AEFI case investigation reports submitted by the district/city corporation AEFI investigation committee chairperson and undertake causality assessment and classify the event as per national AEFI surveillance guideline.
- Following causality assessment of the cases, the committee chairperson will forward the report to the national AEFI Expert Review Committee for COVID-19 vaccine with a copy to the respective Civil Surgeon/Chief Health Officer and PM-EPI and DGDA.
- Chairperson of the committee or any person of his/her nominated member will act as spokesperson for media communication.

- Committee will complete causality assessment and send the report to the Chairperson of the National AEFI Expert Review Committee for Covid-19 vaccine using email address covidpvcell.dgda@gmail.com within 3 days of receiving final investigation report.
- The committee will assist AEFI investigation team if required
- The chairperson of the committee can co-opt members for causality assessment, if needed.

NATIONAL AEFI EXPERT REVIEW COMMITTEE FOR COVID-19 VACCINE

Composition of the committee
1. Director General, DGDA (Chairperson)
2. Paediatrician
3. Director, IEDCR
4. Neurologist
5. Medicine Specialist
6. Pharmacologist
7. Dermatologist
8. Gynaecologist
9. Microbiologist / Virologist
10. Nephrologist
11. Endocrinologist
12. Pulmonologists/ Respiratory disease experts
13. Epidemiologist/ public health specialist
14. Cardiologist
15. Representative from Bangladesh Medical Association (BMA)
16. Member Secretary (Deputy Director, DGDA)

Terms of Reference of the National AEFI Expert Review Committee for COVID-19 Vaccine

- The committee will review the causality assessment reports sent by the Divisional AEFI Expert Review Committee and provide necessary advice to EPI and DGDA.
- For unresolved cases of AEFI, the committee will do the causality assessment and classify.

- The committee will monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events and make recommendations for further investigation
- The committee will advise EPI and DGDA at times of crisis/ emergency.
- Chairperson of the committee or any person of his/her nominated member will act as spokesperson for media communication.
- Committee will meet biweekly or as per need depending on the number of AEFI Causality Assessment reports received from the Divisional AEFI Causality Assessment Committee for COVID-19 vaccine.
- The committee will provide technical advice on strengthening the AEFI surveillance system by reviewing AEFI Surveillance Data.
- The chairperson of the committee can co-opt members for causality assessment or other technical matter related to AEFI surveillance if needed.

Note-1: After getting regulatory recommendations from this committee, DGDA will take regulatory actions and communicate with other regulatory authorities/agencies, WHO-Uppsala Monitoring Centre (UMC) to validate regulatory decision for harmonization and accordingly to circulate regulatory decisions to the MAHs for implementation.

PHARMACOVIGILANCE & COVID-19 SAFETY SURVEILLANCE CELL

There is a Pharmacovigilance & COVID-19 Safety Surveillance Cell for conducting pharmacovigilance (adverse drug reaction/AEFI monitoring) as one of the important regulatory function of DGDA. This Pharmacovigilance & COVID-19 Safety Surveillance Cell is newly formed to provide support to the National AEFI Expert Review Committee. The cell will work at DGDA.

Composition of the Cell
1. Head of Pharmacovigilance & COVID-19 Safety Surveillance Cell (Deputy Director, DGDA)
2. Expert from EPI, DGHS
3. Expert from IEDCR
4. Expert from WHO
5. Experts from Development Partners such as USAID MTaPS, USP-PQM+.
6. Clinician
7. Medical Officer, DGDA
8. Health Statistician
9. IT Experts
10. Member Secretary (Asst. Director, DGDA)

Note -1: The cell may co-opt any expert as member if required.

Terms of Reference of the Pharmacovigilance & COVID-19 Safety Surveillance Cell

- Compilation of AEFI reports, investigation reports and other documents.
- Coordination with different committees as regular follow up and updates.
- The cell will provide secretarial support to the National AEFI Expert Review Committee.
- Literature review for collecting AEFI related global information.
- Maintain data management of vaccine safety surveillance with DGDA.
- Data sharing to WHO-UMC Vigiflow.
- Assist DGDA in the communication and implementation of regulatory decisions regarding AEFI issues.
- Coordinate with national vaccine deployment program, Expanded Program on Immunization (EPI) and other relevant stakeholders.

MANAGEMENT/TREATMENT OF COVID-19 AEFIs

Overall responsibilities for treatment and management of COVID-19 related complications will be performed by Directorate General of Health Services (DGHS). Doctors of health facilities (Upazila health complex / District Hospital / Medical college hospitals) will provide symptomatic treatment to all COVID-19 vaccinees who developed AEFIs. If required, vaccinees could be referred to higher centers for better management. Members of District and Divisional COVID-19 AEFI committees will oversee the treatment of these patients. Divisional Director/Civil Surgeon/Chief Health Officers/Health Officers of city corporation & UHFPO shall ensure AEFI/AESI cases or Serious Adverse Events (SAE) management.

Risk groups

Pregnant women, lactating mothers, patients with co-morbidity (such as DM, HTN, BA, COPD, CHD, IHD etc.), Children, Old people, People having family history of co-morbidity and allergy should be kept in concern.

Risk Categorization

- **High Risk:** Serious AEFIs like death, hospitalization, life threatening, Cluster AEFI and disability.
- **Low Risk:** Pain, tenderness, warmth, redness, swelling, induration, itch, muscle ache etc. at the site of vaccination, fever, chills, rigor, headache, myalgia, nausea, vomiting, malaise, fatigue.

Table-1: Case Management Approach

Following table depicts the onsite management of risk following vaccination

Risk	Low Risk	High Risk
Management	▸ Symptomatic i.e. ▸ Fever with sign of inflammation at injection site -Paracetamol ▸ Itch – Antihistamine ▸ Nausea/vomiting - Antiemetic	Keep patient lying flat on back, ensure airway is clear, keep legs elevated higher than head. Then transfer patient to HF available at vaccination center/to nearby advanced HF. Refer the patient to advanced / tertiary level HF if needed.

