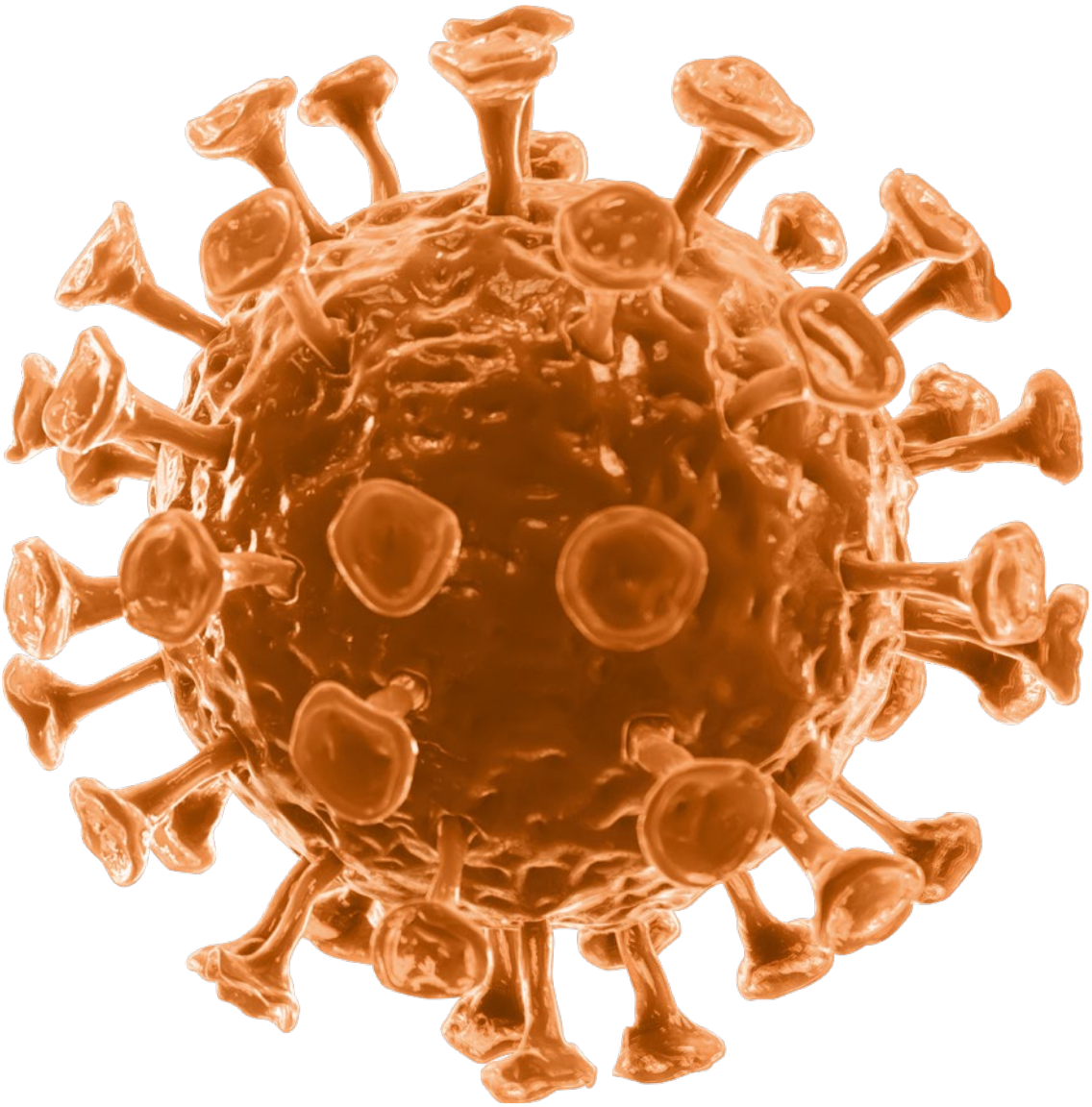
COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

MONITORING AND RESPONDING TO ADVERSE EVENTS OF SPECIAL INTEREST (AESIS)



World Health Organization

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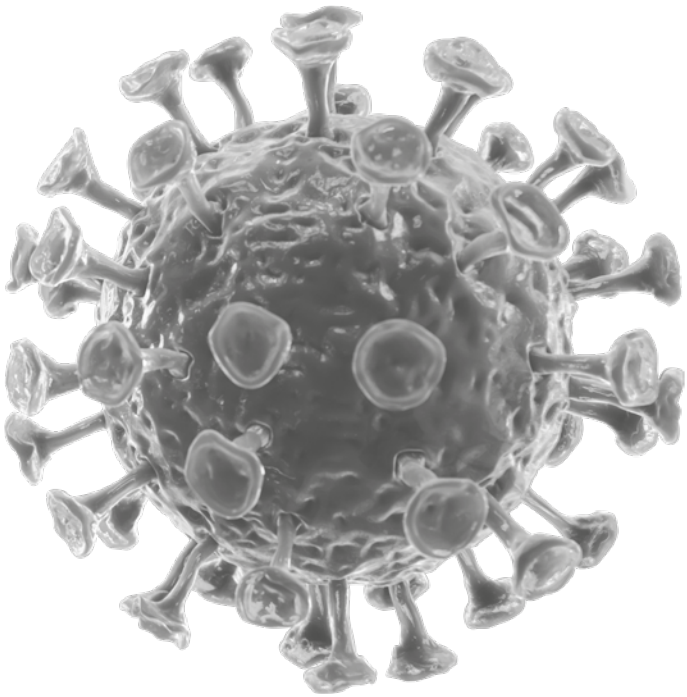

