COVID-19 Vaccines: Safety Surveillance Manual

Module: Responding to adverse events following COVID-19 immunization (AEFIs)

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Abbreviations

AACVS	African Advisory Committee on Vaccine Safety
ACE	Angiotensin-converting enzyme
ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
ARDS	Acute respiratory distress syndrome
AVSS	Active vaccine safety surveillance
CEM	Cohort event monitoring
CEPI	Coalition for Epidemic Preparedness Innovations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
DCVMN	Developing Countries Vaccine Manufactures Network
DL	Data linkage
DNA	Deoxyribonucleic acid
EH	e-Health
EPI	Expanded programme on immunization
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré syndrome
GVAP	Global vaccine action plan
HCW	Health care worker
ICD	International classification of diseases
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
ISoP	International Society of Pharmacovigilance
ISRR	Immunization stress-related response
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
MH	m-Health
MoH	Ministry of Health
mRNA	Messenger RNA
NIP	National Immunization Programme
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authority
PBRER	Periodic benefit-risk evaluation report
PHEIC	Public health emergency of international concern
PLSS	Post-licensure safety studies
PSUR	Product safety update report
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance
RITAG	Regional Immunization Technical Advisory Groups
RMP	Risk management plan
RNA	Ribonucleic acid
SAGE	Strategic Advisory Group of Experts (for immunization)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SKG	Significant knowledge gap
SIA	Supplementary immunization activities
SS	Sentinel surveillance
TGA	Therapeutic Goods Administration (Australian Ministry of Health)
VAED	Vaccine-associated enhanced disease
VLP	Virus-like particles
VPD	Vaccine preventable disease
WHO	World Health Organization

Glossary

Adjuvant	A pharmacological or immunological agent added to a vaccine to improve its immune response.
Adverse event following immunization (AEFI): general definition	Any untoward medical event that follows immunization and that 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.
• AEFI by cause: coincidental events	• An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
• AEFI by cause: immunization anxiety-related reaction	• An AEFI arising from anxiety about the immunization (see immunization stress related responses).
• AEFI by cause: immunization error-related reaction	• An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, that, therefore, is preventable.
• AEFI by cause: 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, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
• AEFI by cause: vaccine-quality defect-related reaction	• An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Adverse event of special interest (AESI)	A preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.
Causal association	A cause-and-effect relationship between a causative (risk) factor and an outcome. Causally-associated events are also temporally associated (i.e. they occur after vaccine administration), but events that are temporally associated may not necessarily be causally associated.
Causality assessment	In the context of vaccine AEFI surveillance, a systematic review of data about the AEFI case(s) to determine the likelihood of a causal association between the event and the vaccine(s) received.
Cluster	Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health facility, and/or a vial of vaccine or a batch of vaccines.
Contraindication	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/severe febrile illness.
Immunity	The ability of the human body to tolerate the presence of material 'indigenous' to the human 'body' (self) and to eliminate 'foreign' (non-self) material. This discriminatory ability provides protection from infectious diseases since most microbes are identified as foreign material by the immune system.
Immunization	Immunization is the process whereby a person is made immune or resistant to an infection, typically by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection

Immunization safety	The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse event surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
Immunization safety surveillance	A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.
Immunization stress related responses (ISRR)	Stress response to immunization that may manifest just prior to, during, or after immunization.
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (e.g. transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).
Mass vaccination campaign	Mass vaccination campaigns involve administration of vaccine doses to a large population over a short period of time.
Non-serious AEFI	An event that is not 'serious' and does not pose a potential risk to the health of the recipient. Non-serious AEFIs should also be carefully monitored because they may signal a potentially larger problem with the vaccine or vaccination or have an impact on the vaccination acceptability; in general.
Risk management plan (RMP)	A risk management plan is a document that describes the current knowledge about the safety and efficacy of a medicinal product. The RMP provides key information on plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine or vaccine. It also describes measures to be undertaken to prevent or minimise risks associated with the use of the product in patients.
Safe injection practice	Practices that ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.
Serious AEFI	An event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.
Severe vaccine reaction	Vaccine reactions can be mild, moderate or severe. Severe reactions may include both serious and non-serious reactions.
Signal (safety signal)	Information (from one or more sources) that 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 verification.
Surveillance	The continual, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.
Trigger event	A medical incident following immunization that stimulates a response, usually a case investigation.
SAGE Values Framework	Values Framework, developed by WHO's SAGE, offers guidance globally on the allocation of COVID-19 vaccines between countries, and guidance nationally on the prioritization of groups for vaccination within countries while COVID-19 vaccine supply is limited
Vaccine	A biological preparation that elicits immunity to a particular disease. In addition to the antigen, it can contain multiple components, such as adjuvants, preservatives, stabilizers, each of which may have specific safety implications.

Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced diseases are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen.
Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or vaccination.
Vaccination failure	Vaccination failure can be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of sero-conversion or sero-protection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to (i) failure to vaccinate, i.e. an indicated vaccine was not administered appropriately for any reason or (ii) because the vaccine did not produce its intended effect
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.
Vaccine safety	The process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.

1. Responding to adverse events following COVID-19 immunization (AEFIs)

As outlined in Module on COVID-19 vaccines [Link to Module COVID-19 vaccines will be added], the unprecedented rapid development of the COVID-19 vaccines on novel platforms followed by its rapid deployment on a mass scale poses unique challenges in monitoring vaccine safety. Timely detection and reporting of adverse events following COVID-19 vaccination is the first step in ensuring the continued safety of the vaccine, immunization safety surveillance and response. In the COVID-19 vaccination context, surveillance systems need to be prepared for identifying and responding to both adverse events following immunization (AEFIs) and adverse event of special interest (AESIs) as well as other safety events that may cause public concern.

Although both AEFIs and AESIs can be detected through passive and active surveillance, if countries do not implement active surveillance for AESIs, all AESI-like adverse events occurring following COVID-19 immunization should be considered as AEFIs and the standard procedure for AEFI response should be adopted as described below. In addition to Module on AESIs in this manual [Link to Module AEFI will be added], the WHO '*Guidance on AESI in preparation for COVID-19 vaccine introduction*' provides detailed information on AESIs including a list of potential AESIs, their case definitions, study protocols, training requirements, data collection tools (including AESI confirmation forms), processing, transmission, analysis and response.

When COVID-19 vaccination is implemented, specific funds should be identified, earmarked and allocated during the planning stage for identifying, reporting and responding to AEFIs/AESIs, as there is likely to be a lot of unknowns because there it is a new infectious disease and there are many vaccines being evaluated, many using novel vaccine platforms [Link to Module COVID-19 vaccines will be added], broad target populations, various manufacturers and variable immunization strategies adopted by different countries.

2. Standard vaccine safety definitions and their implications in vaccine safety in the COVID-19 context

2.1. Adverse event following immunization

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 event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease[1].

- The same definition will continue to be used to identify and report, all AEFI following COVID-19 vaccines
- Investigate relevant cases and come up with a valid diagnosis before proceeding with causality assessment

[1] Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance

2.2. 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 of 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.

2.3. 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.

2.4. 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.

2.5. 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[2]

- *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 analysing if the pooled data points to the occurrence of a new event that could causally related to the vaccine.*

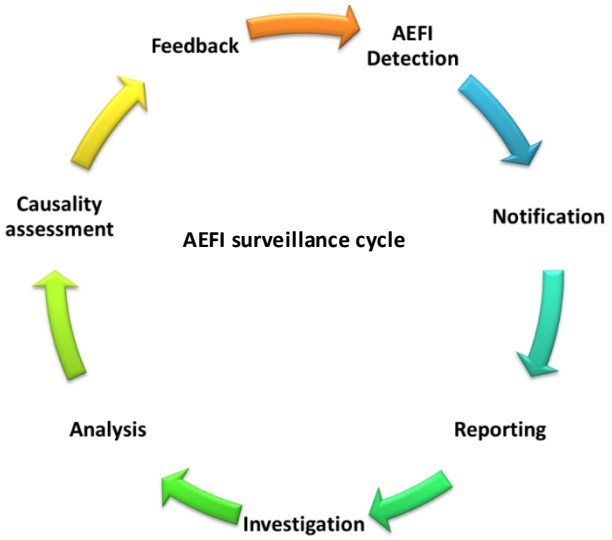
3. Addressing AEFI in the context of COVID-19 vaccine introduction

At the time of vaccine introduction, all countries should at a minimum have an AEFI surveillance system in place as described in the Global Manual on Surveillance of AEFI[3]. The AEFI surveillance cycle (**Fig 1**) outlines the different steps in identification, notification, reporting, investigation, data analyisis, causality assessment and feedback following all AEFI, including AEFI following Covid 19 vaccine.