Risk Control

By taking proper and effective actions against established causes of risk through investigation and assessment. It will be achieved through elimination of causal factors of risk.

Risk Communication

- Disseminating information on safety and appropriate use of vaccine.
- Creating awareness about COVID-19 vaccination among general population.
- Improving knowledge about COVID-19 vaccination among general population and HCP.
- Contributing towards maximum participation of priority target groups in vaccination.

TRAININGS

Training for vaccinators

EPI will provide this training. Following points should be considered during training

- Route of administration like Intra-dermal (ID), Intra-muscular (I/M).
- Precaution like proper sterilization
- How to hold vaccine during administration like 45 / 90 degree
- What AEFIs could happen following immunization/probable AEFIs
- Primary management
- Immediately refer if serious AEFIs to available HF at vaccination center or nearest advanced HF.
- How to fill AEFI form and send to appropriate authority
- Keep record about all vaccinees and regular follow up (active / passive) for any AEFIs.
- To provide Vaccine card with proper information
- Take informed written consent from the participants prior to vaccination to avoid unnecessary hazards.

- Number of dose(s) to be provided.
- Others.

Training for committees

Training should be provided on Reporting, Investigation, Case summary preparation, Causality Assessment, Communication, etc. by both EPI and DGDA.

Training for Pharmacovigilance & COVID-19 Safety Surveillance Cell

DGDA and EPI will arrange necessary trainings for data management, sharing etc.

ANNEXURES

1. Annex-I: AEFI reporting form for COVID-19 vaccine
2. Annex-II: Steps of AEFI Investigation for COVID-19 vaccine
3. Annex-III: AEFI investigation report form for COVID-19 vaccine
4. Annex-IV: Steps of Causality Assessment of AEFI for COVID-19 Vaccine

REFERENCES

1. Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines
2. National Deployment and Vaccination Plan for COVID-19 Vaccines in Bangladesh
3. Vaccine safety manual, WHO
4. National Guidelines on the Pharmacovigilance System in Bangladesh

ANNEX-I

এইএফআই (AEFI) রিপোর্ট ফরম (COVID-19 Vaccine)

এইএফআই রিপোর্টিকারী পুরন করবেন **রিপোর্ট করার তারিখ:** / /

সেকশন ১ : রোগীর তথ্য

রোগীর নাম(*) :..... লিঙ্গ : ☐ পুরুষ ☐ মহিলা ☐ অন্যান্য গর্ভবতী: ☐ হ্যাঁ ☐ না দুগ্ধদানকারী মা: ☐ হ্যাঁ ☐ না

জন্ম তারিখ (দিন/মাস/সাল): _ _/_ _/_ _ বয়স(*) : .....

ফোন নম্বর :..... জাতীয় পরিচয় পত্র নং :..... বাড়ি/জিআর নম্বর : .....

মহল্লা/গ্রাম : ..... ওয়ার্ড (*) : ..... ইউনিয়ন (*): .....

উপজেলা/পৌরসভা/জোন(*) : ..... জেলা/ সিটি করপোরেশন (*): ..... বিভাগ (*): .....

সেকশন ২ : রিপোর্টারের তথ্য

রিপোর্টারের নাম(*) : ..... পদবী : ..... প্রতিষ্ঠান :.....

উপজেলা/পৌরসভা/জোন :..... জেলা/ সিটি করপোরেশন :..... বিভাগ :.....

টেলিফোন:..... ইমেইল (যদি থাকে) :..... স্বাক্ষর : .....

সেকশন ৩ : টিকাদান কেন্দ্রের তথ্য

টিকাদান কেন্দ্রের নাম : ..... টিকাদান কেন্দ্রের ঠিকানা: সাব ব্লক/ মহল্লা ..... ওয়ার্ড.....

ইউনিয়ন ..... উপজেলা/পৌরসভা/জোন ..... জেলা/ সিটি করপোরেশন ..... বিভাগ .....

সেকশন ৪ : টিকা ও ডাইলুয়েন্ট প্রদানের তথ্য

টিকা							**ডাইলুয়েন্ট** (প্রযোজ্য ক্ষেত্রে)				
টিকার নাম (ব্র্যান্ডের নাম)(*)	প্রস্তুতকারীর নাম	**টিকা** প্রদানের তারিখ(*)	**টিকা** প্রদানের সময়(*)	ডোজ (১ম, ২য়, ইত্যাদি)	ব্যাচ/লট নং(*)	মেয়াদোত্তীর্ণ তারিখ	ডাইলুয়েন্টের নাম	ব্যাচ/লট নং(*)	মেয়াদোত্তীর্ণ তারিখ	মেশানোর তারিখ	মেশানোর সময়

ব্যাচ/লট নং এবং মেয়াদোত্তীর্ণ তারিখ জেলা, উপজেলা, মিউনিসিপালিটি, সিটি করপোরেশন, জোন ও ওয়ার্ড (শুধুমাত্র ডিএনসিসি ও ডিএসসিসির ক্ষেত্রে প্রযোজ্য) লেভেলের রিপোর্টিং ফ্যাসিলিটি পুরন করবে।

এইএফআই (AEFI) রিপোর্ট ফরম (COVID-19 Vaccine)