World Health Organization

Covid-19 vaccines: safety surveillance manual

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Key points

- Conventional vaccine safety pharmacovigilance and surveillance systems will need to be adapted rapidly in the context of COVID-19 vaccine introduction to ensure that the safety of the public is not put at risk.
- Shortlisting pre-specified adverse events of special interest (AESIs) before COVID-19 vaccine introduction will enable countries and regions to define events, ensure the availability of suitable tools, provide training for relevant staff and identify disease codes and estimate background rates.
- Before implementing active vaccine surveillance systems (AVSS) countries should have efficient passive surveillance systems for detecting AEFIs.
- AVSS can use different methods to monitor and assess COVID-19 vaccine-related AESIs including sentinel surveillance, data linkage and cohort event monitoring (CEM), depending on available expertise, resources and funding and type of data available for AVSS.
- The use of electronic tools such as m-Health and e-Health can facilitate the implementation of AVSS.
- AVSS can be used to detect delayed, AESIs, serious AESIs, AESIs in specific populations, and AESIs occurring during mass COVID-19 vaccination programmes.
- AESIs should be identified, irrespective of exposure to COVID-19 vaccine, based on a pre-specified list, which will be unique for each country or region, and the diagnosis of each AESI case identified should match an approved case definition.
- Comparing the incidence of the AESI, identified via AVSS, for COVID-19 vaccinated and unvaccinated individuals will enable 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.
- The causality assessment committee should be trained to review population-based scientific data arising from the specific types of studies in active surveillance systems.
- When signals are detected the vaccination programme, national regulatory authorities, the vaccine manufacturers and WHO should be informed so that they can consult other countries and global experts to determine if the signal warrants further verification through specific studies.
- Although no AESIs specific to pregnant women, foetuses or neonates have been reported, when COVID-19 vaccines are deployed it will be essential to follow pregnancy outcomes with, for example, a registry so that follow-up can be maintained for any adverse outcomes to the mother, foetus or new-born.
- Appropriate communication with the community and all stakeholders at all stages of the process of investigation, causality assessment and the outcomes will be critical to maintain confidence in the vaccination programme, the health system and the health authorities.

01 Introduction

In the context of COVID-19 vaccine introduction, conventional vaccine safety surveillance systems will need to rapidly adapt to newer techniques of surveillance and ensure that post-vaccination safety and exposure information are collected and processed rapidly 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 adverse events following immunization (AEFIs) and adverse events of special interest (AESIs). For AEFIs, any event following immunization that is notified is reported and processed as outlined in the module on AEFIs; however pre-specified AESI should be identified through an active process and then reported, investigated and analysed to identify signals.

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

2.1 Adverse events of special interest (AESIs)

The US Food and Drug Administration (FDA) defines an adverse event of special interest (serious or non-serious) as an event of scientific and medical concern specific to the sponsor's product or programme, 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]

1 Guidance for Industry E2F Development Safety Update Report. Available from: https://www.fda.gov/media/71255/download. Accessed 22 November 2020.

Operational definition of an AESI: 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 (AESIs)

AESIs are usually identified through active vaccine safety surveillance (AVSS) systems. Conditions commonly considered as AESIs include serious events that have followed other immunizations, for example:

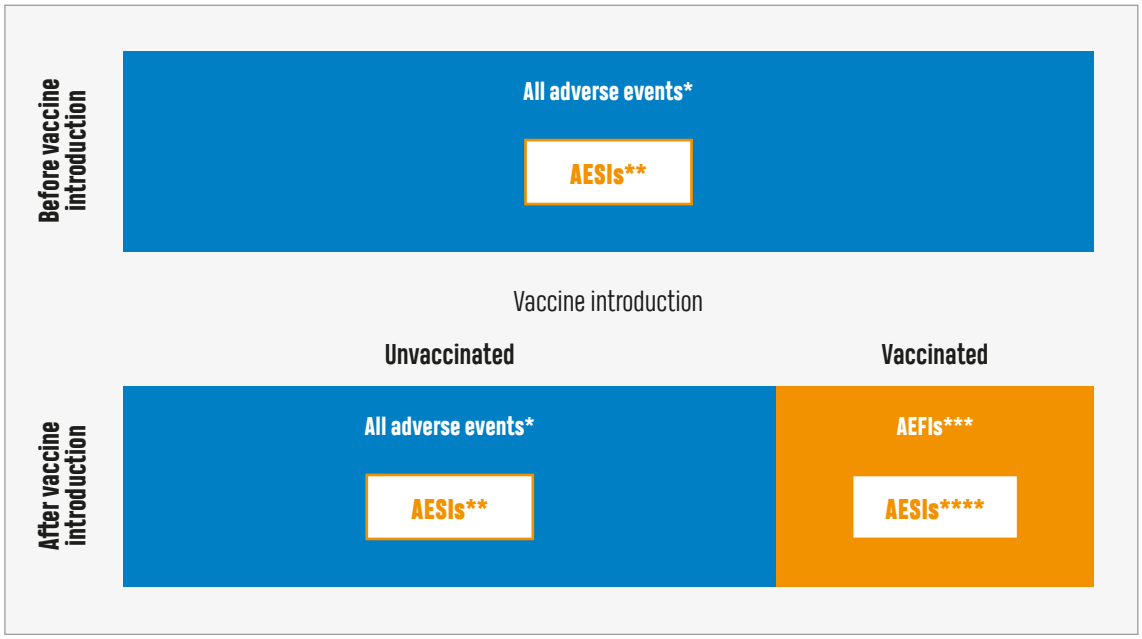
- Guillain-Barré syndrome (GBS);
- acute disseminated encephalomyelitis (ADEM);
- anaphylaxis;
- serious events potentially related to novel platforms;
- serious events potentially related to adjuvants;
- serious events related to vaccine failure/immunogenicity (vaccine-associated enhanced disease (VAED)); or
- events that are potentially important for specific 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 or adjuvant that is being used in any COVID-19 vaccine;
- theoretical concern based on immunopathogenesis of COVID-19 disease;
- theoretical concern related to viral replication during COVID-19 infection; or
- 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** and the differences between AEFIs and AESIs and their practical implications are summarized in **table 1**.

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



** All events in a community that cause morbidity. Background rates provide information on the incidence of such events in the community*
*** Adverse events of special interest (AESIs) for a community defined prior to COVID-19 vaccine introduction. These events are of 'special interest' because although they are known to occur coincidently in the population, they have the potential to be associated with one or more of the COVID-19 vaccine platforms. It is important to estimate the background rates for these events and set up specific surveillance and training*
**** Adverse events following COVID-19 immunization (AEFIs)*
***** AESIs identified following COVID-19 immunization. In addition to following the requirements for AEFI management, there may be special requirements defined for AESIs, including investigation, follow-up and causality assessment activities*

Table 1: Differences between AEFIs and AESIs and practical implications

	AEFI	AESI in the context of COVID-19
What	Any untoward medical occurrence 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.	A pre-specified 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 information	To identify all events after vaccination – determine if serious, investigate (serious) and do causality assessment.	To identify pre-specified specific events by a set criterion and determine if the event is associated with COVID-19 vaccination.
Identification method	Identified via spontaneous reporting by vaccine recipients or their parents, or health care workers or other persons who first notice the event.	Identified via an active surveillance system in sentinel sites or electronic health record (EHR-based cohort studies, CC, SCCS, rapid assessment e.g. VSD, VAC4EU, GVDN) by a health care worker or other staff in the system.
Case definitions	Important	Critical
Type of reporting	All events that follow immunization and are notified to the health care system.	All events identified through active surveillance that fit the case definition, irrespective of immunization status.
Training	All frontline immunization staff in health care facilities (public and private); and other relevant staff for reporting, investigation, data analysis, and causality assessment	Immunization staff and other health care workers in sentinel sites and predefined active surveillance systems, NIP/EPI mangers, NRA, research staff, national AEFI committee
Users	Health care workers, NIP/EPI managers, NRA, surveillance and information managers, epidemiologists, surveillance and information managers, vaccine safety partners including the community	Sentinel site staff, NIP/EPI managers, NRA, epidemiologists, national AEFI committees, study teams.

Abbreviations: CC: case-control; EPI: Expanded programme on immunization; NIP: national immunization programme; NRA: nal regulatory agency; SCCS: self-controlled cohort study

Shortlisting pre-specified AESIs before COVID-19 vaccine introduction will enable countries and regions to prepare for vaccine safety surveillance. This will involve defining the events, ensuring suitable tools are available to detect them, providing training for relevant staff and identifying the disease codes and estimating the background rates for the AESIs. This is important because AESIs are generally detected and reported through active vaccine safety surveillance (AVSS) systems as described below.

03 Active vaccine safety surveillance

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

Active vaccine safety surveillance (AVSS) systems aim to collect complete, accurate information about adverse events following immunization (AEFIs) and their risk factors 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 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;
- 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 those who received a comparator vaccine;
  - the change in the event rate over time;
- the occurrence of events in both vaccinated and unvaccinated individuals in the 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.

04 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 AEFI reporting rates. If passive AEFI reporting rates are below the recommended minimum WHO standard,[4] efforts should be made to improve AEFI reporting through strengthening the existing systems or implementing stimulated passive surveillance.