[2] Practical aspects of signal detection in pharmacovigilance. Report of CIOMS Working Group VIII. Geneva, CIOMS, 2010

[3] https://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

Fig 1 AEFI surveillance cycle



4. Detection, reporting and responding to adverse events following COVID-19 immunization

4.1. AEFI detection

AEFI detection primarily takes place through passive surveillance. This involves vaccine recipients, parents of immunized infants/children, health care providers and staff in immunization or health care facilities detecting the AEFIs and reporting them to any health care provider working within the health care system. AEFIs can also be detected through active surveillance, via sentinel sites. In addition, AEFIs may be detected in phase IV clinical studies of COVID-19 vaccines where they should be independently reported, assessed and processed, in compliance with the study protocol and should not be reported through the passive reporting systems as described in this module.

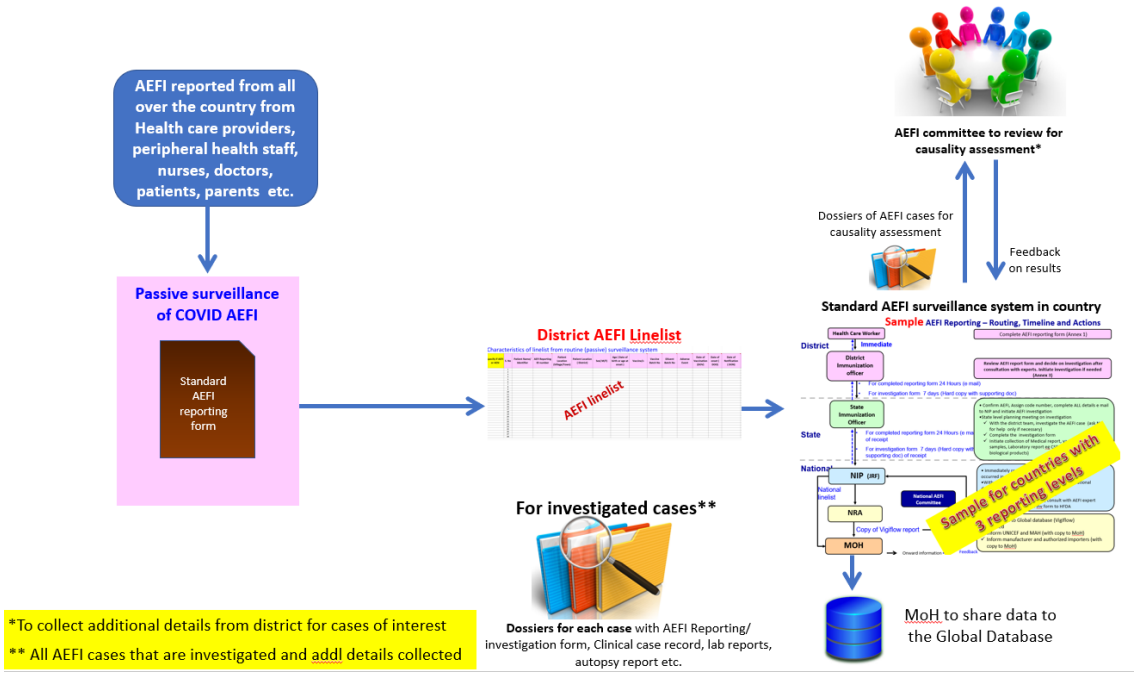
4.2. Routine passive AEFI reporting systems

All AEFIs should be reported using the standard COVID-19 AEFI reporting form (Appendix 8.1) using the fastest means possible. When the AEFI is judged to be serious, reporting should also include a telephone call, direct conversation or notification via a specific application, depending on what is available in the country. AEFI reporting forms contain a minimum set of core variables in order to make the global evaluation of signals possible and thus help countries to evaluates the AEFIs that occur.

For COVID-19 immunization-related AEFIs, in addition to standard information, it is important to record the brand name, the manufacturer, as well as the batch numbers (because vaccines are likely to be manufactured on different platforms, with different antigen targets, adjuvants and dosage forms). A comprehensive complete AEFI report is the primary source for populating an AEFI linelist (Appendix 8.2) which when processed provides key descriptive epidemiological data (time, place and person) that is critical for identifying clusters and for signal detection. The AEFI reporting form also provides information on quality of the passive surveillance system in terms of the completeness and timeliness of the reporting. This is important for monitoring the performance of the pharmacovigilance systems [Module: data management systems – link will be added]. The primary reporter, i.e., the immunization provider / health care professional is responsible for providing all the

information required in the COVID-19 AEFI reporting form. In some countries, vaccine recipients or their parents may fill the form themselves. AESIs may be reported spontaneously after COVID-19 immunization. These will be considered as AEFIs and will be processed through the standard AEFI surveillance system as described in this module (**Fig 2**).