সেকশন ৫(i) : টিকা পরবর্তী বিরূপ ঘটনা(*)		
☐ জ্বর- ≥৩৮° C (≥১০০.৪° F)	☐ খিচুঁনি (Seizure) ☐ জ্বর সহ খিচুঁনি ☐ জ্বর ব্যতীত খিচুঁনি	☐ কাশি (Cough)
☐ বমি বমি ভাব (Nausea)	☐ মাথা ব্যথা (Headache)	☐ অস্থি সন্ধিতে ব্যথা (Joint pain)
☐ ইনজেকশনের জায়গায় শক্ত হওয়া (Nodule)	☐ এনাফাইলেক্সিস (Anaphylaxis)	☐ টক্সিক শক সিনড্রম (Toxic shock syndrome)
☐ মাংস পেশীতে ব্যথা (Muscle pain)	☐ থ্রোম্বসাইটোপেনিয়া (Thrombocytopenia)	☐ অজ্ঞান হয়ে যাওয়া Unconscious)
☐ ইনজেকশনের জায়গায় মারাত্মক প্রতিক্রিয়া: যেমন লাল হওয়া, ফুলে যাওয়া ☐ তিন দিনের বেশি ☐ নিকটবর্তী অস্থিসন্ধি (জয়েন্ট) ছাড়িয়ে যাওয়া	☐ ফোঁড়া (Abscess)	☐ সাময়িকভাবে মূর্ছা যাওয়া (Fainting)
☐ সেপসিস (Sepsis)	☐ এনকেফালোপ্যাথি (Encephalopathy)	☐ ইনজেকশনের জায়গায় অনবরত রক্তক্ষরন
☐ লালচে দানা/ ফুসকুরি (Rash)	☐ অন্যান্য (নির্দিষ্ট করে লিখুন) :.....	
টিকা পরবর্তী বিরূপ ঘটনার বর্ণনা:		
সেকশন ৫(ii) : ☐ হাসপাতালে ভর্তি : ☐ হ্যাঁ ☐ না হাসপাতালে ভর্তি হলে ভর্তির তারিখ : ...../...../.....	☐ মৃত্যু : ☐ হ্যাঁ ☐ না মৃত্যু হলে মৃত্যুর তারিখ : ...../...../.....	

সেকশন ৬ : এইএফআই শুরু ও রিপোর্টের তারিখ	
এইএফআই শুরু হওয়ার তারিখ (*): _ _/__/ শুরু হওয়ার সময় : ..... এইএফআই রিপোর্ট করার তারিখ:...../...../.....	**কোথা থেকে রিপোর্ট করা হয়েছে** ☐ মাঠ পর্যায় ☐ হাসপাতাল

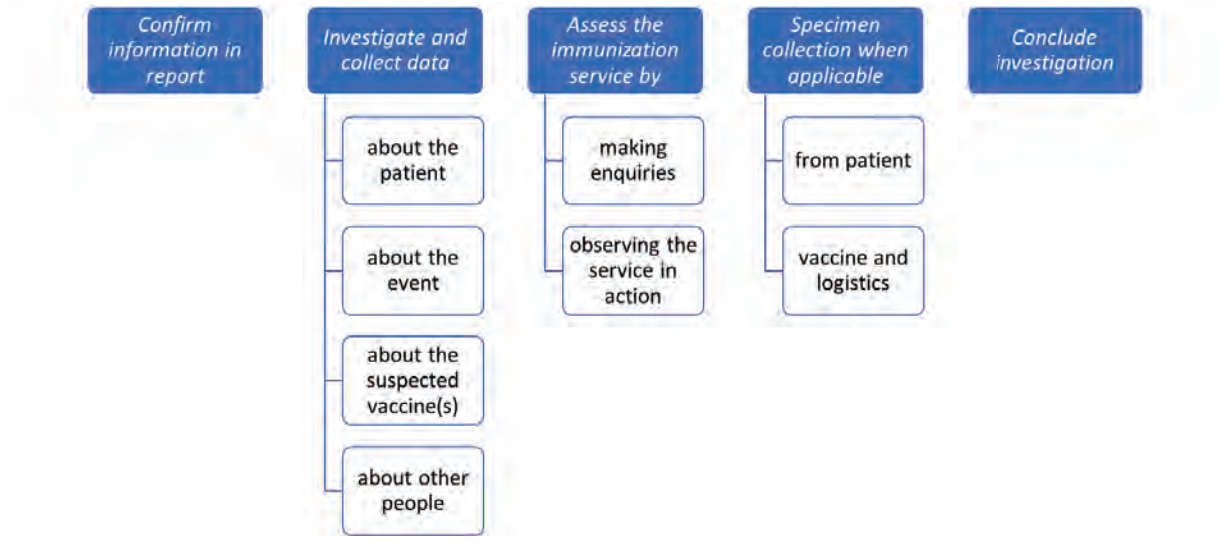
সেকশন ৭ : এইএফআই তদন্ত	
জেলা, উপজেলা, মিউনিসিপালিটি, সিটি করপোরেশন ও জোন লেভেলের রিপোর্টিং ফেসিলিটি পুরন করবে	
মারাত্মক এইএফআই(*) ?: ☐ হ্যাঁ ☐ না হ্যাঁ হলে ☐ মৃত্যু ☐ জীবন আশংকাজনক ☐ বিকলাঙ্গতা ☐ হাসপাতালে ভর্তি ☐ জন্মগত ত্রুটি ☐ অন্যান্য গুরুতর স্বাস্থ্য সংক্রান্ত ঘটনা (নির্দিষ্ট করে লিখুন).....	তদন্তের প্রয়োজন কি-না?: ☐ হ্যাঁ ☐ না
পরিনতি (শুধুমাত্র মারাত্মক এইএফআই-এর ক্ষেত্রে) (*):☐ সুস্থ হচ্ছে ☐ সুস্থ হয়েছে ☐ সুস্থ হয়েছে তবে কিছু সমস্যা রয়ে গেছে ☐ সুস্থ হয়নি ☐ মৃত্যু ☐ অজানা	
কেস আইডি নং (শুধুমাত্র মারাত্মক এইএফআই-এর ক্ষেত্রে): AEFI-BAN-_ _/_ _ _/_ _/_ _ _	
কর্মকর্তার নাম: ..... পদবী : ..... ফোন নম্বর :..... স্বাক্ষর :	
বিশেষ দ্রষ্ঠব্য: তারকা চিহ্নিত ঘরসমূহ অবশ্যই পুরন করতে হবে; এই ফরমটি ফাইলে সংরক্ষন করবেন।	