The COVID-19 surveillance and vaccine and vaccination landscape will vary markedly throughout the world and this will lead to different significant knowledge gaps. The CIOMS guide to active vaccine safety surveillance proposes an algorithm for determining when AVSS systems should be implemented.[2] At the time of COVID-19 vaccine authorization by 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-authorization 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 manufacturer,[5] the Ministry of Health, the national immunization technical advisory group, multilateral and non-governmental organizations, the national regulatory authority and pharmacovigilance centres. Ethical and privacy clearances will be required to collect and analyse identifiable data, as described in the data management module.

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. This coordination will avoid duplication of effort

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.

5 For the purpose of this document, manufacturer also means marketing authorization holder.

and increase the size of the population under surveillance, thus enabling the assessment of very rare events and making comparisons.

4.3 Data collection for AVSS systems

Individual data, linked by a unique identifier, should be 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 or 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 sets, 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
Complete data set	Core data set	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	–	–
		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 and data linkage. Electronic tools, such as m-Health and e-Health, can facilitate the implementation of AVSS. The method selected will depend on factors such as available expertise, resources and funding and what data are needed and available for AVSS.

05 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;
- be considered as complementary to 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; and
- 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

Some AESIs, such as vaccine-associated enhanced disease (VAED) or those with an immunopathogenesis, may have delayed onset. For these events, passive surveillance is often subject to underreporting as events occurring closer to vaccination are more likely to be reported and those occurring at distance to vaccination are less 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 Severe and serious AESIs

In many countries AEFI reporting by health care workers 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 at a background rate in unvaccinated individuals. For this situation, AVSS using sentinel surveillance could be used to identify all those having hospital visits or being admitted for one of the pre-specified AESIs. 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, 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, might be seen 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 are usually high when a new vaccine is introduced, particularly in the setting of mass immunization campaign (see module on communication strategies). In such situations, AVSS systems using tools such as m-Health or e-Health will help obtain near real-time surveillance data for all AEFIs, including AESIs.

5.5 Key resources for evaluating and processing COVID-19 vaccine listed AESIs

Additional unique resources are being developed for identifying and responding to AESIs, including protocols, case definitions, AESI confirmation forms, tabular checklists, automated tools for assessments, background rates and codes. Many of these can also be used in AEFI assessment and interpretation of signals are shown in **Table 3**. This will be consolidated as a separate document for countries and programmes seeking detailed guidance. Some of these resources are already available.

Table 3: Key resources available and being developed 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 https://brightoncollaboration.us/covid-19/ for latest list and definitions
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 LOC for cases	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	

LOC: level of certainty

The resources shown in **Table 3** are being prepared for all the AESI listed in **Table 4** as well as for several others 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. 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.

06 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 based on 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. Countries should have a national causality assessment committee with the necessary expertise. The members of this committee 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 in collaboration with Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC).[6,7] 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. Details are available at https://brightoncollaboration.us/covid-19/. As new information emerges this list will be updated.

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

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

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

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

7 Safety Platform for Emergency vACcines (SPEAC). Available from: https://brightoncollaboration.us/speac/. Accessed 8 December 2020.

Master protocols are being developed to facilitate the implementation of active vaccine safety surveillance for AESIs with COVID-19 vaccines using harmonized methods and standardized tools. This will be posted on WHO website as they become available.

