COVID-19 Vaccines: Safety Surveillance Manual

Module: Establishing active surveillance systems for adverse events of special interest during COVID-19 vaccine introduction

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. Establishing active surveillance systems for adverse events of special interest during COVID-19 vaccine introduction

In the context of Covid 19 vaccine introduction, conventional vaccine safety pharmacovigilance and surveillance systems will need to rapidly adapt to newer techniques of surveillance and ensure that safety and exposure information post vaccination are collected rapidly and processed quickly and responded to in near real time to ensure that the safety of the public is not put at risk.

Preparedness to address safety concerns rapidly is essential to counter real or perceived safety concerns particularly in the context of addressing AEFIs and AESIs. For AEFIs, any event following immunization that is notified is reported and processed as outlined in the module on AEFIs [Link will be added], but events pre-identified as AESI should be specifically identified through an active process, reported, investigated and data analysed to identify signals. The differences between AEFIs and AESIs and the practical implications are summarized in Fig 1.

2. Adverse events of special interest and preparedness prior to COVID-19 vaccine introduction

2.1. Adverse Event of Special Interest (AESI)

The US FDA defines an adverse event of special interest (serious or non-serious) as one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted[1].

AESI - Operational Definition: An AESI is a pre-specified 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 special studies.

2.2. Identifying and shortlisting Adverse Events of Special Interest (AESI)

Conditions commonly considered as AESI include, serious events that have followed other immunizations (e.g. GBS, ADEM, anaphylaxis), serious events potentially related to novel platforms, serious events potentially related to adjuvants, serious events related to vaccine failure/immunogenicity (enhanced disease) or events that are potentially specific to special populations. Such conditions are shortlisted if there is a:

- proven association with immunization that is true for most if not all vaccines;
- proven association with a known vaccine platform and/or adjuvant that is being used in any COVID-19 vaccines;
- theoretical concern based on immunopathogenesis of COVID-19 disease;
- theoretical concern related to viral replication during COVID-19 infection; or

[1] Guidance for Industry E2F Development Safety Update Report. https://www.fda.gov/media/71255/download

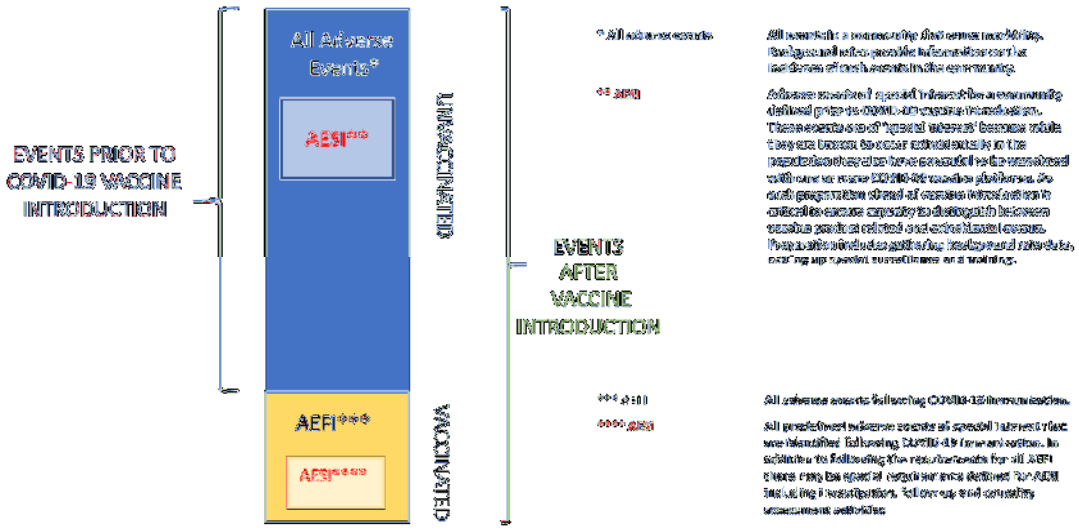
- theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

The relationship between AEFIs and AESIs is shown schematically in Fig 1.

Table 1: Differences between AEFIs and AESIs and its practical implications

	AEFI	AESI in the context of COVID-19
What is it?	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.	A preidentified and predefined event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies
Purpose of collecting this info	To identify all events after vaccination – determine if serious, investigate (serious) and do causality assessment	To identify per-specified specific (rare) events by a set criterion to determine if a COVID-19 vaccine could have caused it
How is this identified	Through spontaneous reporting or detected by health care professionals	Sentinel site surveillance of cases / Electronic Health Record (EHR based studies cohort, CC, SCCS, rapid assessment e.g. as in VSD, VAC4EU, GVDN etc.)
Case definitions	Important	Critical
What is the type of reporting?	All events which follows immunization and notified to the Health System	All events identified through active surveillance that fits the case definition irrespective of immunization status
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
Users	HCW, EPI managers, NRA, surveillance and information managers, epidemiologists, surveillance and information managers Vaccine safety partners including community	Sentinel site staff, EPI managers, NRA, Epidemiologists, National AEFI committees, Study teams.

Fig 1: Schematic representation of the relationship between AESIs and AEFIs.



Shortlisting and defining specific AESI prior to vaccine introduction enables a country/region to prepare for vaccine safety by defining the events, ensuring availability of tools, training relevant staff and having codes ready as well as background rates in place. This is important because AESIs are generally detected and reported through specifically establishing and operationalizing Active Vaccine Safety Surveillance (AVSS) systems as described below.

3. Active vaccine safety surveillance (AVSS)

Passive surveillance systems collect information on adverse events follow immunization (AEFIs) and are useful for the identification of potential safety signals for adverse events that were unknown at the time of vaccine marketing authorization or that are unexpected. However, these passive systems are unable to differentiate between a reaction following immunization from a coincidental event.