ANNEX-II

STEPS OF AEFI INVESTIGATION FOR COVID-19 VACCINE

Steps in an AEFI investigation

The following steps to be followed for AEFI investigation:



Step 1: Confirm information in report

- *Obtain patient's medical file (or other clinical records, lab investigation reports etc.)*
- *Check details about the patient and event from the medical records*
- *Verify with AEFI report form, obtain missing details*
- *Identify any other cases that need to be included in the investigation*

Step 2: Investigate and collect data

Step 2a: Investigate and collect data about the patient

Review patient records for

- *immunization history*
- *previous medical history, including prior history of similar reaction or other allergies*
- *family history of similar events.*

Step 2b: Investigate and collect data about the event

- *History of the event in chronological order to explore the underlying factors, if any*
- *Detailed clinical description including sequence of clinical manifestations and the response to treatment*
- *Relevant laboratory tests and other investigations (X-ray, ECG etc.) performed, and results*
- *Details of treatment and outcome.*

Step 2c: *Investigate and collect data about the* suspected vaccine(s)

- *Storage of vaccines and diluents*
- *Temperature record of ILR*
- *The condition of vaccine vial monitor (VVM)*
- *Lot/batch no of vaccine, manufacturer and expiry dates.*
- *Use of vaccine carriers, condition of ice packs*
- *Conditioning of frozen ice packs*
- *Condition of vaccine labels and date of previous use in case of reuse of previously opened vaccine vials under MDVP*
- *Vaccine handling*
- *Identify where the vaccine(s) were distributed*
- *Transportation of vaccine to the vaccination site*
- *Disposal of vaccine*

Step 2d: Investigate and collect data about *other persons*

- *Whether others in the community had similar illness; determine the vaccination status of the affected*
- *If possible, try to obtain details of other beneficiaries who received the vaccine from*
  - *the same centre*
  - *the same vial*
  - *the same vaccine lot/batch*

Step 3. Assess the immunization service

Step 3a: Assess the immunization service by making enquiries

- *Use of vaccine and diluent in the correct dosage, person, site and technique*
- *Vaccine handling*
- *Reconstitution procedure and time between reconstituting and administration*
- *Use of AD syringes for vaccination and reconstitution*
- *Staff training on immunization*

Step 3b: Assess the immunization service by observing it in action

- *How vaccines are placed in the cold chain*
- *If other drugs are stored with vaccines/diluents*
- *Whether any vials have lost their label*
- *Batch numbers and expiry dates*
- *If any of the opened vials look contaminated*
- *Directly observe the immunization procedures (reconstitution, drawing up vaccine, injection technique, safety of needles and syringes)*
- *Whether multi dose vial policy (MDVP) is followed as per guideline*
- *Disposal of opened vials.*

Formulate working hypotheses

After collecting sufficient information, a working hypothesis should be formulated as to what was the probable cause of the AEFI. For example:

i. Immunization error - related reaction
   - vaccine transportation or storage error
   - reconstitution error
   - un-sterile practice
   - incorrect administration technique
   - any other

ii. Vaccine reaction (product related or quality defect related)
   - known vaccine reaction
   - vaccine manufacturer error

iii. Coincidental

iv. Immunization anxiety related reaction

The working hypothesis may be a simple statement linking the suspected cause with the reported AEFI. For instance, an abscess following immunization may initially be investigated with the following hypothesis: “An abscess following immunization due to incorrect technique”. The working hypothesis may change during the course of the investigation. In this example, additional information may reveal that there are similar cases from more than one clinic and therefore the working hypothesis could be modified as “Abscess following immunization due to cold chain failure in vaccine storage”. The focus of the investigation should be to seek to confirm the working hypothesis.

No action should be taken based on the hypothesis, until it is confirmed with reasonable certainty. It is the responsibility of investigation team to form, test and confirm /discard the working hypothesis in a scientific manner.

Step 4: Specimen collection

Once a working hypothesis is formulated, it should be apparent whether specimens are required to confirm or rule out the suspected cause. Only appropriate specimens necessary for investigation should be collected, and a clear explanation should be sent to the laboratory of why they were taken and what information is required

It is difficult to generalize what specimens will be required in a given situation. It will much depend on symptoms and signs and clinical diagnosis. A good communication between clinician and investigation team is important to make a good decision on what specimens to be collected and where to be sent for investigation etc.

Step 4a: Specimen collection: human specimen

For biochemical, histopathological and microbiological examination, specimens should be processed at the local hospital. In case facilities are unavailable locally, specimens should be forwarded to the most suitable laboratory in the country or even an accredited laboratory abroad if warranted.

It is recommended investigation team to contact the laboratory and get advice on specimen collection, transport etc., well before the specimen collection and dispatch.

