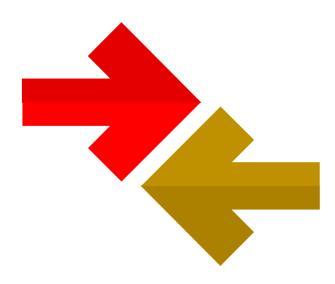
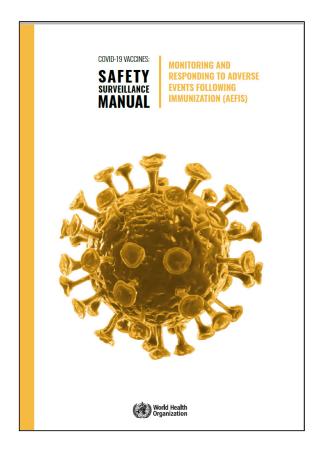
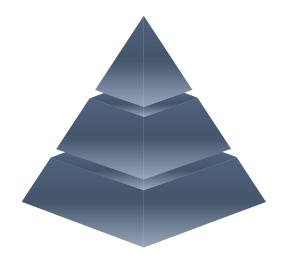
Monitoring and responding to adverse events following immunization (AEFIs)



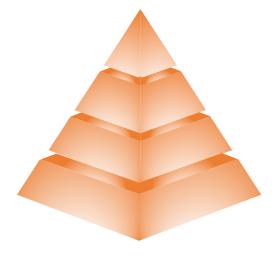




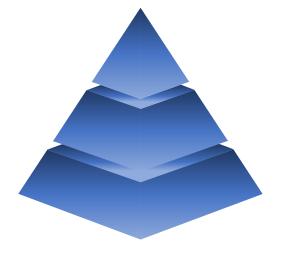
Learning objectives: The learner will be able to



Review the key vaccine safety definitions and their implications in COVID-19 vaccine safety



Apply the various tools and resources available for COVID-19 vaccine safety in specific contexts



Operationalize reporting, investigation and causality assessment in the COVID-19 vaccine safety context



Presentation structure

Key vaccine safety definitions and their implications in the COVID-19 context

Resources available for each stage of COVID-19 vaccine safety surveillance

Uniqueness in AEFI reporting, investigation and causality assessment in the COVID-19 context



Key definitions and implications in the COVID-19 context **Adverse event following immunization**



Definition

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



Implications in

COVID-19 context

- 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



Key definitions and implications in the COVID-19 context

Vaccine product-related reaction



Definition

 An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.



Implications in

COVID-19 context

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



Key definitions and implications in the COVID-19 context **Vaccine quality defect-related reaction**



Definition

• 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.



Implications in

COVID-19 context

- 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.
- The rapid scaling up of vaccine production poses additional potential risks and identification of the exact substance causing the event is needed.



Key definitions and implications in the COVID-19 context **Immunization error-related reaction**



Definition

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



Implications in

COVID-19 context

- 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.
- 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



Key definitions and implications in the COVID-19 context **Immunization anxiety-related reaction**



Definition

 An AEFI arising from anxiety about the immunization



Implications in

COVID-19 context

 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



Key definitions and implications in the COVID-19 context **Coincidental event**



Definition

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



Implications in

COVID-19 context

- Because of potential comorbidities in vaccinees, it will be challenging to differentiate true coincidental events from COVID-19 vaccine product related reactions or drug reactions or interactions.
- Coincidental events can 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.



Key definitions and implications in the COVID-19 context

A serious AEFI



Definition

 A serious adverse event results in death, hospitalization or prolongation of an existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or could be life-threatening.



Implications in

COVID-19 context

 Information on serious rare and very rare adverse events following COVID-19 vaccines is lacking currently.



Key definitions and implications in the COVID-19 context **Cluster**



Definition

 A cluster occurs when two or more AEFIs related in time, place and/or vaccine* occur together.

* Vaccine here may refer to a certain batch (lot), a vaccine product from a certain manufacturer or vaccine(s) or vaccines from a particular vaccination centre.



COVID-19 context

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.