Active vaccine safety surveillance (AVSS) systems collect complete, accurate information about adverse events following immunization (AEFIs) in a defined population via a continuous organized process. The information is collected with defined objectives which are to investigate one or more AEFIs that are pre-specified adverse events of special interest (AESIs).[2] AVSS, unlike passive surveillance systems, collect relevant data from all individuals within a well-defined population, thereby minimizing under-reporting.

AVSS systems can also be used for signal detection[3] (like passive surveillance systems) but they can also be used to determine:

- the rate of an event, in a defined population;

[2] CIOMS. Guide to Active Vaccine Safety Surveillance. Available from: https://cioms.ch/publications/product/cioms-guide-to-active-vaccine-safety-surveillance/. Accessed 28 October 2020.

[3] In some countries AVSS is used for signal detection. Data Linkage is used in the United States of America https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html and m-Health is used in Australia. https://www.westernalliance.org.au/2016/05/mhealth-using-mobile-technologies-to-improve-access-and-efficiency-in-health-care-delivery

- the relative risk of the event:
    - the chance of the event occurring in those who were vaccinated with the specific vaccine, compared with those who were not or who received a comparator vaccine;
    - the change in the change of the event occurring over time;
- the occurrence of events in both vaccinated and unvaccinated individuals in the defined population.

4. Key considerations for implementing AVSS systems

Countries should first establish efficient passive surveillance systems as the basic system for detecting AEFIs. AVSS systems should not be implemented to increase passive reporting rates. If passive reporting rates are below the recommended minimum WHO standard[4], efforts should be made to improve reporting rates through strengthening the existing systems or implementing stimulated passive surveillance.

The COVID-19 surveillance and vaccine landscape will vary markedly throughout the world and this will lead to different significant knowledge gaps. The CIOMS guideline proposes an algorithm for determining when AVSS systems should be implemented.[Erreur ! Signet non défini.] At the time of COVID-19 vaccine licensure a national regulatory agency, a risk management plan (RMP) should define any anticipated risks from the vaccine. At this point the AVSS algorithm can be used to determine what surveillance methods and post-licensure clinical trials or studies should be implemented.

4.1. Resources, governance and ethical considerations

AVSS systems will require more planning, resources (including funding) and expertise to set up than passive systems. They should be implemented using a collaborative approach, involving stakeholders, such as the vaccine marketing authorization holder, the Ministry of Health, the National Technical Advisory Group, multilateral and non-governmental organizations, the national regulatory authority, pharmacovigilance centres. Ethical and privacy clearances will be required to collect and analyse identifiable data (see data management module [link will be added]).

4.2. Co-ordination of AVSS systems

Ideally there should be a global coordination of AVSS systems, as well as regional or national coordination, through the proposed or existing governance and research structures, as described in the module on stakeholders [link to module will be added]. This coordination will avoid duplication and increase the size of the population under surveillance, thus enabling the assessment of very rare events and making comparisons.

[4] Lei J, Balakrishnan MR, Gidudu JF, Zuber PLF. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000-2015. Vaccine. 2018;36(12):1577-1582. doi: 10.1016/j.vaccine.2018.02.012.

4.3. Data collection for AVSS systems

Individual data, linked by a unique identifier, are collected in the defined population for vaccination events, health events or outcomes and demographic characteristics. This identifier could be a national identification number, such as a social security number, a trial or study participant number, and if not, available linkage could be done using demographic identifiers, such as initials, date of birth, address.

The tools for data collection for AESI in AVSS systems are described below and provided in the Appendices. Table 2 describes the core and complete data points to be collected for AVSS. Ideally electronic databases should be used for analysis.

Table 2: Core and complete data, linked through a unique individual identifier or initials, date of birth, address, to be collected for the AVSS system

	Vaccination data	Health events or outcomes	Demographic data
Core data	Vaccine brand name	Adverse event(s)	Age at onset
	Lot number	Date of onset of symptoms	Gender
	Date of vaccination	Serious	Medical conditions
	Dose number	Outcome	Medication
	Site of vaccination	–	–
Complete data	Place of vaccination	Place of care	–
	Vaccine antigens	–	–
	Concomitant vaccines	–	–
	Route administration	–	–

4.4. Specific methods used for AVSS

The methods that can be used in AVSS systems for the collection of data on COVID-19 vaccine-related AESIs are described in Appendix 7.1. These methods include cohort event monitoring (CEM), sentinel surveillance, data linkage m-Health and e-Health. The method selected will depend on factors such as available expertise, resources and funding and what data sets are already available for AVSS.

5. Implementing AVSS systems for COVID-19 vaccine-related AESIs

The implementation of COVID-19 vaccine-related AVSS systems for AESIs should,

- be considered when it is important to define the risk and risk factors in the population immunized with COVID-19 vaccines;
- complement existing passive surveillance systems;
- be considered when significant knowledge gaps cannot be addressed through enhanced passive surveillance;
- use harmonized protocols wherever possible;
- have sufficient funding and robust governance systems;
- operate independently without conflicts of interests;
- have systems in place to share collected data widely and transparently.

Some of the types of AESIs that can be identified with AVSS systems are described below.

5.1. Delayed AESIs

A delayed onset is possible for some AESIs, such as vaccine-associated enhanced disease or those with an immunopathogenesis. For these events, passive surveillance is often subject to underreporting as events occurring closer to vaccination are more likely to be reported. The type of specific AVSS systems that could be implemented for these delayed AESIs include CEM and sentinel surveillance. Data linkage) could be used for hypothesis testing to establish if a causal relationship exists between a particular AESI and a COVID-19 vaccine.