Guide to Human Specimen Samples Collection Following Selected AEFI

Hypothesis	Specimen	Reason	Specimen collection
Suspected bacterial sepsis due to contaminated vial, needle contamination, coincidental	Whole blood	Bacterial culture	Blood 8-10 ml in each of 2 blood culture bottles.
	CSF	Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other)	Sterile container Viral culture media
	Serum	IgM and IgG antibodies	Clotted blood 5-10 ml

Suspected viraemia due to vaccine virus or coincidental disease		for viral pathogens	
	CSF	Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other)	Sterile container Viral culture media
	Skin vesicle	Viral culture	Sterile container Viral culture media
Suspected anaphylaxis	Serum	Mast cell tryptase	Clotted blood 5–10 ml
		Specific IgE	Clotted blood 5-10 ml
Suspected toxin or drug injection/ingestion, either programme error or coincidental	Urine	Drug screen	Sterile container 1 ml
	Blood	Chemistry when indicated, liver enzymes, glucose, electrolytes	Clotted blood or in Li Heparin 5-10 ml
Suspected VAPP or coincidental encephalitis	Stool	Enterovirus and viral culture	Sterile container

The collection and storage of specimens following serious AEFI (e.g. deaths, anaphylaxis, toxic shock syndrome) is important. Therefore, as soon as information is received about a suspected AEFI, the hospital staffs are advised to collect all relevant samples such as blood, urine, cerebrospinal fluid (CSF), vomitus, faeces, sputum, swabs etc. If there is a delay in transport to the laboratory, samples should be stored in a refrigerator at the recommended temperature, depending the type of sample and the facilities available.

Step 4b: Specimen collection: Vaccine and Syringe

Laboratory testing may sometimes confirm or exclude the suspected cause. However, testing should be requested based on clear suspicion and not as a routine procedure, and never before the working hypothesis has been formulated. Laboratory testing is always costly. Determination of which samples to test, if any, depends on the working hypothesis for the cause of the event .

The vaccine may be tested for sterility, toxicity and content (e.g. Aluminium content); the diluent for sterility and chemical composition; and the needles and syringe for sterility.

Laboratory Testing to Investigate AEFI by Working Hypothesis

Working Hypothesis	Specimens to send	Laboratory Test
Vaccine transportation or storage error	Vaccine vial	Visual test for clarity, presence of foreign matter, turbulence, discoloration or flocculation (examine under magnification)
Reconstitution error	Vaccine vial and/or diluents	Chemical composition analysis for abnormal components (e.g. suspect medicine used instead of vaccine or diluent), or microbiological culture for bacterial contamination
Non-sterile injection	Needle, syringe, vaccine vial and diluents	Sterility, if an infectious cause is suspected
Vaccine problem	Vaccine vial	Chemical composition analysis: preservatives, adjuvant level, etc. (e.g. aluminium content) or biological tests for foreign substances or toxins if abnormal toxicity is suspected

Key Points:

Specimen testing is not a routine requirement but may be a part of an investigation.

- Specimen testing is costly and is recommended only when it is necessary.
- However, securing samples (vaccine vials, syringes, blood etc.) is important because later investigation may require them.
- Therefore, proper storage and transport of suspected samples is recommended. Investigation team to contact the laboratory and get advice on specimen collection, storage and transport well before the specimen collection and dispatch

ANNEX-III

AEFI INVESTIGATION REPORT FORM FOR COVID-19 VACCINE

(Only for Serious Adverse Events Following Immunization - Death / Disability / Hospitalization / Life-threatening / Cluster)

Section A	**Basic details**	
District : _____	**Upz/Mun/CC.** _____	**NID :** **Case ID :**

Place of vaccination *(✓)*:❑Govt. health facility ❑Private health facility ❑Other (specify)

Vaccination in *(✓)*:❑Campaign ❑ Routine | Type of Site *(✓)* : ❑ Fixed ❑ Outreach ❑ Other

Name of responsible officer leading the investigation (CD/ CHO/DCS/MOCS/HO/ZMO/AHO/MO):_____

Designation:_____

Telephone/ Mobile number : :

e-mail:

❑ Preliminary Report ❑ Final Report

Date of investigation: ____/_____/_____

Date of filling this form : ____/_____/_____

Patient Name : _____ Sex : ❑ M ❑ F

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

Date of birth (DD/MM/YYYY): _____/_____/_____ Phone Number :

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

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

Recent Immunization History

Date of vaccination	*Time of Vaccination*	*Dose number (e.g. 1st, 2nd)*	*Site of administration*	*Name of Vaccination center*	*Vaccinated by (name & Designation)*

Information about the vaccines and diluents administered:

Vaccines (Brand Name)	*Manufacturer*	*Lot no. / batch no.*	*Expiry Date*

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)*: _____/_____/_____ Time :	
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 / Unknown	
Adverse event after any previous vaccination(s)?	Yes / No / Unknown	
History of allergy to vaccine, drug or food?	Yes / No / Unknown	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unknown	
Pre-existing acute illness (30 days) prior to vaccination?	Yes / No / Unknown	
Has the patient tested Covid19 positive prior to vaccination?	Yes / No / Unknown	
History of hospitalization in last 30 days, with cause?	Yes / No / Unknown	
Was the patient receiving any concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unknown	
Family history of any disease (relevant to AEFI) or allergy?	Yes / No / Unknown	

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 with phone number :

Name of other persons treating the patient with phone number: 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**
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 constitution/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)	Yes* / No / Unable to assess		
m. Is this case a part of a cluster?	Yes / No / Unknown		
1. 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 / Unknown		
b) If no, number of vials used in the cluster (enter details separately)			
Section E	**Immunization practices at the place(s) where concerned vaccine was used** ***(Complete this section by asking and/or observing practice)***		
Syringes and needles used:			
Are AD syringes used for immunization?	Yes / No / Unknown		
If no, specify the type of syringes used : ❑ Glass ❑ Disposable ❑ 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	Yes	No	NA

Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	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 of vaccinator(s): (Observe another session in the same locality or different place of the same vaccinators) :			
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?	Yes / No		
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 / Unknown		
Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unknown		
Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unknown		
Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unknown		
Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unknown		
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 / Unknow		
Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unknow		
Was a conditioned ice-pack used?	Yes / No / Unknow		
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?		
Of those affected, how many are		
Vaccinated:_____	Not vaccinated:_____	Unknown: _____
Other comments:		
Section H	**Other findings/observations/comments**	
Section I	**Follow up information of the serious AEFI case**	
Date:	**Remarks :**	
Date:	**Remarks :**	
Investigation Date :		
District/CC Investigation Team Details:		
Name :	**Designation:**	**Signature :**
Name :	**Designation:**	**Signature :**
Name :	**Designation:**	**Signature :**
Name :	**Designation:**	**Signature :**
Name :	**Designation:**	**Signature :**
Name :	**Designation:**	**Signature :**
Name :	**Designation:**	**Signature :**
Name :	**Designation:**	**Signature :**