Key definitions and implications in the COVID-19 context **Signal**



Definition

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

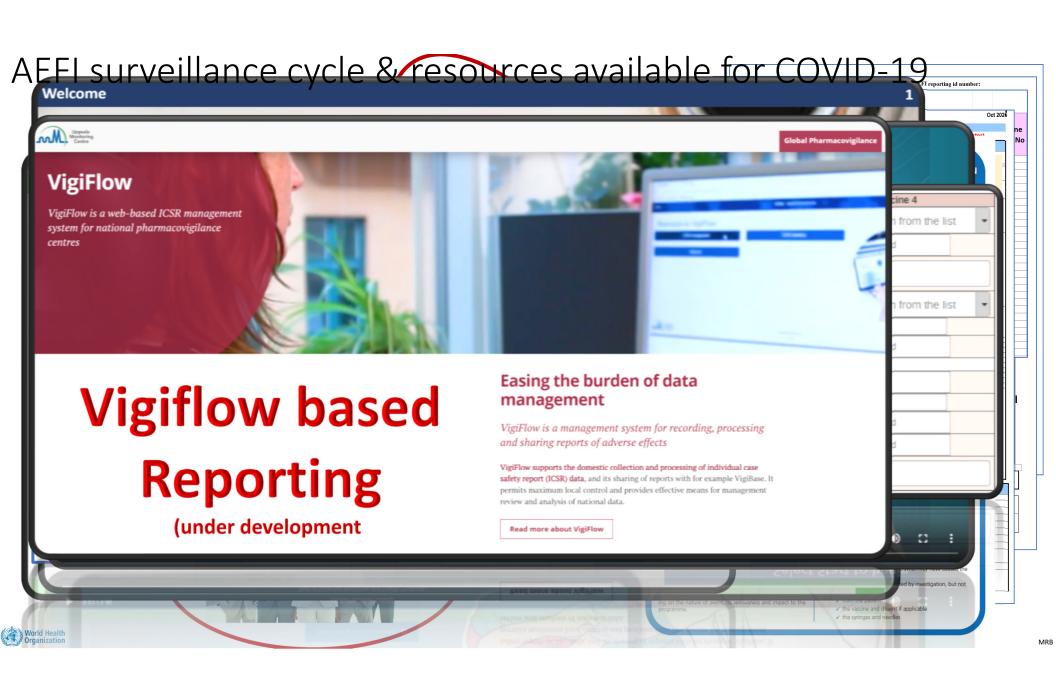


Implications in

COVID-19 context

Signal detection, verification and response is a key activity that has to be specially addressed in the COVID-19 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.





AEFI Detection in the COVID-19 context



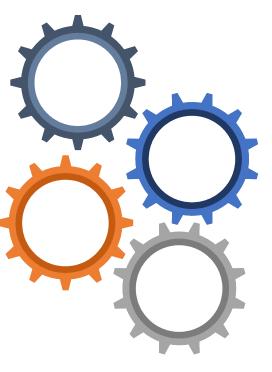
Primarily takes place through passive surveillance when vaccine recipients, parents of immunized infants/children, health care providers and staff in immunization or health care facilities detecting the AEFIs and notify them to a health care provider

AEFIs can also be detected through active surveillance, via sentinel sites.

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.



Reporting COVID-19 vaccine related AEFI

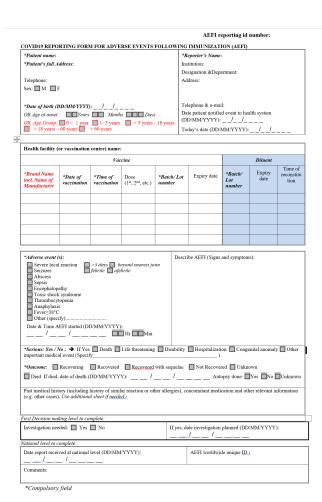


All AEFIs should be reported using the standard COVID-19 AEFI reporting form

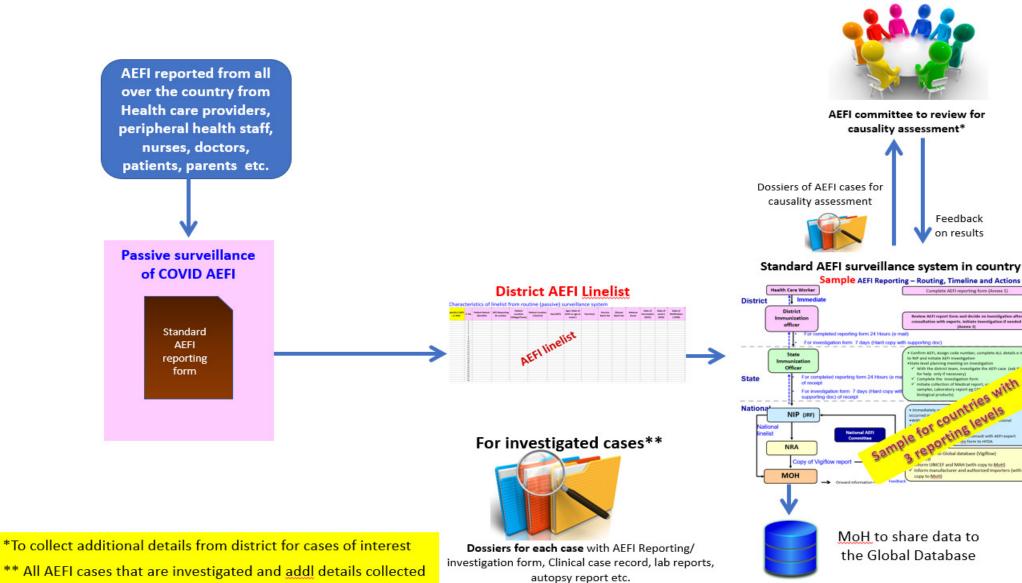
All AEFIs should be reported using the standard COVID-19 AEFI reporting form