5.2. Serious AESIs resulting in hospital visits or admission

In many countries AEFI reporting from healthcare professionals is inadequate because of poor knowledge of what defines an AEFI and barriers to reporting. Many of the COVID-19 vaccine-related AESI that have been identified for surveillance are severe or serious, or both, resulting in hospital visits or admissions. In addition, the COVID- 19 vaccine-related AESIs that have been identified also occur in unvaccinated individuals at a background rate. For this situation, AVSS using sentinel surveillance could be used to identify all those having hospital visits or being admitted for an AESI. If electronic vaccination history and health event data are available for a large population, data linkage could be used.

5.3. Identified AESIs in priority target groups

It is likely that the authorized COVID-19 vaccines will have different reactogenicity profiles and will be used in populations with different ages and different co-morbidities, concomitant medications and vaccine exposure. In the elderly, who are likely to be a priority vaccine target group, some of the COVID-19 vaccine-related AESIs, e.g., coronary artery disease, cerebrovascular disease, in the absence of COVID-19 immunization (background rate). Focused AVSS systems, using CEM should be considered for an elderly vaccinated cohort and sentinel surveillance could be used for conditions that are likely to result in hospital visits or hospitalization.

5.4. Surveillance of AESIs during mass COVID-19 immunization campaigns

If COVID-19 vaccines are delivered via mass immunization campaigns, many individuals will be exposed to the vaccines in a short time, with limited time for AEFI detection and analyses. Community concerns around vaccine safety usually high when a new vaccine is introduced in the setting of mass immunization campaign (see module on communication strategies |Link will be added], In such situations, AVSS systems using m-Health or e-Health will help obtain near real-time surveillance data for all AEFIs, including AESIs.

5.5. Instruments to process AESI

The instruments that have been developed for AESIs, many of which can also be used in AEFI assessment and interpretation of signals are shown in Table 3.

Table 3: Key instruments for evaluating and processing COVID-19 vaccine listed AESIs (can also be used for AEFIs)

Description	Purpose	Settings for use
Brighton case definitions	To provide a standard case definition so safety data are comparable	See Table 4 for status in terms of availability
AESI confirmation and interpretation forms	Detailed data form to facilitate standardized data collection and interpretation focused on the Brighton criteria to assess LOC.	• case investigation and assessment • AEFI signal / cluster investigation • outcome validation for analytic and epidemiological studies
Tabular checklist and algorithm to determine certainty	Abbreviated tabular form to summarize available case data and assign LOC	• same as above but where data have been collected and data abstraction is not needed
Automated tool to determine level of certainty (LOC) of case	To replace the previous Brighton online ABC tool	• training for LOC determination • causality assessment where first step is to determine LOC • any setting where LOC needs to be assessed
Background rates and risk factors of AESI	To provide summarized data on incidence of event as coincidental events by age, gender and geography	• epidemiologic studies where expected versus observed are compared • public reassurance in terms of 'expected' coincidental events
ICD and MedDRA codes	To assist in identifying or coding events from or for health care or pharmacovigilance databases	• AEFI MedDRA coding • coded database searches
Template protocols	Assess background rates, conduct active surveillance	

The tools shown in Table 3 are being prepared for all the AESI listed in Table 4 as well as for several related to maternal, foetal and neonatal outcomes, narcolepsy and sudden unexpected death. These will be made available at the Brighton collaboration website (www.brightoncollaboration.us) at a specific site dedicated to COVID-19 (link to be provided by end of September). From the COVID-19 webpage links will be provided to a spreadsheet listing AESI in separate rows. The spreadsheet columns, will have embedded links for each AESI to enable access to the published or newly drafted case definitions, the data abstraction and interpretation forms, the tools for assigning level of certainty, background rates, risk factors, ICD and MedDRA codes and template protocols. For any tools not yet developed, the spreadsheet will provide a date by which it is planned to have a tool available.

6. Identifying, reporting and responding to COVID-19 vaccine-related AESIs

AESI detection can only start after the country finalizes the list of events that are considered as AESIs to be monitored in vaccinated and unvaccinated individuals. The list of AESI conditions should be

developed taking the recommendations of their technical advisory group or from the list in Table 4. If possible, the background rates of these conditions should be known before COVID-19 vaccine introduction. The countries should have a national causality assessment committee with the necessary expertise, who should be specifically trained to review population- based scientific data obtained from AESI cases and have the capacity to process them as outlined below.

At the 42nd meeting of the Global Advisory Committee on Vaccine Safety (GACVS) in May 2020, a list of potential AESIs were identified with Brighton Collaboration/ SPEAC.[5],[6] It was recommended that available and newly generated Brighton Collaboration case definitions for AESIs and tools to assess certainty of cases should be shared widely for countries to use and to be aligned. Table 4 lists the vaccine platform and COVID-19 disease-related AESI from the May SPEAC list and the Brighton collaboration case definition status. Details are available at www.xxx.yyy.com [placeholder for URL]. As new information emerges this list will be updated.

Depending on the AESI surveillance methodology and protocol decided by the country (Appendix 7.1), AESIs can be detected through:

- prospective surveillance, which requires that health care professionals are trained to detect AESIs, using simplified case definitions, as they occur;
- retrospective surveillance, which requires designated surveillance staff to conduct systematic searches for prespecified AESIs, using a simplified case definition, in the target population by examining patient records at facilities; or
- other electronic methods.

The AESIs should be identified irrespective of the exposure to COVID-19 vaccine based on a prespecified list, which will be unique for each country or region and diagnosis of each AESI case identified should match an approved case definition.