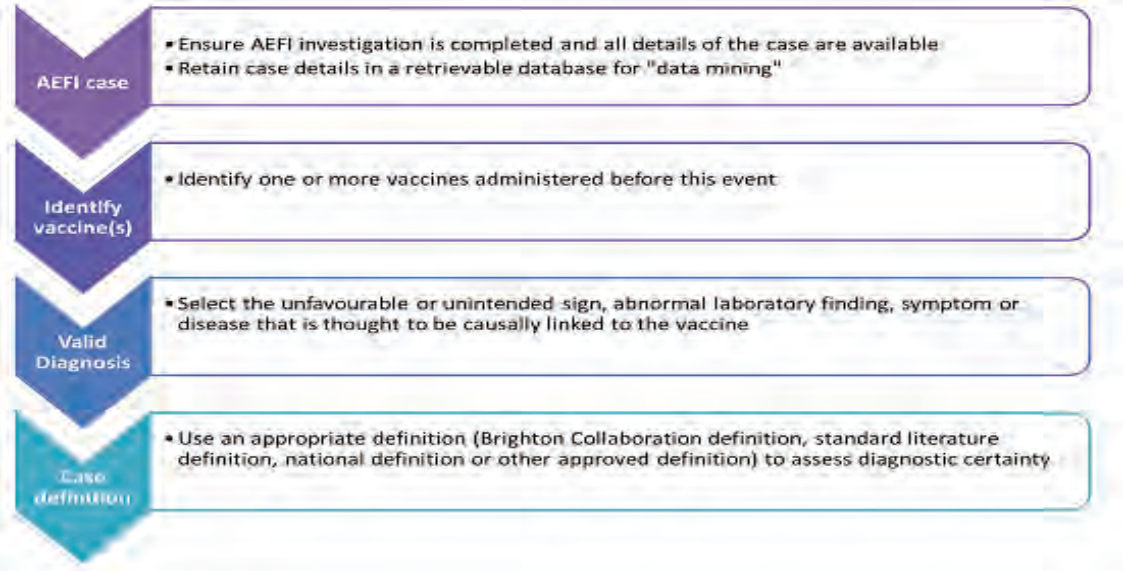
Annex-IV

Steps of Causality Assessment of AEFI for Covid-19 Vaccine

Step 1: Eligibility

The AEFI case need to satisfy the minimum criteria for causality assessment as outlined below figure.

Causality Assessment: Eligibility



Valid Diagnosis

It is also essential to have a valid diagnosis for the reported AEFI, which could be an unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease. The valid diagnosis refers to the extent to which the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease is defined, and whether it is well founded and corresponds accurately to the event being assessed.

The valid diagnosis should meet a standard case definition (or it could also be a syndromic case definition). If available, it is best to adopt the Brighton Collaboration case definition which can be accessed online. However, when a valid diagnosis exists but a case definition does not; case definitions can be adopted from standard medical literature or national guidelines, or may also be adopted locally by the reviewers. 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.

Cases ineligible for causality assessment are those where the amount of information initially available to the assessor is so limited that the assessment cannot be initiated. For example if the name of the vaccine or the valid diagnosis are not available at the time of assessment.

Unclassifiable cases occur in instances where the reviewer is able to initiate an assessment, but during the process, discovers that some key elements are unavailable to permit a logical classification.

In either situation, reasons for not proceeding with the classification have to be provided

At this stage it is also essential for the reviewers to define the "causality question". Examples of causality questions are:

- "Has the vaccine A caused hepatomegaly?" (an example of an unfavourable or unintended sign).
- "Has the vaccine B caused thrombocytopenia?" (an example of a laboratory finding).
- "Has the vaccine C caused itching?" (an example of a symptom).
- "Has the vaccine D caused meningitis?" (an example of a disease).

Causality Question

Create your question on causality here

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

For a given assessment only one valid diagnosis and one vaccine administered can be assessed at one time. If multiple vaccines are administered to the patient at the same time, each vaccine should be assessed separately; when faced with multiple presumptive diagnoses, the reviewer should consider doing a separate causality assessment for each diagnosis. Likewise, for a cluster of AEFI, each individual case must be assessed separately

At this point of the assessment, the assessor has to make a decision if the information that is available at hand is sufficient to proceed (eligibility for assessment), if not the assessment should be postponed until the basic information is obtained.

Step 2. Checklist

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

- Evidence for other causes

- Association of the event and the vaccine/vaccination with the vaccine product(s), immunization error or immunization anxiety (if there is an association, it is also important to find out if the event occurred within a plausible time window)
- Evidence against a causal association
- Other qualifying factors for classification such as previous history of a similar event, the background rate of the event, pre-existing, present and past health conditions, potential risk factors, other medications, exposure to triggering factors etc.

The causality assessment checklist

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
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.)?	☐☐☐☐	
Immunization anxiety (Immunization Triggered Stress Response - ITSR)		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
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.