Fig 2: In-country reporting and processing of AEFI



5. AEFI reporting flow

As outlined above, when a COVID-19 standard AEFI reporting form (Appendix 8.1) is received at the district, it should be reviewed for seriousness and transmitted to the province and national levels and AEFI linelists populated (Fig 2) at specific levels as described in the Global manual on surveillance of adverse events following immunization[4]. If the AEFI is considered to be a minor AEFI or NOT serious AEFI, detailed investigation and causality assessment will not be required; this should be noted on the form. Detailed investigation and causality assessment will be required if the AEFI is considered to be:

- a serious AEFI (death, hospitalization, significant disability, life threatening, or congenital anomaly/ birth defect), or is a part of a cluster; or
- a part of a group of events with an unexpected high rate or severity, or a suspected signal.

6. Investigating potential COVID-19 vaccine-related AEFIs

Chapter 6 of the Global Manual on Surveillance of AEFI[4] describes:

- why AEFIs should be investigated
- which AEFIs should be investigated

[4] WHO; Global manual on surveillance of adverse events following immunization. Available from: https://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf. Accessed 28 October 2020

- who should investigate AEFIs
- when AEFIs should be investigate
- how to investigate AEFIs
- laboratory testing of specimen
- investigating AEFI clusters and investigation of deaths following immunization.

For AEFIs following COVID-19 immunization, the same processes and methodology should be followed, after the relevant staff have been trained on the specific manifestations of COVID-19 vaccine-associated AEFIs. During the investigation, it is important to remember that, like all other vaccines, attention should be paid to identify and rule out immunization (or programme) error-related AEFIs, immunization stress related responses and coincidental events that could manifest as a COVID-19 vaccine-related AEFI.

If the district authorities and experts feel that the AEFI investigation can be done locally, they can visit the patient and locality and initiate the detailed investigation with appropriate members of the local health care team. If not, assistance should be solicited from the higher levels of the hierarchy. For deaths, national investigations should be led by a team from the National AEFI Committee, supported in the investigation by the Expanded Programme for Immunization (EPI) or National Immunization Programme (NIP), the National Regulatory Authority and other experts, as needed. During field investigations, the COVID-19 specific AEFI investigation form, the WHO AEFI investigation software[5] and aide memoire[6] should be used to guide the process.

6.1. Causality assessment of potential COVID-19 vaccine-related AEFIs

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. All countries must establish a process for causality assessment prior to the introduction of COVID-19 vaccines. In addition to having a functional post-marketing pharmacovigilance or AEFI surveillance system, there must be access to a functional expert group for causality assessment either at national, subnational, or regional levels. This step is critical for any country to ensure the scientific evaluation of potential COVID-19 vaccine-related AEFIs. Smaller countries who do not have enough experts may collaborate with neighbouring countries (or use regional resources), and larger countries may have committees at the subnational level.

The *Causality assessment of an adverse event following immunization (AEFI), user manual for the revised WHO AEFI causality assessment classification*[7] outlines the scientific basis for causality assessment and performing the assessment in a four-step process. The same causality assessment principles and process should be applied for the assessment of COVID-19 vaccine-related AEFIs.

[5] WHO AEFI investigation software. Available from: https://www.who.int/vaccine_safety/software-assistance-guiding-hq-AEFI-investigations/en/. Accessed 28 October 2020.
[6] WHO AEFI investigation aide mémoire. Available from: https://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf?ua=1. Accessed 28 October 2020.
[7] WHO Causality assessment of an adverse event following immunization (AEFI), user manual for the revised WHO AEFI causality assessment classification (2nd edition). Available from: https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf;jsessionid=3C1EA7F511C8868B9748D57DA6045797?sequence=1 . Accessed 28 October 2020.

However, because COVID-19 vaccines are novel vaccines, with multiple vaccine platforms, antigen targets and adjuvants produced by various manufacturers and will probably have differing implementation strategies adopted by different countries for broad target populations, information on risk of rare serious vaccine reactions will be limited at the time of regulatory assessment and registration of the COVID-19 vaccines. The adaptation of causality assessment approaches must be envisaged to allow the efficient identification, monitoring and evaluation of suspected signals to allow necessary regulatory and programmatic decisions to be taken in a timely manner.