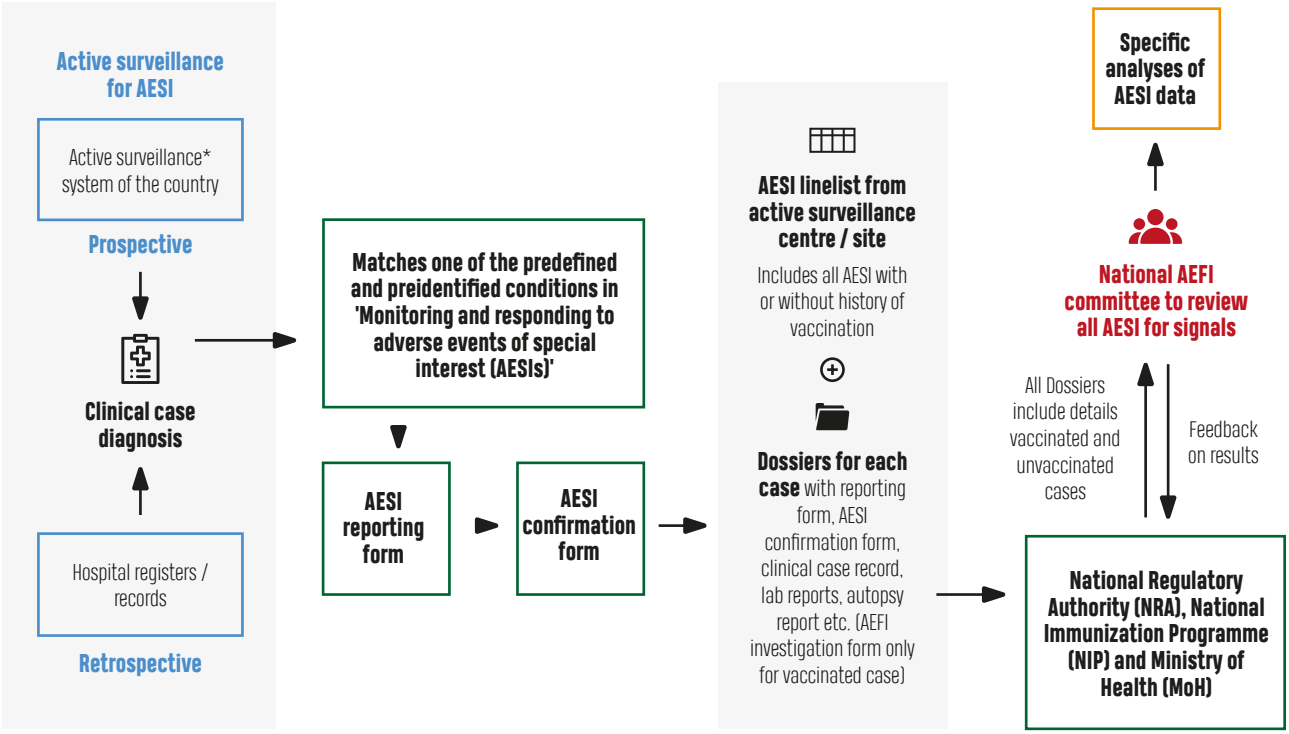
Table 4: List of AESI defined for COVID-19 vaccines (May 2020)

AESI
Vaccine-associated enhanced disease
Multisystem inflammatory syndrome in children
Acute respiratory distress syndrome
Acute cardiovascular injury (microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia, myocarditis)
Coagulation disorder (thromboembolism, haemorrhage)
Acute kidney injury
Generalized convulsion
Guillain Barré Syndrome
Acute liver injury
Anosmia, ageusia
Chilblain – like lesions
Single organ cutaneous vasculitis
Erythema multiforme
Anaphylaxis
Acute aseptic arthritis
Meningoencephalitis
Acute disseminated encephalomyelitis
Thrombocytopenia

6.1 AESI reporting and response mechanisms in AVSS systems

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

Fig 2: In-country reporting and processing of AESIs



* Data flow can be customized according to the active surveillance methods adopted by the country

6.1.1 AESIs detected though active vaccine safety surveillance systems

AESI cases can be detected through different modes of active surveillance such as cohort event monitoring (CEM), sentinel surveillance (SS) and data linkage (DL) using case definitions. Specific AVSS tools such as m-health (MH) and e-health (EH) are available for this purpose. Additional efforts should be made to obtain vaccine exposure information in AESIs identified through active surveillance to enable its association with the vaccine to be assessed. In such instances the AESI reporting form (**Appendix 7.2**), AESI confirmation form[8] 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 or site responsible for AESI surveillance. Dossiers for each case in the AESI linelist should be submitted to the national level (NRA/NIP/EPI/MoH) in compliance with the country protocol and through them shared with the national AEFI committee that has been specifically trained for population-specific analyses of AESI data.

8 To be published in the AESI investigation guidance document that will be developed

6.1.2 Investigating AESI in patients exposed to COVID-19 vaccination

As mentioned above, any AESI matching the list of pre-specified AESI conditions should undergo detailed investigation, unless specified otherwise in the country's protocol. Since they are vaccinated, such cases are considered to be AEFIs and investigation should be done using the COVID-19-specific AEFI investigation form and causality ascertained as described in the AEFI module. When such cases from AEFI surveillance systems are being reviewed by the causality assessment committee, after confirming the absence of programmatic errors, Immunization stress related responses 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.[9]

6.1.3 Data analyses for AESI cases from active surveillance systems

Reviewing data from both vaccinated and unvaccinated AESI cases identified via the active AESI surveillance systems will enable 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 individuals within a specific population and identification of signals for further characterization and investigation.

The causality assessment committee can perform these analyses if they have the necessary expertise and if they have been trained to review population-based scientific data arising from the specific types of studies in active surveillance systems. In this case, 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, e.g., clusters of similar events in space, time and vaccine administered.

In countries or regions 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.

6.2 Reconciling AESI data

Information about AESIs will be obtained from a passive AEFI surveillance system or from an 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. All documentation for the AESIs should be archived.

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9 World Health Organization. AEFI causality assessment user manual for the revised WHO classification. Available from: https://www.who.int/vaccine_safety/CA_manual_second_edition/en/. Accessed 8 December 2020.

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 vaccine manufacturers and WHO should be informed so that they can consult 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 should be defined in the country's protocol. Countries may determine the profile of health care workers who will be responsible for reporting, when defining 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.

6.3 Tools for active surveillance of AESIs

Some of the existing tools as outlined in WHO's global manual on surveillance of adverse events following immunization can also be used for AESIs.[10] A summary of the available tools and how they can be accessed is given in **Table 5**.