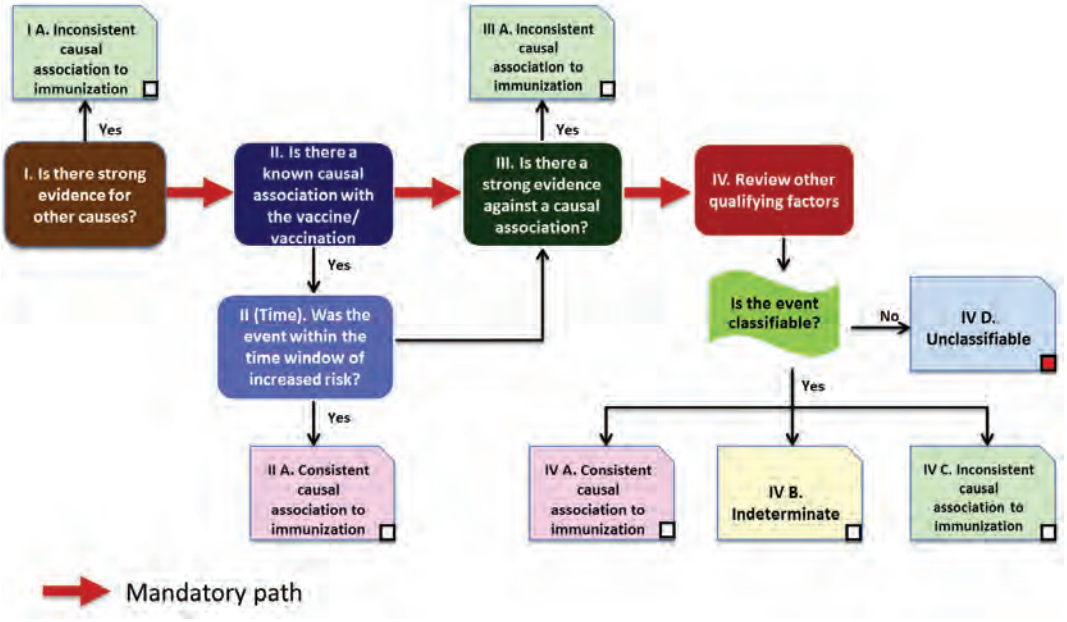
It is essential that all questions in the checklist be answered with any one of the options, "Yes", "No", "Unknown" or "Not applicable". When there is a positive response to any question, ("Yes" response), it is essential to provide an explanation for the positive response

in the corresponding row under remarks. It will be observed that sometimes explanations for other responses ("No", "Unknown" or "Not applicable") are also important to determine causality; therefore, it is essential that the "Remarks" column is used to provide detailed explanation on the reasons.

Step 3. Algorithm

After the checklist is completed, data related to the association under investigation is ready to be applied to the algorithm. The algorithm aims to be a roadmap for the decision-making of the reviewers, but it does not, and should not, take away the expert and deductive logical process inherent in linking a diagnosis to its potential cause. The stepwise approach of the algorithm helps to determine if the AEFI could be consistent or inconsistent with an association to immunization, an indeterminate outcome or unclassifiable.

Figure : Causality Assessment: Algorithm



The algorithm allows the reviewers to focus logically and document their observations to the appropriate conclusions. "Yes" responses in the checklist should have corresponding conclusions in the algorithm. The boxes on the mandatory path (red arrow) correspond to the four major sections in the checklist (I to IV). It is essential that the reviewers evaluate all four boxes using the responses in the checklist.

During the initial stages of the assessment when considering the eligibility (step 1), the reviewer may consider the available information to be sufficient for initiating the causality assessment process. However after completing the checklist (step 2), it may be discovered that the information is insufficient to arrive at a definite conclusion. At this stage of the review, the reviewer may decide to categorize the case as "Unclassifiable" (check-box marked in red in Figure). When the conclusion is "unclassifiable", the reviewers should determine the reasons and document why classification was not possible, and all attempts should be made to obtain the necessary supporting evidence for classification.

Step 4. Classification

The final classification is based on the availability of adequate information.

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

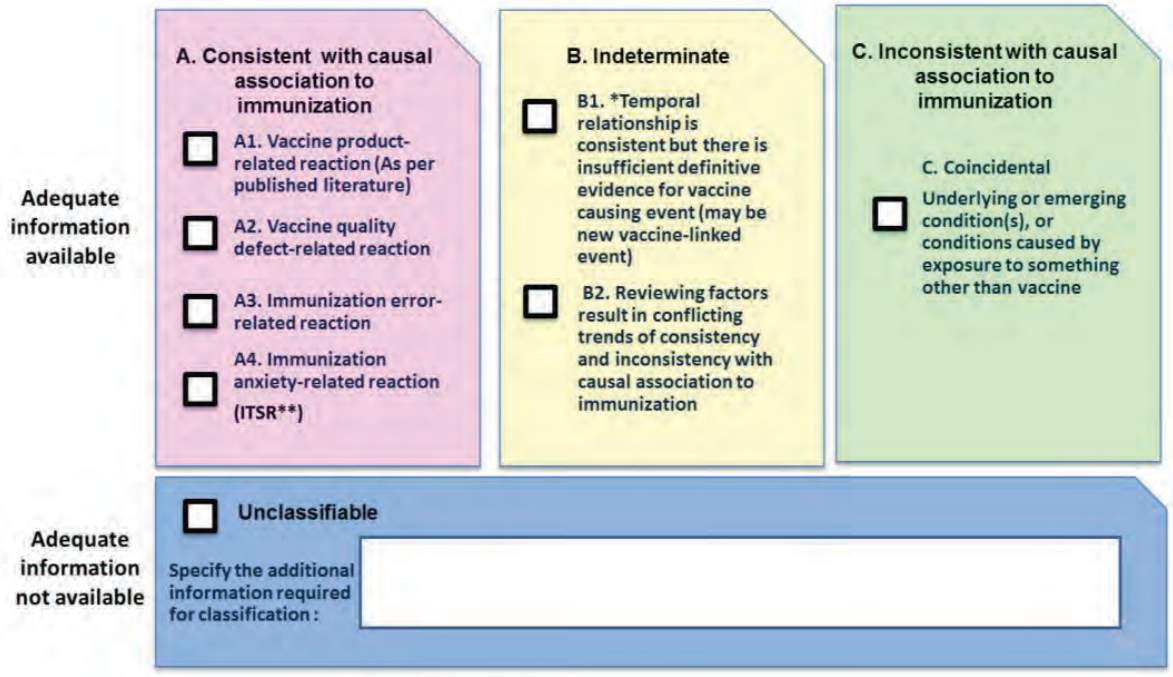
A. Consistent causal association to immunization
A1. Vaccine product-related reaction; or
A2. Vaccine quality defect-related reaction; or
A3. Immunization error-related reaction; or
A4. Immunization anxiety-related reaction.