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).

All effort should be taken to complete the reporting as much details as possible at the first point of contact





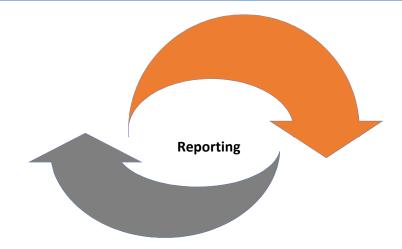


COVID-19 AEFI reporting flow

When a COVID-19 standard AEFI reporting form is received at the district, it should be reviewed for seriousness and transmitted to the province and national levels and AEFI linelists populated

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.

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 Brand	Manufacturer name	Dose	Vaccine Batch No
						-				1	
						-				-	
						-				1	
						-				-	
										1	





Investigating potential COVID-19 vaccine-related AEFIs

For deaths, national Investigate serious (death, If the district authorities investigations should be led by hospitalization, significant and experts feel that the a team from the National AEFI disability, life threatening, **Initial steps** AEFI investigation can be **Expert** Tools & Committee, supported in the or congenital anomaly/ done locally, they can visit assistance investigation by the Expanded resources birth defect), or is a part the patient and locality Programme for Immunization of a cluster or a part of a and initiate the detailed (EPI) or National Immunization group of events with an investigation. Programme (NIP), the National unexpected high rate or Regulatory Authority and other severity, or a suspected experts. signal. 6 First identify and rule out Sometimes expert During field investigations, immunization (or assistance should be the COVID-19 specific AEFI programme) error-related solicited from the higher investigation form, the AEFIs, immunization stress levels. WHO AEFI investigation related responses (ISRR) software and aide What to and coincidental events **Decision Deaths** memoire should be used that could manifest as a to guide the process.

making



investigate

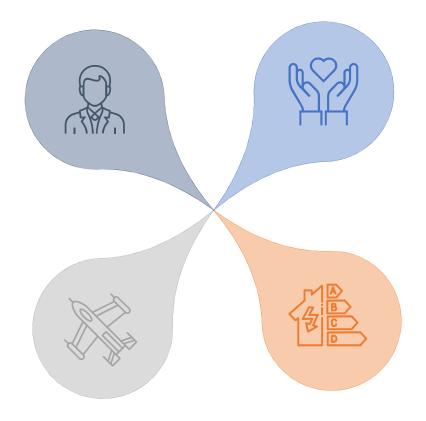
COVID-19 vaccine-related

AEFI.

Unique aspects of COVID-19 vaccine-related causality assessments

Information on risk of rare serious vaccine reactions will be limited at the time of regulatory assessment and registration of the COVID-19 vaccines because

- COVID-19 vaccines are novel vaccines, multiple vaccine platforms, antigen and adjuvants produced by various manufacturers
- Vaccine storage, reconstitution and administration techniques are different
- Differing implementation strategies
- Broad target populations.



If COVID-19 vaccines are used through emergency use listing/ ongoing phase III clinical trials, then, AEFI committees should have access to the periodic safety updated reports (PSURs).

Global information and information from other regions should be available for the causality assessments, to help to identify signals and enabling collection of more detailed information.

Serious adverse event rates could be made available by the COVID-19 manufacturer to the committee.



Unique aspects of COVID-19 AEFI Committees

Non-traditional experts to the AEFI causality assessment committee include geriatricians, pulmonologists, cardiologists, nephrologists who should be invited as vaccines given to all ages.

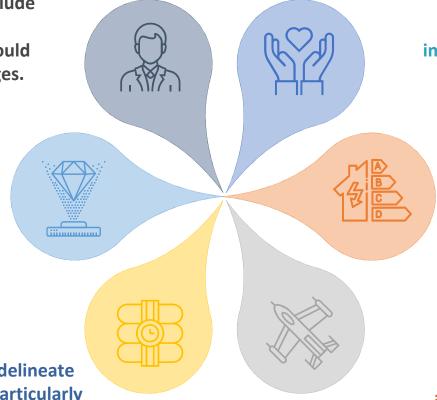
If countries decide to use the AEFI committees to review AESI cases to identify signals, the committees will need to be strengthened with additional expertise from statisticians and epidemiologists trained in research methodology.