6.4 Prioritizing preparedness for AESI

At the time of vaccine authorization, countries need to review the risk management plan (RMP) and discuss the risks and benefits with their respective in-country national immunization technical advisory groups (NITAGS) or regional immunization technical advisory groups (RITAGS). They need to determine if they have the capacity to implement active surveillance for AESIs as described in the module on establishing surveillance systems to supplement data obtained via the passive surveillance systems.

The many unknowns for COVID-19 vaccine use in a country and the limited knowledge about its safety profile make it difficult to set priorities for the AESIs that are most relevant to a given setting. In general, countries should prepare to address quickly signals for events that have the highest likelihood to derail a vaccination campaign. Several of the AESIs on the list in **Table 4** have been included because of a known association with vaccination. On this basis, generalized convulsions, thrombocytopenia and anaphylaxis would all be priority AESIs. Generalized convulsions would be an even higher priority for vaccines that induce a high frequency of fever and for those vaccines that will be used for children aged less 6 years of age. GBS should also be a priority, given its global occurrence, its known association with some vaccine platforms and its known increased frequency in older populations who are very likely to be in the priority target groups for COVID-19 immunization programmes.

Vaccine-associated enhanced disease, acute respiratory distress syndrome and multisystem inflammatory syndrome in children will all be of high priority although

10 World Health Organization. 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.

they will be very difficult to assess and interpret in the context of active COVID-19 infection in the community. Priority should be given in surveillance 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. Vaccine-associated enhanced disease (VAED) could occur before a protective immune response is expected, particularly for vaccines that require more than one dose to Induce immunity. A non-protective immune response could be associated with VAED. 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.

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

Description	Purpose	Status for COVID-19	Hard copy
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[11]	Being developed separately in additional 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)	Being developed separately in additional guidance on AESI in preparation for COVID-19 vaccine introduction
AESI reporting form	To collect information for 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	Being developed separately for each condition and to be included in additional guidance on AESI in preparation for COVID-19 vaccine introduction
Investigation form for AESI cases that have history of COVID-19 vaccination	To collect detailed information when serious AEFI cases are investigated	Adapted to include COVID-19 specific questions	**Appendix 7.5.** This is the same as the COVID-19 AEFI investigation form

11 Brighton definitions: https://brightoncollaboration.us/category/pubs-tools/case-definitions/

Description	Purpose	Status for COVID-19	Hard copy
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 used for AEFI unchanged	Causality assessment of an adverse event following immunization (AEFI)
Detailed analysis format of AESI as per protocol	To determine if the incidence of the pre-specified AESI is higher in vaccinated individuals than unvaccinated individuals	Will depend on study protocol	Will depend on study protocol

Anosmia and ageusia are so common with acute COVID-19 infections that they have been proposed for the COVID-19 screening. It is recommended that relatively high priority should be placed on raising awareness about these conditions and determining their background rates, since they are also known to occur with other viral respiratory infections like influenza. This will be especially high priority in settings where there is ongoing community spread of COVID-19 disease.

Coagulation disorders should be of higher priority in settings where there are other infections that could present with bleeding, such as dengue. It will be important to have testing in place to establish if any observed coagulation disorders are coincidental to immunization or are caused by immunization.

Acute cardiac injury, acute liver injury and acute kidney injury would be of higher priority in settings and populations 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 individuals. Although currently it seems unlikely that there will be live-attenuated COVID-19 vaccines in use, but if they are implemented, meningoencephalitis should be a higher priority in the AESI surveillance than for programmes that implement inactivated vaccines.

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

Acute disseminated encephalomyelitis (ADEM) occurs rarely and has not been proven to be caused by immunization. Despite this, a single ADEM case could completely disrupt an immunization programme, which is why it has been identified as an AESI. It would be useful to have population prevalence data for ADEM if incidence data are not available or unobtainable.

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 individuals

The full impact of COVID-19 disease on pregnancy outcomes for mother and foetus as well as for new-borns is still unclear.[12,13] 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 any apparent long-term sequalae.

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. Pregnancy registries are important tools to determine pregnancy outcomes when vaccines are likely to be used inadvertently or intentionally during pregnancy or for women who may become pregnant post-vaccination. Furthermore it is recommended 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. The COVAX Maternal Immunization Working Group is developing guidance for approaches for the evaluation of COVID-19 vaccine safety for pregnant women and their infants for the post-licensure period.[14]

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

6.6 Sudden unexpected death as an AESI

Without question, sudden unexpected death occurring within days of immunization is a major threat to 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 and are related to thromboembolic phenomena such as stroke, pulmonary embolus and coronary thrombosis.[15] However, it will be essential to be prepared for such occurrences to enable rapid response in terms of investigation and communication to the public.

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12 Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6):521-531. doi: 10.1016/j.ajog.2020.03.021.

