COVID-19 Vaccines: Safety Surveillance Manual

Module: Establishing surveillance systems in countries using COVID-19 vaccines

Contents

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. Introduction

The role of vaccine safety surveillance during COVID-19 vaccine introduction is to facilitate the early detection, investigation and analysis of adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) to ensure an appropriate and rapid response. This will decrease the negative impact of these events on the health of individuals and the immunization programmes and maintain the confidence of health care professionals and the general population. To achieve this, the global goals of COVID-19 vaccine safety surveillance are to:

- detect serious AEFIs/AESIs rapidly to provide timely data that can be shared with relevant stakeholders for action;
- generate data to characterize the safety of the COVID-19 vaccines in use;
- identify, investigate, assess and validate safety signals and recommend appropriate public health or other interventions; and
- support public and stakeholder confidence in vaccines and immunization by ensuring high quality safety surveillance.

The type and scope of vaccine safety monitoring activities that countries choose to adopt to achieve these goals will depend on the resources available and the maturity of their pharmacovigilance surveillance systems. However, all countries should aim to strengthen their ability to detect, investigate, assess, report and respond to serious AEFIs before and during COVID-19 vaccine introduction. The key objectives are to:

- strengthen routine passive surveillance reporting systems to be able to cope with the expected increase in frequency or severity of AEFI (mild, moderate, and severe);
- detect and investigate potential safety signals or clustering of serious events, immunization errors, community concerns etc.);
- perform systematic causality assessments for AESIs;
- prepare comprehensive plans to respond rapidly to any COVID-19 vaccine-related events; and
- be able to respond to any concerns expressed by health care professionals and maintain community confidence.

Countries that have mature pharmacovigilance systems or have special situations such as, the introduction of a novel vaccine platform, requiring enhanced safety monitoring may consider the following additional safety monitoring objectives:

- implementing active surveillance systems for AESIs;
- conduct research on identified or newly observed vaccine safety concerns, for example, vaccine-associated enhanced disease (VAED) in large populations or target groups;
- Improve the use of local and national safety data to generate information to inform effective communicate strategies about the safety of the COVID-19 vaccines being used, targeting the public, the community, media, national regulatory authorities (NRAs), vaccine manufacturers and marketing authorization holders (MAHs), WHO and other stakeholders regarding; and

2. Key considerations for adaptation of vaccine safety surveillance systems

To prepare for COVID-19 vaccine introduction, countries will need to adapt their established AEFI surveillance systems to address several key challenges specific to the COVID-19 pandemic. Due to the variety of vaccine platforms being developed, there may be more than one vaccine type used simultaneously or sequentially in the same setting. Hence, the surveillance systems must be able to collect information on which type of vaccine had been administered to the person who had an AEFI. Following up specified vaccinated cohort for at least one year will enable the detection of potential vaccine-type specific AESIs, including potential VAED in vaccinated individuals who develop COVID-19 disease.

It is likely that COVID-19 immunization programmes will focus on adult populations initially. Hence, it will be important to ensure that the surveillance systems are capable of capturing AEFIs in adults, as is necessary for seasonal influenza and pneumococcal polysaccharide vaccination used in adults and other novel vaccines that have been introduced, e.g., Ebola, meningococcal A vaccine and pandemic influenza.[1] [2] Clinics, hospitals or other settings that care for adults may not be familiar with AEFI reporting processes. As adults have higher rates of co-morbid conditions than children, there may be higher rates of coincidental AEFIs. In addition, expert AEFI committee for AEFI/AESI review and causality assessment may not exist everywhere, and when they do, they may have limited experience in the evaluation of AEFI/AESI in adults and people with complex medical conditions.

Surveillance systems will need to be able to accommodate the large numbers of AEFI/AESI reports expected because of the large proportion of the population who will be vaccinated. AEFI reporting from health facilities or districts may need to be more frequent than routinely, to ensure that any safety signals can be detected rapidly and responded to in an appropriate and timely manner.

Finally, as for any new vaccine, the safety data from clinical trials that will be available at the time of the COVID-19 vaccine introduction will be limited and insufficient to detect rare adverse events and limited safety data for certain populations and for adverse events with a latency longer than the trial study period. There will be a need to communicate rapidly about any adverse events and to respond to public concerns in order to maintain public confidence, in the setting of high media and public attention on COVID-19 vaccines. To prevent alarm or uncertainty in public opinion and in the media, it will be essential to develop an appropriate communication strategy on COVID-19 vaccine safety. Please refer to the communication module for further information [link to module will be added].