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.

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



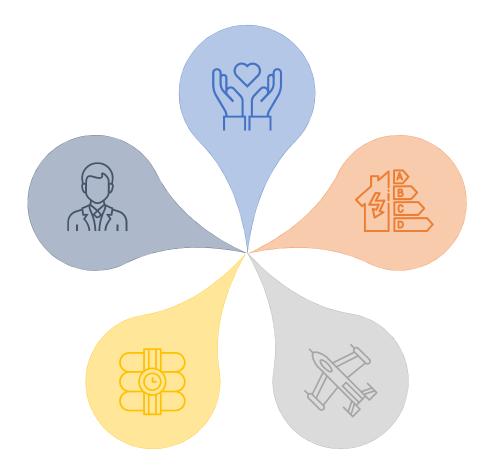


Unique aspects of COVID-19 AEFI committee functioning

Countries with existing AEFI causality assessment committees should conduct a refresher training focusing on **COVID-19 vaccine-specific AEFIS.**

Operationalising AEFI causality assessment committees for COVID-19

- Tackle increase load of serious AEFIs
- Timely causality assessments
- Increased frequency of AEFI causality assessment committee meetings



Countries that do not have **AEFI** causality assessment committees should establish such a committee prior to **COVID-19 vaccine** introduction

Countries where the population and geographical territory are large, decentralization should be considered by establishing sub-national AEFI causality assessment committees.

Establishing an international or regional technical committee for causality assessment can be considered for countries with limited internal expertise and resources. MRB



Unique aspects of COVID-19 vaccine-related causality assessments

N°	Criteria	Implication in COVID-19 vaccine-related causality assessments					
1	Evidence for causes other than COVID-19 vaccines	Prior knowledge on background rates of AEFIs help to determine if coincidental events in adult population, particularly those with chronic diseases have been responsible for the adverse event.					
2	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.					
3	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					
4	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.					
5	Vaccine- enhanced COVID-19 disease	 Vaccine associated enhanced disease (VAED) can occur with some live attenuated vaccines. COVID-19 vaccination itself may be associated with VAED. There is potential risk for COVID-19 vaccinees developing 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 					

Key points to remember



covidence implications need to be considered in the context of the novelty of the vaccines developed and used in unique and novel circumstances



The existing tools and methods available for vaccine safety can be used but need to be modified and adapted to the evolving vaccine safety scenario



Since multiple stakeholders and partners are involved in COVID-19 vaccines' safety, good technical expertise, coordination mechanisms, maintaining transparency and communication are critical for important decisions to be made.



Resources

- AEFI reporting
 - AEFI reporting form: https://vaccine-safety-training.org/tl_files/vs/pdf/WHO-standard-AEFI-reporting-form.pdf
 - Vigiflow: https://vigiflow.who-umc.org/
 - DHIS2: https://www.dhis2.org/
 - · Link to PowerPoint Slide set on standard AEFI reporting
- AEFI investigation
 - AEFI investigation form https://www.who.int/vaccine safety/initiative/investigation/AEFI Investigation form 2Dec14.pdf
 - AEFI investigation aide memoire https://www.who.int/vaccine-safety/initiative/investigation/New-aide-memoire-AEFI.pdf
 - AEFI investigation eLearning: https://www.who.int/vaccine-safety/AEFI ELearning/en/
 - AEFI investigation software https://www.who.int/vaccine_safety/software-assistance-guiding-hq-AEFI-investigations/en/
 - Link to PowerPoint Slide set on standard AEFI investigation
- AEFI causality assessment
 - AEFI causality assessment manual: https://www.who.int/vaccine_safety/publications/CausalityAssessmentAEFI_EN.pdf?ua=1
 - AEFI causality assessment aide memoire: https://www.who.int/vaccine_safety/initiative/investigation/New_aide_mem_causal_assmt.pdf?ua=1
 - AEFI causality assessment software http://gvsi-aefi-tools.org/
 - · AEFI causality assessment eLearning
 - Link to PowerPoint Slide set on AEFI causality assessment



References

 Practical aspects of signal detection in pharmacovigilance. Report of CIOMS Working Group VIII. Geneva, CIOMS, 2010 https://cioms.ch/wp-content/uploads/2018/03/WG8-Signal-Detection.pdf