[5] Global Advisory Committee on Vaccine Safety, 27-28 May 2020 https://www.who.int/vaccine_safety/committee/reports/May_2020/en/

[6] Safety Platform for Emergency vACcines (SPEAC) https://brightoncollaboration.us/speac/

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AESI	Brighton Collaboration case definition status	Link to access the definition	Recommended length of post-vaccine surveillance
Vaccine-associated enhanced disease	Case definition submitted for publication Sept 2020	Link will be provided-	1 year
Multisystem inflammatory syndrome in children	Under development and targeted for Oct 15, 2020	For all under development – they will be posted at time of submission for publication	1 year
Acute respiratory distress syndrome	Under development and targeted for Oct 15, 2020	-	1 year
Acute cardiovascular injury (microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia, myocarditis)	Under development and targeted for Nov 15, 2020	-	1 year
Coagulation disorder (thromboembolism, haemorrhage)	Under development and targeted for Nov 15, 2020	-	1 year
Acute kidney injury	Planned start in Sept and targeted completion by Nov 30, 2020	-	1 year
Generalized convulsion	Published 2004	10.1016/j.vaccine.2003.09.008	LA vaccines: 4 weeks Others: 1 week
Guillain Barré Syndrome	Published 2011	10.1016/j.vaccine.2010.06.003	4-6 weeks
Acute liver injury	Planned start in Sept and targeted completion by Nov 30, 2020	-	4-6 weeks
Anosmia, ageusia	Planned start in Sept and targeted completion by Nov 30, 2020	-	4-6 weeks
Chilblain – like lesions	Planned start Jan 2021 and targeted completion by Apr 30, 2021	-	4-6 weeks
Single organ cutaneous vasculitis	Published 2016	10.1016/j.vaccine.2016.09.032	4-6 weeks
Erythema multiforme	Planned start Jan 2021 and targeted completion by Apr 30, 2021	-	4-6 weeks
Anaphylaxis	Published 2007	10.1016/j.vaccine.2007.02.064	2 days
Acute aseptic arthritis	Published 2019	10.1016/j.vaccine.2017.08.087	
Meningoencephalitis	Published 2007	10.1016/j.vaccine.2007.04.060	LA vaccines: 4 weeks
Acute disseminated encephalomyelitis	Published 2007	10.1016/j.vaccine.2007.04.060	4-6 weeks
Thrombocytopenia	Published 2007	10.1016/j.vaccine.2007.02.067	4-6 weeks

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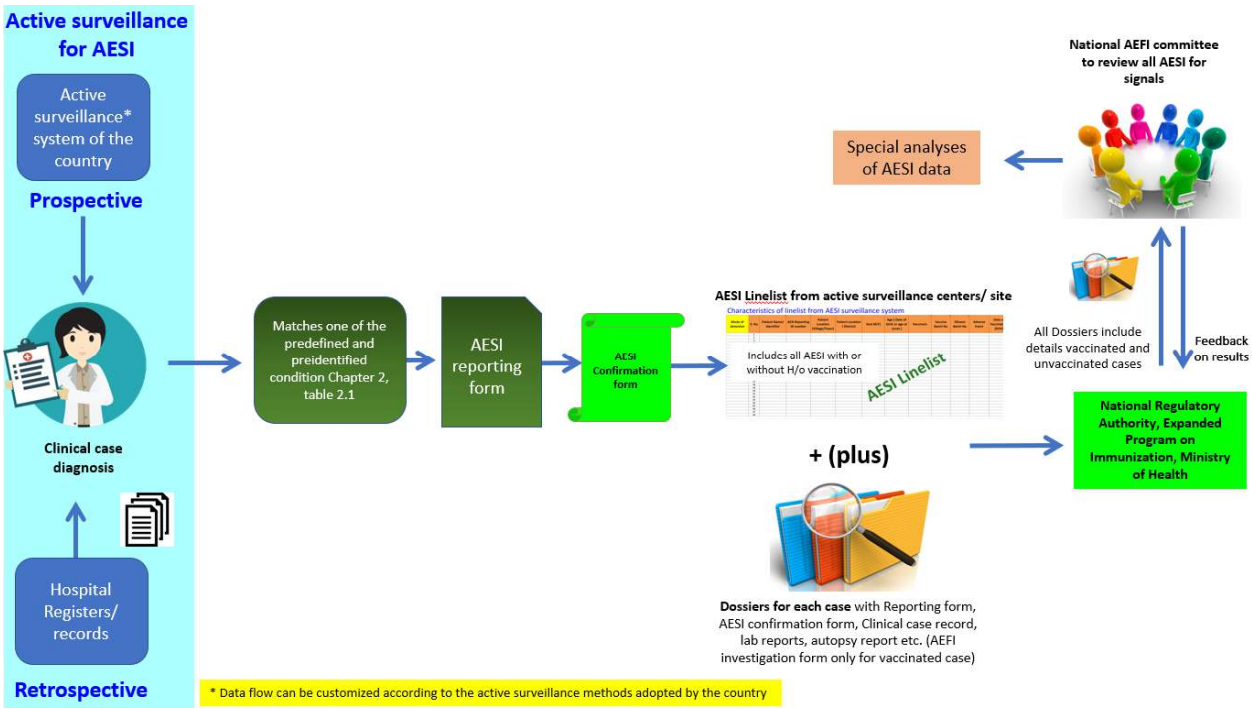
6.1. AESI reporting and response mechanisms in AVSS systems

Fig 2: shows the a schematic representation of AESI reporting and response mechanisms in AVSS systems.