B. Indeterminate
B1. Temporal relationship is 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).

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.

II. Case without adequate information for causality conclusion
As mentioned above, such cases are categorized as “unclassifiable” and requires additional information for further review of causality. The available information on unclassifiable cases should be placed in a repository or an electronic database which should be periodically reviewed to see if additional information is available for classification and to perform analyses for identifying signals.

Figure : Causality Assessment Classification



*B1: This is a potential signal and maybe considered for investigation
** Immunization Triggered Stress Response

Worksheet for AEFI causality assessment

Patient ID/ Name : **DoB/ Age:** **Sex: Male/ Female**

Step 1 (Eligibility)

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)

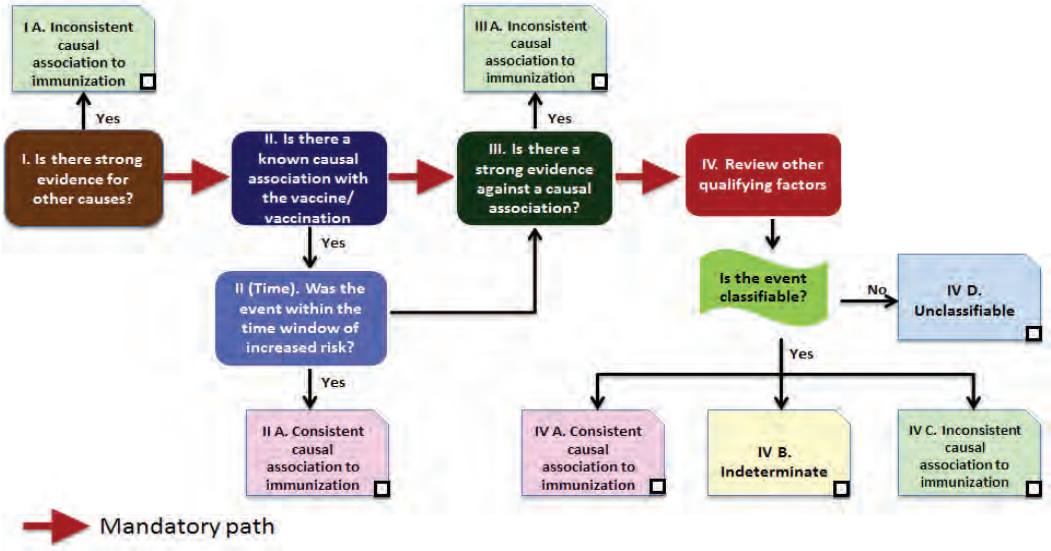
Is this case eligible for causality assessment? Yes/ No; If, "Yes", proceed to step 2

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

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
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.)?	☐☐☐☐	
Immunization anxiety (Immunization Triggered Stress Response -ITSR)		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
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.)?	☐☐☐☐	

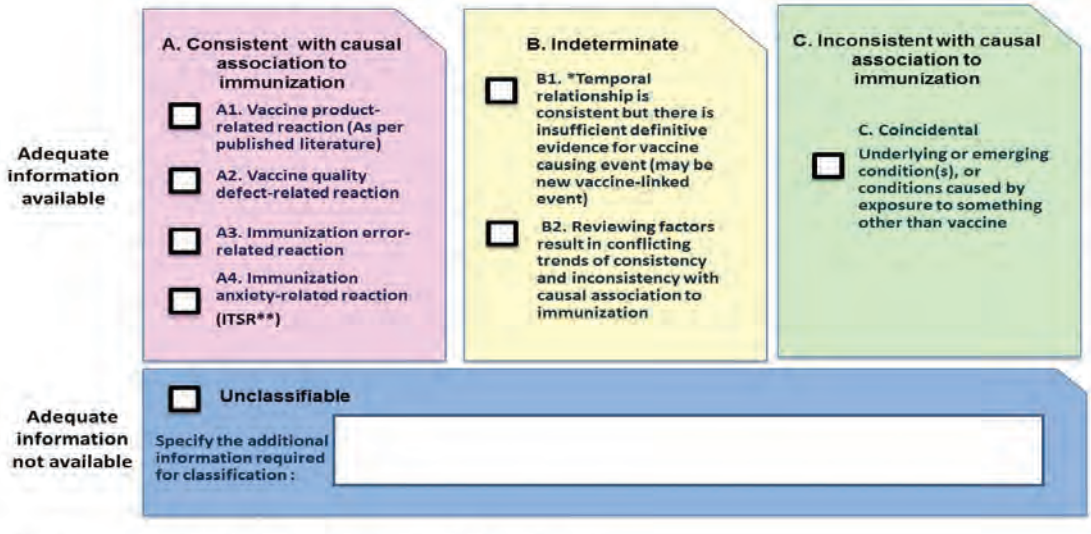
Y: Yes N: No UK: Unknown NA: Not applicable or Not available

Step 3 (Algorithm) review all steps and ✓ all the appropriate boxes



Notes for Step 3:

Step 4 (Classification) ✓ all boxes that apply



*B1: This is a potential signal and maybe considered for investigation
** Immunization Triggered Stress Response

Summarize the classification logic in the order of priority:

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

With available evidence, we could **NOT** classify the case because:_____

PHARMACOVIGILANCE PROTOCOL

FOR

COVID-19 VACCINES