In the event that phase III clinical trials are ongoing simultaneously with the widespread use of COVID-19 vaccines due to their emergency use listing, AEFI committees should have access to the periodic safety updated reports (PSURs). In addition, serious adverse events rates could be made available by the COVID-19 manufacturer to the committee. Global information and information from other regions should be available for the causality assessments, to help to identify signals and situations that could require collection of more detailed information.

6.2. Country preparedness and capacity required for causality assessment for potential COVID-19 vaccine-related AEFIs

The AEFI causality assessment committee should include experts from paediatrics, neurology, general medicine, forensic medicine, pathology, microbiology, immunology and epidemiology. In addition, other external specific medical experts such as geriatricians, pulmonologists, cardiologists, nephrologists should be invited following the introduction of COVID-19 vaccines as they will be administered to individuals of all ages. If countries decide to use the AEFI committees to review AESI cases to identify signals, the committees will need to be strengthened with additional expertise from statisticians and epidemiologists trained in research methodology. The presence of a communication spokesperson in the committee will delineate the official lines of communication particularly with the media and other stakeholders.

The committee needs to be independent and should have secretarial support from both the immunization programmes (EPI or NIP) and the NRA. Alternatively, drug safety committees that evaluate adverse drug reactions could perform the causality assessment if training on AEFI causality assessments is provided. National pharmacovigilance centres play an important role in vaccine safety and their roles and responsibilities in causality assessment should be defined, taking into consideration the country context.

Countries with existing AEFI causality assessment committees do not need to establish a separate committee for COVID-19 vaccines. However, a refresher training focusing on COVID-19 vaccine-specific AEFIs before COVID-19 vaccine introduction is warranted in the light of the unique challenges described above. Countries that do not have AEFI causality assessment committees should aim to establish such a committee prior to COVID-19 vaccine introduction to allow adequate time for training and preparation.

Countries where the population and geographical territory are large, decentralization should be considered by establishing sub-national AEFI causality assessment committees, provided that the requisite expertise and other resources are available. This will enable timely AEFI causality assessment and reduce the workload for the national AEFI causality assessment committee. However, the sub-national committees should share all AEFI causality findings with the national committee. The sub-national level of AEFI causality assessment could also be considered as an

interim stage of AEFI causality assessment for complex cases with national interest, for which the final assessment should be done by the national committee.

AEFI causality assessment committees should anticipate an increase in reporting of serious AEFIs following the introduction of COVID-19 vaccines due to the novelty of COVID-19 vaccines, the high vigilance for AEFIs, and broad range of target populations. While this will increase their workload, the causality assessment must be performed in a timely manner to enable appropriate decision making and early response. This will be essential to maintain the confidence and trust of the community in the COVID-19 vaccines. The frequency of AEFI causality assessment committee meetings should be adjusted to meet this demand.

Countries requiring special technical expertise for causality assessment (such as specific training on COVID-19 AEFI causality assessment or advice for laboratory tests) should contact their WHO national or regional office. Assistance is also available from WHO at the global level by contacting: gvsi@who.int.

Establishing an international or regional technical committee for causality assessment with collaborative mechanisms for a broader range of expertise and experience in causality assessment will support countries with limited internal expertise and resources. The success of this strategy will depend on the country willingness to share information while maintaining confidentiality, where necessary. In addition, this regional committee could provide advice for Member States on the trends and patterns of safety signals for COVID-19 vaccines in use in the region.

6.3. Case selection and prerequisites for individual causality assessment

The selection of AEFI cases reported from passive surveillance systems for causality assessment should 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, or result in a congenital anomaly/birth defect;
- the 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 (and that are not listed in the product information);
- events causing significant parental, family or community concerns.

6.4. Key considerations during causality assessment for COVID-19 vaccine-related AEFIs

Performing a scientific causality assessment requires a comprehensive, completed AEFI investigation dossier, with all the necessary information including a 'valid diagnosis' and details of the vaccine administered and an independent AEFI causality assessment committee. At the time of assessment, the AEFI case investigation should have been completed, all details of the case such as the COVID-19 AEFI report form, case investigation form, completed clinical case record, laboratory report, autopsy report, details of field investigations should be available.