Fig 2: In-country reporting and processing of AESI



6.1.1. AESIs detected though AVSS systems

AESI cases can be detected through different modes of active surveillance such as Cohort event monitoring (CEM), Sentinel surveillance (SS), Data Linkage (DL) m-Health (MH) and e-Health (EH) using case definitions. Additional effort should be undertaken to solicit vaccine exposure information in AESIs identified through active surveillance to assess its association with vaccine. In such instances the AESI reporting form (Appendix 7.2), AESI confirmation form[7] for the specific AESI, detailed clinical records and results of additional tests must be collated and linelisted in an AESI linelist (Appendix 7.3) by the relevant centre/ site responsible for AESI surveillance. Dossiers for each case with the AESI linelist should be submitted to the national level (NRA/EPI/ MoH) as per the country protocol and through them shared with the National AEFI committee specially trained for population specific special analyses of AESI data

6.1.2. Investigating AESI in patients exposed to COVID-19 vaccination

As mentioned earlier, any AESIs matching the list of predetermined and predefined AESI conditions warrant detailed investigation. All such conditions should undergo a detailed investigation. Such cases are considered AEFI and investigation should be done using the COVID-19-specific AEFI investigation form and causality ascertained as described in the AEFI module [link to be added]. When such cases

[7] To be developed by Barbara Law and put into the separate AESI investigation guidance document planned to be developed

from AEFI surveillance systems are being reviewed by the causality assessment committee, after confirming the absence of programmatic errors, ISRR or coincidental events, vaccinated AESI cases will have to be categorised by the committee as *"B1 -Indeterminate" because the temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (it may be a new vaccine-linked event)* at the time of assessment. Details of the classification methodology are available in the AEFI causality assessment user manual for the revised WHO classification[8].

6.1.3. Data analyses for AESI cases from active surveillance systems:

A key outcome anticipated from reviewing data from both vaccinated and unvaccinated cases obtained from active AESI surveillance systems, that correspond to prespecified conditions is to ascertain if there is a link between the AESI and the COVID-19 vaccine product and if there is need for further specific studies to confirm such an association. This can be done by comparing the incidence of the AESI among the COVID-19 vaccinated and unvaccinated within a specific population and identification of signals for further characterization and investigation.

The same causality assessment committee as mentioned in section 6.2.5.1 can be used, provided they have the necessary expertise and have been specially trained to review population based scientific data arising from such special studies in active surveillance systems. In such instances, it is important that the committee also review the, national, regional and global epidemiological data to determine if there is a pattern in the profile of reports received, for example clusters of similar events in space, time and vaccine administered.

In areas that do not participate in AVSS systems for AESI, the routing of information about AESIs and response will follow the standard AEFI routing and response channels recommended in the country as described in the AEFI Module [link to be added].

6.2. Reconciling AESI data

All documentation for the AESIs should be archived. Information about AESIs will be obtained from a passive AEFI surveillance system or from a AVSS system, as described above. These data cannot be collated because the data collection methods are different, and they represent different cohorts of individuals and should, therefore, be analysed separately.

Signals are identified when a particular AESI occurs more frequently in the vaccinated population than in unvaccinated population (the background rate). When this occurs, the vaccination programme, national regulatory authorities, the MAH and WHO should be informed so that they collaborate with other countries and global experts to determine if the signal warrants further verification through specific studies.

The periodicity of AESI reports to the relevant administrative levels is defined in the country's protocol. Countries may determine the profile of healthcare workers who will be responsible for reporting, when determining the active surveillance methods for AESI surveillance. Countries may establish a target for AESI reporting for all regions in the country, based on the background rates for the AESIs.

[8] AEFI causality assessment user manual for the revised WHO classification https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf;jsessionid=9BEA02377FAF07FE3CC0921AC35D92BA?sequence=1

6.3. Tools for AESI

Some of the existing AEFI tools as outlined in WHO's Global manual on surveillance of adverse events following immunization can also be used for AESI.[9] A summary of the available tools and how they can be accessed is given in Table 5.

[9] 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.

255 **Table 5:** Summary of tools recommended for AESI reporting investigations and causality assessment

Description	Purpose	Status for COVID-19	Hard copy	Electronic tool
Detailed Case definitions for AESI	To determine if clinical details comply with standard case definition by an expert	Available for some conditions and under development for others	Provided separately in "Guidance on AESI in preparation for COVID-19 vaccine introduction"	
Simplified case definitions for AESI	To determine if clinical details comply with standard case definition by a frontline health care provider	To be developed (some available for RTS,S)	Provided separately in "Guidance on AESI in preparation for COVID-19 vaccine introduction"	Barbara Law to provide information
AESI reporting form	To collect basic reports of all AESI cases that have been notified in a standard common format for linelisting	Separate AESI reporting form developed for COVID-19	Appendix 7.2	
AESI linelist	To collate the AESI details from AESI reporting forms	Separate AESI linelist format developed for COVID-19	Appendix 7.3	
AESI confirmation form	To collect confirmation information when AESI cases are identified. Separate form for each condition	To be developed	To be developed for each condition and to be included in "Guidance on AESI in preparation for COVID-19 vaccine introduction"	AEFI investigation software can be tweaked to collect information on AESI as well http://investigation.gvsi-aefi-tools.org/investigation/index.html#step-1
Investigation form for AESIs that have history of COVID-19 vaccination	To collect detailed information when serious AEFI cases are investigated	Adapted to include COVID specific questions	Appendix 7.5	AEFI investigation software http://investigation.gvsi-aefi-tools.org/investigation/index.html#step-1

Description	Purpose	Status for COVID-19	Hard copy	Electronic tool
Causality assessment for AESI cases that have history of COVID-19 vaccination	To determine case classification of all AESI cases that have a history of COVID-19 vaccination reported from the passive surveillance system	Retain current method unchanged	https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf;jsessionid=4670F3DD797CEE4E1D08F2A30721D5CA?sequence=1	http://gvsi-aefi-tools.org/
Detailed analysis format of AESI as per protocol	To determine if the incidence of the shortlisted event is higher in vaccinated individuals than unvaccinated individuals	Will depend on study protocol	Will depend upon study protocol	

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6.4. How can countries prioritize preparedness for AESI?