It is highly likely that phase III clinical trials will still be ongoing when some widespread COVID-19 vaccination programmes are implemented with COVID-19 vaccines that have been granted emergency use listing status. It will be important that rapid access to periodic product safety update reports (PSURs) and other safety reports is coordinated between regulatory agencies and vaccine sponsors and manufacturers in each country. This shared information will be useful for interpreting passive system safety data and for conducting causality assessments by AEFI committees.

[1] WHO. Guidance for establishing AEFI surveillance systems in countries planning to use Ebola vaccines. Available from: https://www.who.int/csr/resources/publications/ebola/GEVIT_guidance_companion-tool_AEFI.pdf?ua=1. Accessed 29 October 2020.

[2] Ateudjieu J, Stoll B, Bisseck AC, Tembei AM, Genton B. Safety profile of the meningococcal conjugate vaccine (Menafrivac™) in clinical trials and vaccination campaigns: a review of published studies. Hum Vaccin Immunother. 2020;16(6):1245-1259. doi: 10.1080/21645515.2019.1652041.

Lack of experience in the management of the new COVID-19 vaccines with special handling conditions (e.g., vaccine storage at -80°C or new administration devices or methods) and the participation of health care staff who are not traditionally involved in vaccination in many countries could increase immunization-error related reactions. Depending on the specificities of the vaccine administration devices for the COVID-19 vaccines that will be implemented, medical devices surveillance units from the NRAs, the National Immunization Programme (NIP) or the Expanded immunization Programme (EIP) or the Ministry of Health (MoH) should also be involved in planning the responses to suspected adverse events.

Table 1 summarizes the recommended safety surveillance activities for all countries introducing COVID-19 vaccine(s) regardless of AEFI surveillance capacity.[3]

[3] [placeholder]: Link to WHO Country Readiness assessment and HW booklet

88 **Table 1:** Recommended AEFI surveillance activities for all countries introducing COVID-19 vaccination, regardless of their AEFI surveillance capacity.

Objective	Recommended AEFI surveillance activities
Strengthen routine passive AEFI surveillance reporting systems for the management of increased frequency or severity of AEFI reports (mild, moderate and severe)	1. Conduct training on identification and reporting of AEFI for health care professionals. 2. Update, print and distribute AEFI surveillance tools. 3. Use both vaccine tracking information and passive AEFI reporting information to perform vaccine-specific safety analyses. 4. Review and adapt processes for timely reporting, review and data sharing nationally, regionally and globally (e.g. uploading data to global databases such as the WHO VigiBase) 5. Develop clear standard operating procedures (SOPs) for the coordination process between the NRA, NIP/EIP, and other institutions with responsibilities for AEFI surveillance. 6. Consider coordination of activities with Public Health Emergency Units. 7. Consider setting up AEFI committees at subnational as well as national level, particularly in large countries.
Investigate potential AEFIs causing concern, such as clusters, serious events, programmatic errors, community concerns	1. Prepare investigation teams and train them for AEFI investigation activities that are relevant in the population being vaccinated. 2. Update, print and distribute AEFI investigation tools to obtain information on specific outcomes. 3. Ensure the collection and storage of all relevant data to help make a causality assessment (AEFI reporting and investigation forms, clinical case record, laboratory reports, autopsy reports, etc.)
Perform systematic causality assessment of AEFIs causing concern	1. Constitute an National AEFI committee to review and respond to AEFI safety signals and public concerns or contact the WHO Country or Regional Office or send email to gvsi@who.int for assistance. 2. Provide training on causality assessment processes using WHO causality assessment guidelines for members of the National AEFI committee. 3. Ensure regular updates to the Committee members on COVID-19 vaccine development and safety data, including safety reports from ongoing phase III clinical trials or any events reported in clinical trials. 4. Foster and use the committee's expertise to identify AEFI cases in need of further investigation, such as AESIs. 5. Anticipate an increased number of AEFI reports that will need to be reviewed and consider including AEFI committees at subnational as well as national level, particularly in large countries.
Use AEFI and disease surveillance data to detect potential safety signals or clustering of events	1. Regularly review and report AEFI surveillance data, particularly those relevant to AESIs or other conditions identified during pre-licensure COVID-19 vaccine clinical trials. 2. Explore the use of disease surveillance data to complement AEFI surveillance systems for the detecting of AESIs, if indicated. 3. Consider use of early signal detection methods, especially for certain AESIs.