13 Castro P, Matos AP, Werner H, Lopes FP, Tonni G, Araujo Júnior E. Covid-19 and pregnancy: an overview. Rev Bras Ginecol Obstet. 2020;42(7):420-426. doi: 10.1055/s-0040-1713408.

14 To be published soon.

15 Avila J, Long B, Holladay D, Gottlieb M. Thrombotic complications of COVID-19. Am J Emerg Med. 2020 Oct 1:S0735-6757(20)30860-3. doi: 10.1016/j.ajem.2020.09.065.

Selected events that could result in death,[16] although rare, have been identified as cause-specific AEFIs that could be seen following immunization including:

- vaccine product related reaction: anaphylaxis;
- vaccine quality defect: wild type disease following incompletely attenuated live viral vaccine as occurred with the Cutter incident with polio vaccination;[17]
- immunization-error: sepsis following contamination of multidose vials; use of a drug (e.g. anaesthetic drug, insulin) to reconstitute vaccine; instead of the diluent supplied;
- anxiety-related reaction: fatal head injury associated with syncope in settings where post-immunization safety is not assured;[18] and
- coincidental reaction: likely to be the underlying cause of the majority of sudden deaths 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 immunization, a thorough field investigation should be conducted without delay, and an autopsy performed according to the protocol developed for people with a suspected COVID-19 cause of death.[19] Knowing regional and age-specific background incidence of sudden deaths as well as relevant risk factors will be essential to 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 will be critical to maintain confidence in the vaccination programme, the health system and the health authorities.

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16 Gold MS, Balakrishnan MR, Amarasinghe A, MacDonald NE. An approach to death as an adverse event following immunization. Vaccine 2016;34:212-217. doi: 10.1016/j.vaccine.2015.

17 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.

18 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.

19 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.

07 Appendices

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

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.[20] A vaccinated cohort is established and followed for any predefined AEFIs (Including AESIs) that occur over a defined period. Demographic data are collected to enable risk factors to be characterized.	**Vaccination history** Details of COVID-19 vaccine or other vaccines collected at the time of enrolment **Health event(s)** Pre-specified COVID-19-related AESIs and constitute the health outcome under surveillance. **Demographic data** Data collected that could be relevant to outcome, for example, those factors associated with severe COVID-19 disease (diabetes, obesity, medication).	**Advantages** Data from CEM can be used to define AESI rates, within a vaccinated cohort, but is dependent 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** Data from CEM cannot be used to estimate relative risk of AESIs compared with an unvaccinated population but is able to define a relative risk if more than one COVID-19 vaccines are under surveillance. To define the rate of a rare AESI a large observational cohort would be required.

20 World Health Organization. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. Available from: https://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf. Accessed 22 November 2020.

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 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 are 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 events** COVID-19 related AESI, AEFI, or a specific health condition is specified. Every patient attending or admitted to the sentinel facility is screened to see if the definition is met, regardless of vaccination status. **Demographic data** Demographic data are collected only if the patient meets the case definition of the condition under surveillance. The data collected could include possible risk factors.	**Advantages** It is possible to collect detailed data on the health event, outcome and demographics. It may be possible to estimate the relative risk for events where the post-vaccination onset time is clearly defined using a self-controlled case-series analysis. **Disadvantages** It is not possible to estimate the rate of the health event under surveillance. Data collection can be costly and time consuming. Vaccination data for the patient with the AESI may not be readily available.

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19-related surveillance
Data linkage (DL)	DL involves linking electronic data, from different data collections, where the data have usually been collected prior to linkage. Vaccination, health event and demographic data, often from many thousands of individuals which are stored in different databases 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 events** Health events under surveillance (e.g., COVID-19 related AESIs) need to be coded (ICD coding) and stored electronically. **Demographic data** Demographic data are 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-19 disease (diabetes, obesity, medication)	**Advantages** 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 between COVID-19 vaccination and an AESI. If linked databases are established, DL can be used for regular rapid review of safety signals. **Disadvantages** Few countries have the capacity and ready access to large established databases containing vaccination, health event and demographic data that can be linked. DL can be resource intensive in terms of the cost and expertise required for linkage. In many countries there are significant barriers to data access, because of privacy and confidentiality laws. DL is most often used to link to hospital events and is more difficult to use for conditions that do not lead to hospitalization.

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19-related surveillance
Example of tools for CEM: m-Health (MH) and e-health (EH)	MH and EH are evolving ways to monitor for health events following immunization or medication use. They become more feasible because of the increasing use of mobile phones and access to the internet. MH and EH can target individuals for surveillance via various methods such as SMS, reporting apps, direct telephone calls, emails and on-line surveys.	**Vaccination history** Details of COVID-19 vaccine or other vaccines collected at the time of enrolment **Health event** COVID-19 related AESIs 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** Low cost and can target individuals (vaccinees or their parents) directly. Can be used for 'real-time' surveillance and for vaccine safety signal generation. Rates of AEFIs can be estimated but large samples may be required. **Disadvantages** Network coverage, mobile phone and internet costs maybe a barrier to reporting. Significant resources could be required to verify reports.