At the time of vaccine licensing, countries need to review the RMP, discuss the risks and benefits with their respective in-country National Immunization Technical Advisory Groups (NITAGS) or Regional Immunization Technical Advisory Groups (RITAGS), identify the in-country capacity to monitor AESIs and determine if they have the capacity to implement active surveillance for AESI as described in chapter 4 5 and 6 to supplement the work done by passive surveillance systems.

The many unknowns regarding COVID-19 vaccine use in a country and the limited knowledge about its safety profile make it difficult to set priorities for which AESI are most relevant to a given setting. In general, countries should prepare to quickly address signals for events that have the highest likelihood to derail a vaccination campaign. Several of the AESI on the list in Table 4 are there because of a known association with vaccination in general. Generalized convulsion, thrombocytopenia and anaphylaxis would all have priority on this basis. For convulsion it will be an even higher priority if the vaccine to be used induces a high frequency of fever and if children aged under 6 years of age are targeted for immunization. GBS should also be given priority given its global occurrence, known association with some vaccine platforms and known increased frequency in older populations who are very likely to be prioritized for inclusion in immunization programmes.

Vaccine-associated enhanced disease (VAED), ARDS and the multisystem inflammatory syndrome in children will all be of high priority albeit these will be very difficult to assess and interpret in the context of active COVID-19 infection in the community. Priority will need to be placed on systems to ensure that individual immunization records are readily available. Once immunization programmes finalise the type of vaccine(s) to be used, it will be essential to define the timeframe during which occurrence of COVID-19 infection would be considered evidence of vaccine failure. Enhanced disease could occur before a protective immune response is expected especially for vaccines that require more than one dose to achieve immunity. A non-protective immune response could be associated with enhanced disease. These cases would occur closer to the time of immunization than cases that are caused by waning of neutralizing antibodies, which is why it is recommended to monitor for at least 1-year following immunization.

Anosmia and ageusia are so common with acute COVID-19 infections that they have been proposed for screening for COVID-19. As such relatively high priority should be placed on awareness of these conditions and determining background rates useful since they are also known to occur with other viral respiratory infections like influenza. This would be especially true in settings where there is ongoing community spread of COVID-19.

Coagulation disorders would be of higher relevance in situations where there are other infections that could present with bleeding (e.g. dengue) wherein it would be important to have testing in place to establish that such occurrences are coincidental to immunization as opposed to be caused by immunization.

Acute cardiac injury, acute liver injury and acute kidney injury would be of higher priority in settings where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, chronic renal failure).

Meningoencephalitis is an issue for live attenuated vaccines, especially in immunocompromised hosts. At present it seems unlikely that there will be live attenuated COVID-19 vaccines in use; but if so, then meningoencephalitis would be given higher priority than for inactivated vaccine programmes.

Acute aseptic arthritis is a concern where the vaccine platform involves vesiculostomatitis virus (rVSV).

Acute Disseminated Encephalomyelitis (ADEM) occurs rarely and has not been proven to be caused by immunization. That said a single case could completely disrupt an immunization programme which is why it has been identified as an AESI. It would be useful to have prevalence of the condition within the population if incidence data are not available or obtainable.

Of lower priority would be chilblain like lesions, erythema multiforme and single organ cutaneous vasculitis.

6.5. AESI for special populations: pregnant women, neonates and immunocompromised

The full impact of COVID-19 on pregnancy outcomes for mother and foetus as well as for new-borns is still unclear. Vertical transmission appears to be rare. There have been reports of maternal deaths and foetal loss, but it is not yet known if the frequency is higher than expected during pregnancy. Increased frequency of caesarean section and premature delivery have been observed among pregnant women who developed COVID-19 infection in the third trimester. Neonatal COVID-19 infections have been reported including some with fatal outcome, but most infants have survived infection without apparent long-term impact. Thus, to date, AESI specific to obstetric outcomes have not been identified by SPEAC, because trials rarely include pregnant women. This could change as more evidence is published. However, in the post-introduction phase it will be essential to plan to follow pregnancy outcomes with, for example, a registry of all such occurrences so follow-up can be maintained for any adverse outcomes to the mother, foetus or new-born. Furthermore it would be prudent to determine the background rates of obstetric and neonatal outcomes, such as maternal mortality, stillbirth, miscarriage, neonatal mortality and congenital anomalies, using standardised case definition prior to initiation of COVID-19 immunization programmes.

It is not yet clear whether vaccine will be recommended for pregnant or immunocompromised individuals. As a general rule, live vaccines are contraindicated for both, but there should be several inactivated vaccine candidates available.

6.6. Sudden unexpected death as an AESI

Without question, sudden unexpected death occurring within days of immunization disrupts immunization programmes. Sudden death has not yet been added to the AESI list. While it has been observed in association with COVID-19 infection such occurrences are rare, related to thromboembolic phenomena such as stroke, pulmonary embolus and coronary thrombosis. That said, it will be essential to be prepared for such occurrences in order to respond rapidly both in terms of investigation and public communication. These are addressed in greater detail in chapters 6 and 8.

In relation to the cause-specific AEFI definitions selected events that could result in death have been identified[10] that could be seen, rarely, following immunization including:

- Vaccine product related reaction: Anaphylaxis

[10] Gold MS, Balakrishnan MR, Amarasinghe A, MacDonald NE. an approach to death as an adverse event following immunization. Vaccine 2016;34:212-217.