Objective	Recommended AEFI surveillance activities
Prepare comprehensive plans to respond rapidly to any COVID-19 vaccine-related event	1. Outline roles and responsibilities of key stakeholders (including the private sector) for the implementation of safety surveillance activities and responding to vaccine-related events. 2. Keep stakeholders up to date with COVID-19 vaccine safety information. 3. Communicate with WHO regions and globally and share data on outcomes of AEFIs and AESIs in a rapid, timely and regular manner.
Address concerns of health care professionals and maintain community confidence. (Link to communication module to be added)	1. Create and share a COVID-19 vaccine safety communication plan with relevant stakeholders. 2. Train and support personnel at all levels to address concerns that may arise before, during and after COVID-19 vaccine introduction. 3. Develop, print, and distribute messages concerning the safety COVID-19 vaccines.

89

90

3. Surveillance strategies to be adapted to COVID-19 vaccination strategies

The adaptations needed of AEFI surveillance systems will depend on the current capacity and functionality of the existing systems. All countries should strive to strengthen or enhance their routine passive surveillance. Increasing functionality by introducing stimulated passive surveillance, sentinel site-based active reporting, and use of electronic data systems (at sentinel sites or at population level, if possible) should be considered. In addition, some countries may consider active surveillance or specific studies and to assess the causal relationship between specific events and COVID-19 vaccination.

3.1. Application of surveillance concepts to COVID-19 vaccine-related AEFI and AESI

The primary purpose of passive AEFI surveillance is to identify and respond to events that are temporally associated with vaccination. In contrast, AESI surveillance focuses on the specific events irrespective of vaccination, and the assesses if the event occurs more frequently in vaccinated individuals than in non-vaccinated individuals.

As there are similarities between the terminology used for the surveillance of AEFIs and AESIs, it is important that health care professionals are trained to understand the differences and the implications of the differences. Some key basic concepts are outlined below.

- **Passive surveillance:**. Cases are not actively sought; surveillance sites passively notify a network when they encounter a AEFI and reports are generated and sent by local staff.[4] In some countries passive surveillance also includes spontaneous reporting by patients themselves.
- **Active surveillance:**[5] Active surveillance involves having designated staff visiting health care facilities, talking to health-care professionals and reviewing medical records to identify suspected cases of AESI. This can also be done remotely in electronic health databases. When cases are identified, their vaccination status is determined.
- **Stimulated passive surveillance:** Health care providers who are trained to encouraging reporting and follow-up of those vaccinated through defined channels, e.g., phone call, email, home visit report AEFIs. The system is closely monitored by a central coordinating unit through identified reporting points. Stimulated passive reporting could be useful for close monitoring of serious AEFIs and abnormal signals following the introduction of COVID-19 vaccines or after mass COVID-19 vaccination campaign.
- **Sentinel surveillance:** This system is used when high-quality data are needed for a particular disease that cannot be obtained through a passive system. Selected reporting units, with a high probability of seeing patients with the disease, good laboratory facilities and

[4] WHO. National passive surveillance: Available from: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/en/. Accessed 29 October 2020.
[5] WHO. Accelerated disease control: Available from: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/en/. Accessed 29 October 2020.

experienced well-qualified staff, identify and report cases. Unlike most passive surveillance systems that receive data from as many health workers and health care facilities as possible, a sentinel system deliberately collects data from only a limited network of carefully selected reporting sites.

3.2. Passive surveillance for AEFIs following COVID-19 vaccine introduction

Passive surveillance, whether in electronic- or paper-based system, is the fundamental and basic type of surveillance for all immunization strategies, i.e., routine, supplementary immunization activities, mass campaigns. It aims to generate potential safety signals for further evaluation (sometimes from media reports and public concerns), identify rare AEFIs and immunization-error related adverse reactions, address reporting of clusters, and generate hypothesis for AESI. It allows comparison of AEFI reported rates by different populations (age, occupation, potential condition, etc.) and by the type of COVID-19 vaccine received.