Due to unique challenges associated wth COVID-19 vaccines, the AEFI causality assessment committee should consider each of the following factors:

- *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. This is important to support for the classification of coincidental events in adult population, particularly those with chronic diseases.
- *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.
- *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:* Vaccine-enhanced disease is known to be a AEFI associated with some live attenuated vaccines. COVID-19 vaccination itself may be associated with an increased risk of developing COVID-19-like disease or its complications. There is 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

7. Tools for AEFI

It is recommended to use the existing data collection tools, as described in the Global Manual on Surveillance of AEFIs[4] for data collection, collation and processing for AEFIs. Some of the tools need to be amended and adapted to the context of the COVID-19 vaccine safety. The details of the available tools and details of their access are provided in **Table 1**.

297 Table 1 Tools recommended for COVID-19 vaccine-related AEFI reporting, investigation, management and causality assessments

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Description	Purpose	Status for COVID-19	Hard Copy	Electronic tool
AEFI reporting form	To collect basic reports of all AEFI cases that have been notified	COVID-19 standard AEFI reporting form that includes the name of the manufacturer and brand name	Appendix 8.1	In-country tools if available; if not WHO recommends Vaccine specific Vigiflow https://www.who-umc.org/global-pharmacovigilance/vigiflow/
AEFI linelist	To collate the details in the reporting form	COVID-19 standard linelist that includes the name of the manufacturer and brand name	Appendix 8.3	https://www.who-umc.org/global-pharmacovigilance/vigiflow/
AEFI investigation form	To collect detailed information when serious AEFI cases are investigated	Adapted to include COVID-19 specific questions	Appendix 8.3	AEFI investigation software http://investigation.gvsi-aefi-tools.org/investigation/index.html#step-1
AEFI causality assessment	To determine case classification of serious AEFI cases	Retain unchanged	https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf;jsessionid=4670F3DD797CEE4E1D08F2A30721D5CA?sequence=1	http://gvsi-aefi-tools.org/

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8. Appendices

8.1. Appendix 8.1: standard COVID-19 AEFI reporting form

AEFI reporting id number:

COVID-19 REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

***Patient name*:** ***Patient's full Address*:** Telephone: Sex: ☐ M ☐ F ***Date of birth (DD/MM/YYYY)*: _ _/_ _/_ _ _ _** *OR Age at onset :* ☐☐*Years* ☐☐ *Months* ☐☐☐ *Days* *OR Age Group:* ☐ 0 < 1 year ☐ 1- 5 years ☐ > 5 years - 18 years ☐ > 18 years – 60 years ☐ > 60 years	***Reporter's Name*:** Institution: Designation &Department: Address: Telephone & e-mail: Date patient notified event to health system (DD/MM/YYYY): _ _/_ _/_ _ _ _ Today's date (DD/MM/YYYY): _ _/_ _/_ _ _ _

Health facility (or vaccination centre) name:

Vaccine						***Diluent***		
Brand Name incl. Name of Manufacturer	***Date of vaccination***	***Time of vaccination***	Dose (1st, 2nd, etc.)	***Batch/ Lot number***	Expiry date	***Batch/ Lot number***	Expiry date	Time of reconstitution

Adverse event(s): ☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint* ☐ Seizures ☐ *febrile* ☐ *afebrile* ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever≥38°C ☐ Other (specify)..... Date & Time AEFI started (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ ☐☐ Hr ☐☐Min	Describe AEFI (signs and symptoms):

Serious: Yes / No ; ➔ If Yes ☐ Death ☐ Life threatening ☐ Disability ☐ Hospitalization ☐ Congenital anomaly ☐ Other important medical event (Specify_____)

Outcome: ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Died If died, date of death (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ Autopsy done: ☐Yes ☐No ☐Unknown

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

First Decision making level to complete:

Investigation needed: ☐ Yes ☐ No	If yes, date investigation planned (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

National level to complete:

Date report received at national level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __	AEFI worldwide unique ID **:**
Comments:	

**Compulsory field*

8.2. Appendix 8.2: AEFI linelist

COVID19 AEFI linelist

Source	S. No	Patient Name/ Identifier	AEFI Reporting ID number	Patient Location (Village/Town)	Patient Location (District)	Sex (M/F)	Age (Date of brith or age at onset)	Vaccine/s	Manufacturer	Dose	Vaccine Batch No	Diluent Batch No	Adverse Event	Place of vaccination	Date of Vaccination (DOV)	Date of onset (DOO)	Date of Notification (DON)

8.3. Appendix 8.3: AEFI investigation form adapted for COVID-19 immunization

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	
Is the patient currently on 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)

	Status		
• Reconstitution procedure (✓)			
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:

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Section H	Other findings/observations/comments

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