- Vaccine quality defect: Wild type disease following incompletely attenuated live viral vaccine as occurred with the polio Cutter incident[11] (ref)
- Immunization error: Sepsis following contamination of multidose vials; use of a drug (e.g. anaesthetic drug, insulin etc) instead of the diluent for reconstituted vaccine
- Anxiety related reaction: Fatal head injury associated with syncope in settings where post-immunization safety is not ensured[12].
- Coincidental reaction: Likely to be the underlying cause of the majority of sudden death following immunization including but not limited to sudden infant death syndrome, sudden cardiac death, sudden unexpected death in epilepsy (SUDEP), anaphylaxis related to food, insects, environmental toxins, overwhelming sepsis.

To assess the cause of any unexpected death following immunisation, a thorough field investigation should be conducted without delay, and an autopsy performed as per recommendation of the WHO Global Manual on surveillance of AEFI[13]. Knowing regional and age-specific background incidence of sudden deaths as well as relevant risk factors will be very helpful in terms of knowing what is 'expected' in the population targeted for immunization and would inform the causality assessment. Appropriate communication with the community and all stakeholders at all stages of the process of investigation, causality assessment and its outcomes is critical to maintain confidence in the health system and health authorities.

[11] Fitzpatrick M. The Cutter Incident: How America's First Polio Vaccine Led to a Growing Vaccine Crisis. J R Soc Med. 2006;99(3):156.
[12] Woo EJ, Ball R, Braun MM. Fatal syncope-related fall after immunization. Arch Pediatr Adolesc Med. 2005 Nov;159(11):1083. doi: 10.1001/archpedi.159.11.1083.
[13] WHO. Global Manual on Surveillance of AEFI. Available from: https://www.who.int/vaccine_safety/publications/Global_Manual_revised_12102015.pdf?ua=1. Accessed 30 October 2020.

7. Appendices

7.1. Appendix 7.1: Summary of methods that can be used for active vaccine safety surveillance systems

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19 related surveillance
Cohort event monitoring (CEM)	CEM is a prospective, observational, cohort study of adverse events associated with a medication or vaccine[14]. A vaccinated cohort is established and followed in a systematic and regular way for any predefined AEFIs (Including AESIs) that occur over a defined period. Demographic data is collected so risk factors can be characterized	Vaccination history Details of COVID-19 vaccine and/or other vaccines collected at the time of enrolment Health event COVID-19 related AESI predefined and constitute the health outcome under surveillance. Demographic Data collected that could be relevant to outcome, for example, those factors associated with severe COVID disease (Diabetes, obesity, medication)	Advantages CEM is able to define the rate of an AESI, within the vaccinated cohort. However, this would depend on the rate of the AESI and the size of the observational cohort. CEM may not require extensive resources and may not require the infrastructure for more sophisticated forms of AVSS (such as data linkage) Disadvantages CEM is not able to define a relative risk of an AESI compared with the unvaccinated population but is able to define a relative risk if more than one COVID-19 vaccine product is under surveillance. To define the rate of a rare AESI a very large observational cohort would be required.

[14] A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. https://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19 related surveillance
Sentinel surveillance (SS)	SS involves identifying sentinel sites usually a health facility. The population is defined as patients attending and/or admitted to the health facility. AVSS involves systematically ascertaining if an individual has attended the facility with symptoms/signs or laboratory information that meet a specific case definition (for example those of a COVID-19 related AESI). If the case definition is met further data is collected – for example, vaccination status, outcome and demographic data	Vaccination history Details of COVID-19 vaccination is collected only if the patient meets the case definition of the AESI, AEFI or condition under surveillance. Health event COVID-19 related AESI's, an AEFI's, or a specific health condition is specified. Every patient attending/admitted to the sentinel facility is screened to see if the definition is met, regardless of vaccination status. Demographic Demographic data is collected only if the patient meets the case definition of the condition under surveillance. The data collected could include possible risk factors.	Advantages SS is able to collect very detailed data on the health event, outcome and demographics. For events where the onset time post-vaccination is clearly defined, a relative risk may be able to be calculated using a self-controlled case series analysis. Disadvantages SS is not able to define the rate of the health event under surveillance. SS data collection can be costly and time consuming. The vaccination data of the individual affected with the surveillance condition may not be readily available.

Data Linkage (DL)	DL involves the joining of electronic data, from different data collections. This electronic data has usually been collected, prior to linkage. Vaccination, health event and demographic data, often from many thousands of individuals which are stored in different databases and can be linked by a unique identifier or based on matching according to other identifiers such as name, date of birth, and address.	Vaccination history Usually obtained from pre-existing electronic databases such as a national vaccine register or an administrative database. Databases would need to capture COVID-19 vaccines for the age group under surveillance. Health event Health events under surveillance (eg COVID-19 related AESI's) will need to have been coded (ICD coding) and stored electronically. Demographic Demographic data is collected only if the patient meets the case definition of the AESI under surveillance Data collected that could be relevant to outcome, for example, those factors associated with severe COVID disease (Diabetes, obesity, medication)	Advantages DL can be used to examine associations between vaccination and rare or very rare events. This method would be ideally suited for hypothesis testing of the causal relationship COVID-19 vaccination and an AESI. If databases are established and linked then DL can be used for a rapid cycle review of safety signals. Disadvantages Few countries have the capacity and ready access to large established data bases containing vaccination, health event and demographic data which can be linked. DL can be resource intensive in terms of the cost and expertise required for linkage. In may countries there are significant barriers to data access, because of privacy and confidentiality. DL most often used to link to hospital events and it is more difficult to use surveillance for conditions that do not lead to hospitalization.