However, routine passive reporting systems will be insufficient to enable the rapid assessment and adequate public health response that will be needed during COVID-19 vaccine introduction. Routine systems will need to be enhanced with stimulated passive surveillance to improve detection of AEFIs. Another approach to enhancing passive systems could involve raising stakeholders' awareness, including the National AEFI committee, about certain events reported as AEFIs that should trigger additional investigation and potential categorization of specific events.

3.3. Active surveillance for AESIs following COVID-19 vaccine introduction

One of the primary aims of active surveillance systems is to estimate the risk of a AESI in a population exposed to a vaccine. As this surveillance is focused on a well-defined population, it can be used to estimate event rates accurately.[6] The staff of active surveillance systems initiate and maintain regular contact with health care professionals to identify cases of the health condition(s) of interest. This information can also be obtained by regularly extracting data from health care databases. Some approaches used for active surveillance of AESIs are cohort event monitoring (CEM), sentinel surveillance, data linkage m-Health and e-Health. These are described in detail in the module on AESIs [link to module will be added] and Appendix 5.1: Summary of methods that can be used for active vaccine safety surveillance systems.

3.4. Specific provisions for additional national safety monitoring activities by COVID-19 vaccine manufacturers and MAHs

COVID-19 vaccine manufacturers and MAHs are also responsible for monitoring the safety of the COVID-19 vaccines introduced and addressing safety issues that emerge. Additional safety surveillance activities should be carried out by vaccine manufacturers and MAHs to continue to collect more information on safety beyond that collected during pre-licensure COVID-19 vaccine trials.

The processes of engaging with the pharmaceutical industry, reviewing risk management plans and outlining the legal provision and guidelines for COVID-19 vaccine safety are described in the engaging with the pharmaceutical industry module [link to the module will be added]. Additional pharmacovigilance activities such as post-licensure safety studies (PLSS) that should be performed to

[6] CIOMS Guide to Active Vaccine Safety Surveillance. Available from: https://cioms.ch/publications/product/cioms-guide-to-active-vaccine-safety-surveillance/. Accessed 29 October 2020.

address important identified and potential risks and provide important missing information are also described.

A comparison of passive surveillance, active surveillance for AEFIs and AESIs and for PLSSs is presented in Table 3.

171 Table 2: Recommended activities for enhancing safety surveillance systems in countries, based on their current surveillance systems

Level of existing surveillance capacity	Relevant additional objectives	Recommended additional activities
Established passive surveillance – partially functioning	• improve the use of local and national safety data to generate information to communicate with the public, the community, media, NRAs, manufacturers, WHO and other stakeholders about the safety of COVID-19 vaccines being used; • be instrumental in continuously updating the safety profile of COVID-19 vaccines being used; and • implement active surveillance for AESI.	1. assess the functionality of the existing AEFI surveillance system to identify key gaps and ability to expand capacity to take on additional safety activities 2. strengthen National AEFI committee capacity to review and respond to AEFI safety signal, public concerns or collaborate with WHO to provide this service 3. consider sentinel site surveillance for AESIs if the above can be achieved and activities can be supported.
Established passive surveillance – fully functioning	• implement active surveillance for AESIs; • improve the use of local and national safety data to generate information which can be used to effectively communicate with the public, the community, media, NRAs, manufacturers, WHO and other stakeholders about the safety of COVID-19 vaccines being used; and • be instrumental in continuously updating the safety profile of COVID-19 vaccines being deployed in countries.	1. establish active AESI surveillance at selected sentinel sites; 2. inform the National AEFI committee about potential concerns for COVID-19 vaccines; 3. share information within the region; 4. countries could act as resource for neighbouring countries with less capacity; 5. review sources of epidemiological information at the national and subnational level that could provide information on background rates of selected AESIs (i.e. disease surveillance systems, national or subnational health surveys, specific epidemiological research projects). If information from disease surveillance systems is not available, then consider potential secondary sources that could be used to measure them.