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*

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)	Vaccine/s	Manufacturer	Dose	Vaccine Batch No	Diluent Batch No	Place of vaccination	Date of Vaccination (DOV)	Reported by	Reporter Location 1	Reporter Location 2	AESI Confirmation initiated? (Y/N)	Field investigation planned? (Y/N)

Appendix 7.4: COVID-19 AESI confirmation forms (under development)

- 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

Appendix 7.5: AEFI investigation form adapted for AESI following COVID-19 immunization

Oct 2020

AEFI FOLLOWING COVID 19 VACCINATION - INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A Basic details

Province/State **District** **Case ID**

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐Other (specify) _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Address of vaccination site:

Name of Reporting Officer:

Date of investigation: __ __ / __ __ / __ __ __ __
Date of filling this form: __ __ / __ __ / __ __ __ __

Designation / Position:

This report is: ☐ *First* ☐ *Interim* ☐ *Final*

Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐M ☐ F

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

Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

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

OR *Age group:* ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years - 18 years* ☐ *> 18 years – 60 years* ☐ *> 60 years*

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

Brand name of vaccines (including manufacturer) /diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom *(hh/mm)*: __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __
Date first reported to the health authority *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Status on the date of investigation (✓): ☐ Died ☐ Disabled ☐ Recovering ☐ Recovered completely ☐Unknown

If died, date and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ *(hh/mm)*: __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B Relevant patient information prior to immunization

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event?	Yes / No / Unkn	
Adverse event after any previous vaccination(s)?	Yes / No / Unkn	
History of allergy to vaccine, drug or food?	Yes / No / Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unkn	
Pre-existing acute illness (30 days) prior to vaccination?	Yes / No / Unkn	
Has the patient tested Covid19 positive prior to vaccination?	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause?	Yes / No / Unkn	
Was the patient receiving any concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy?	Yes / No / Unkn	
For adult women • Currently pregnant? Yes (weeks) _____ / No / Unknown • Currently breastfeeding? Yes / No		

For infants
The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

Section C Details of first examination** of serious AEFI case

Source of information (✓ *all that apply*): ☐ **Examination by the investigator** ☐ **Documents** ☐ **Verbal autopsy**
☐ **Other**_____ *If from verbal autopsy, please mention source* _____

Name of the person who first examined/treated the patient:_____
Name of other persons treating the patient: _____
Other sources who provided information (specify): _____

Signs and symptoms in chronological order from the time of vaccination:

Name and contact information of person completing these clinical details:	Designation:	Date/time

****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports, prescriptions for concomitant medication) and then complete additional information NOT AVAILABLE in existing documents, i.e.**

- ***If patient has received medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- ***If patient has not received medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D Details of vaccines provided at the site linked to AEFI on the corresponding day

Number immunized for each antigen at session site. Attach record if available.	Vaccine name									
	Number of doses									

a)	When was the patient immunized? (✓ the ☐ below and respond to ALL questions)	
	☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown	
	In case of multidose vials, was the vaccine given ☐ within the first few doses of the vial administered? ☐ within the last doses of the vial administered? ☐ unknown?	
b)	Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No
c)	Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes* / No / Unable to assess
d)	Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes* / No / Unable to assess
e)	Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes* / No / Unable to assess
f)	Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes* / No / Unable to assess
g)	Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes* / No / Unable to assess
h)	Number immunized from the concerned vaccine vial/ampoule	
i)	Number immunized with the concerned vaccine in the same session	
j)	Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations: _____	
k)	Could the vaccine given to this patient have a quality defect or is substandard or falsified?	Yes* / No / Unable to assess
l)	Could this event be a stress response related to immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	Yes* / No / Unable to assess
m)	Is this case a part of a cluster?	Yes* / No / Unkn
	i. If yes, how many other cases have been detected in the cluster?	
	a. Did all the cases in the cluster receive vaccine from the same vial?	Yes* / No / Unkn
	b. If no, number of vials used in the cluster (enter details separately)	

* ***It is compulsory for you to provide explanations for these answers separately***

Section E Immunization practices <u>at the place(s) where concerned vaccine was used</u>

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn

If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled disposable ☐ Other _____

Specific key findings/additional observations and comments:

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA

Specific key findings/additional observations and comments:

Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)	
• Correct dose and route?	Yes / No
• Time of reconstitution mentioned on the vial? (in case of freeze dried vaccines)	Yes / No
• Non-touch technique followed?	Yes / No
• Contraindications screened prior to vaccination?	Yes / No
• How many AEFI were reported from the centre that distributed the vaccine in the last 30 days?	
• Training received by the vaccinator? (If Yes, specify the date of last training _____)	Yes / No
Specific key findings/ additional observations and comments?	

Section F	**Cold chain and transport** *(Complete this section by asking and/or observing practice)*
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation:	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Section G Community investigation (Please visit locality and interview parents/others)

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those effected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

Other comments:

Section H Other findings/observations/comments

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

World Health Organization

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