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19 related surveillance
m-Health (MH) and e-Health (EH)	MH and EH are evolving ways to monitor for health events following immunization or medication use. This method has become more feasible because of the increasing use of mobile phones and access to the internet. MH and EH can target consumers for surveillance with a variety methods such as SMS, reporting Appps, direct telephone calls, emails and on-line surveys.	Vaccination history Details of COVID-19 vaccine and/or other vaccines collected at the time of enrolment Health event COVID-19 related AESI's or other surveillance conditions could be predefined and occurrence of the event ascertained by a survey administered through an electronic platform. Demographic Limited demographic data collected through a survey.	Advantages MH/EH is low cost and can target consumers (vacinees or their parents) directly. Can be used for "real-time" surveillance and can be applied for vaccine safety signal generation. Rates of an AEFI can be determined but large sample size maybe required. Disadvantages Network coverage, mobile phone and internet costs maybe a barrier to consumer reporting. Significant resources could be required to verify consumer reports of an AEFI

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7.2. Appendix 7.2: COVID-19 AESI reporting form

AESI reporting id number:

REPORTING FORM FOR SUSPECTED ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

*Patient name: *Patient's full Address: Telephone: Sex: ☐M ☐F *Date of birth: _ _/_ _/_ _ _ _ OR Age at onset : ☐☐Years ☐☐ Months ☐☐☐ Days OR Age Group: ☐< 1 Year ☐ 1 to 5 Years ☐ > 5 Years	Reporting source: ☐ Hospitalised ☐ outpatient (e.g. clinic) Process of detection: ☐ Patient-reported ☐ Part of active surveillance *AESI Reporter's Name: Institution: Designation & Department: Address: Telephone & e-mail: Date patient notified event to health system _ _/_ _/_ _ _ _ Today's date (DD/MM/YYYY): _ _/_ _/_ _ _ _

*Adverse event(s) of special interest:		Describe AESI (Signs and symptoms):
☐ Acute aseptic arthritis ☐ Acute cardiovascular injury ☐ Acute disseminated encephalomyelitis ☐ Acute liver injury ☐ Acute kidney injury ☐ Acute respiratory distress syndrome (Microangiopathy, Heart failure, Stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis) ☐ Anaphylaxis ☐ Anosmia, ageusia ☐ Chilblain – like lesions	☐ Coagulation disorder (Thromboembolism, Haemorrhage) ☐ Enhanced disease following immunization ☐ Erythema multiforme ☐ Generalized convulsion ☐ Guillain Barré Syndrome ☐ Meningoencephalitis ☐ Multisystem inflammatory syndrome in children ☐ Single Organ Cutaneous Vasculitis ☐ Thrombocytopenia	
☐ Other (specify).....		
*Date & Time AESI started: __ __ /__ __ /__ __ __ __ ☐☐ Hr ☐☐ Min		
Did this AESI cause? ☐ Death ☐ Life threatening ☐ Disability ☐ Hospitalization ☐ Other important medical event (Specify_____)		
*Outcome at the time of reporting: ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown ☐ Died If died, date of death: __ __ /__ __ /__ __ __ __ Full Autopsy done: ☐ Yes ☐ No ☐ Unknown If No, Verbal Autopsy Done? ☐ Yes ☐ No		
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:		

*Did this patient receive COVID19 Vaccine? ☐ Yes ☐ No ☐ Unknown; If Yes, Complete the table below

Health facility (or vaccination centre) name:

COVID19 Vaccine								Diluent	
*Brand Name	Manufacturer	Dose	*Date of vaccination	Time of vaccination	Immunization record No.	*Batch/ Lot number	Expiry date	*Batch/ Lot number	Expiry date
		1							
		2							
		3							

Details of Non-COVID19 vaccines received in the last 1 year (please use the next page if there are more vaccines)

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

*First Decision making level to complete – for ALL AESI cases including COVID19 vaccinated and unvaccinated:

AESI Confirmation initiated: ☐ Yes ☐ No If Yes, Confirmation done by Dr/ Mr/Ms_____ Date of Confirmation:
Is this AESI Linelisted? ☐ Yes ☐ No
For COVID 19 vaccinated cases: Field investigation planned with AEFI investigation form? ☐ Yes ☐ No If yes, date planned _ _/_ _/_ _ _ _

*Mandatory fields to be completed

7.3. Appendix 7.3: COVID 19 AESI linelisting form

COVID19 AESI linelist

Source	S. No	Reporting source	Detecting process	Patient Name/ Identifier	AESI Reporting ID number	Patient Location (Village/Town)	Patient Location (District)	Sex (M/F)	Age (Date of birth or age at onset)	AESI	Date of onset (DOO)	Date of Notification (DON)	Date of Reporting (DOR)	Manifestation	Outcome	Autopsy conducted in case of death (Y/N/NA)

7.4. Appendix 7.4: COVID-19 AESI confirmation forms

- Acute aseptic arthritis
- Acute cardiovascular injury
- Acute disseminated encephalomyelitis
- Acute liver injury
- Acute kidney injury
- Acute respiratory distress syndrome (microangiopathy, heart failure, stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis)
- Anaphylaxis
- Anosmia, ageusia
- Chilblain – like lesions
- Coagulation disorder (thromboembolism, haemorrhage)
- Enhanced disease following immunization
- Erythema multiforme
- Generalized convulsion
- Guillain Barré Syndrome
- Meningoencephalitis
- Multisystem inflammatory syndrome in children
- Single organ cutaneous vasculitis
- Thrombocytopenia

7.5. Appendix 7.5: 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 Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine 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		