Level of existing surveillance capacity	Relevant additional objectives	Recommended additional activities
Established passive, active (e.g. database or other) surveillance systems Ability to detect and evaluate signals consistently	• implement active surveillance for AESIs; • conduct research on predefined or newly identified important vaccine safety concerns in large populations or particular target groups, e.g., VAED; • improve the use of local and national safety data to generate information which can be used to effectively communicate with the public, the community, media, NRAs, manufacturers, WHO and other stakeholders about the safety of COVID-19 vaccines being used; • be instrumental in continuously updating the safety profile of COVID-19 vaccines being used.	1. inform the National AEFI committee about potential concerns for COVID-19 vaccines; 2. consider which AESIs should be monitored using active surveillance; 3. establish background rates for the selected AESIs; 4. consider participation in regional and global safety surveillance data networks; 5. countries could act as resource for neighbouring countries with less capacity; 6. consider specific studies, for example, plan to identify and evaluate VAED in context of vaccine failure.

Table 3: A comparison of post-licensure pharmacovigilance with passive and active surveillance systems for AEFIs and AESIs and for post-licensure safety studies

	Passive surveillance for AEFIs	Active surveillance for AESIs	Post Licensure safety studies (PLSS)
Purpose of information collection	To identify AEFIs and assess their severity and perform causality assessment	To identify predefined specific (rare) events and assess if associated with COVID-19 vaccination	To provide safety information missing at the time of licensure
Relevant for	HCPs, EPI managers, NRAs, surveillance and information managers, epidemiologists, surveillance and information managers, media, vaccine safety partners, including the community	Sentinel site staff, NIP/EPI managers, NRAs, epidemiologists, national AEFI committees, study teams	NRAs, NIP/EPI, MAHs
Method for data collection	Through spontaneous reporting or detection by HCPs	As per specific protocol for AESIs by sentinel site surveillance of cases or electronic health record using various methods	As per study protocol designed by MAH and approved by relevant authorities
Initiated by	Pre-existing system	Countries or regions wants to investigate significant knowledge gaps	Vaccine manufacturer or MAH
Responsibility	NIPs/EPIs, NRAs and MoHs	Principal Investigator appointed by the country	Vaccine manufacturer or MAH with oversight from relevant authorities
Data sharing	NIPs/EPIs, NRAs, MoHs, WHO (VigiBase), MAHs	NIP/EPI, NRAs, MoHs, WHO (VigiBase), MAHs	MAHs, NIP/EPI, NRAs
Preparedness assessment	Preparedness checklist	Protocol review by the NITAG/ National AEFI committee	Based on criteria for site selection by NRA, NIP/EPI and MAHs
Stakeholder training	All frontline immunization staff in healthcare facilities (public and private); and other relevant staff in reporting, investigation, data analysis, and causality assessment	Sentinel site staff-Immunization Staff and clinicians in sentinel sites and predefined active surveillance systems, EPI Mangers, NRA, research staff, AEFI national committee	Principle Investigator at Study Site

4. Serious AEFIs and AESIs

Serious AEFIs and AESIs are events that results in death, are life-threatening, require in-patient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, or are congenital anomalies or birth defects. In the event of serious AEFIs or AESIs all documentation generated during the management of the event, including hospitalization, should be appended to the investigation form and submitted as a dossier to the National AEFI committee for causality assessment.

The risk communication team should be made aware of the occurrence of a serious event as soon as possible to support communication response at the appropriate level. This will be particularly important during the introduction of COVID-19 vaccines as misinformation may spread rapidly. Further details can be found in communication module [link to the module will be added].

5. Deaths following COVID-19 immunization

All countries should define specific protocols for investigating deaths following COVID-19 vaccination. Guidance on investigating deaths following vaccination are provided in the global guidelines on AEFI surveillance.[6] Deaths in individuals who have received COVID-19 vaccination, including those in which any related diagnosis is an AESIs, should be included in the protocol for investigating deaths following COVID-19 vaccination. Due to the high number of deaths during a pandemic, coordination with all stakeholders handling deaths should be established for reporting deaths in persons with a history of COVID-19 vaccination. Some specific protocols for studying COVID-19 deaths have been developed, and these could be used for the autopsy of COVID-19 vaccinated individuals who die.[7] If indicated, tissue samples should be collected for in-depth pathologic, virologic and genetic testing. If an autopsy is not done, a complete verbal autopsy using standard protocol should be conducted and the findings documented and sent to the national AEFI committee.

[7] Carpenito L, D'Ercole M, Porta F, Di Blasi E, Doi P, Fagara GR, et al. The autopsy at the time of SARS-CoV-2: protocol and lessons. Ann Diagn Pathol. 2020;48:151562. doi: 10.1016/j.anndiagpath.2020.151562..