COVID-19 Vaccines: Safety Surveillance Manual

Module: Safety surveillance of COVID-19 vaccines in pregnant and breastfeeding women

Abbreviations and acronyms

ACT	Access to COVID-19 tools
AACVS	African Advisory Committee on Vaccine Safety
ACE	Angiotensin-converting enzyme
ACT	Access to COVID-19 tools
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
BMI	Body-mass index
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
FIND	Foundation for Innovative New Diagnostics
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré syndrome
GMP	Good manufacturing practices
GVAP	Global vaccine action plan
HCW	Health care worker
HELLP	Haemolysis, elevated liver enzymes, low platelet count
ICD	International classification of diseases
ICSR	Individual case safety report
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
iS PSUR	Interim simplified periodic safety update report
ISoP	International Society of Pharmacovigilance
ISRR	Immunization stress-related response
LMIC	Low- and middle-income country
LMP	Last menstrual period
MedDRA	Medical dictionary for regulatory activities
MAH	Marketing authorization holder
MH	m-Health
MoH	Ministry of Health
mRNA	Messenger RNA
NIP	National Immunization Programme
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authority
PASS	Post-authorization safety studies
PBRER	Periodic benefit-risk evaluation report
PER	Pregnancy exposure register
PHEIC	Public health emergency of international concern
PIDM	Programme for International Drug Monitoring
PSUR	Periodic 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
STI	Sexually transmitted infection
TGA	Therapeutic Goods Administration (Australian Government Department of Health)
UMC	Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring)
US	Ultrasound
VAED	Vaccine-associated enhanced disease
VLP	Virus-like particles
VPD	Vaccine preventable disease
WHO	World Health Organization

11 Glossary

Active safety surveillance	Active (or proactive) safety surveillance is an active system for the detection of adverse events. This is achieved by active follow-up after vaccination. Events can be detected by asking patients directly or by screening patient records. It is best done prospectively.
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 early detection, reporting, investigating, and quickly responding to AEFIs.
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)	The risk management plan is a document established by the vaccine manufacturer that contains the following elements: (a) identification or characterization of the safety profile of the medicinal product(s) concerned; (b) indication of how to characterize the safety profile of the medicinal product(s) concerned further; (c) documentation of measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; (d) documentation of post-authorization obligations that have been imposed as a condition of the marketing authorization.
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	Based on its intensity vaccine reactions can be mild, moderate or severe. The event itself, however, may be of relatively minor medical significance. Severe events do not have regulatory implications unless they are also serious.
Signal (safety signal)	Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
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.
VigiBase	WHO global database of individual case safety reports (ICSRs) including ADRs and AEFIs, maintained by Uppsala Monitoring Centre.
VigiFlow	A web-based individual case safety report (ICSR) management system (E2B compatible) for medicines and vaccines, developed and maintained by Uppsala Monitoring Centre.

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40 ## Key points

- Pregnant women may experience more severe disease and have a higher risk of mortality associated with COVID-19 infection compared with nonpregnant women.
- COVID-19 infection may increase the risk of preterm delivery. Studies are underway globally to assess the risk-benefit profile of COVID-19 vaccines in pregnant and breast-feeding women.
- Immunization programmes need to incorporate surveillance of women who have been vaccinated either intentionally or inadvertently during pregnancy, and their children.
- Passive surveillance approaches need to take into consideration three potential scenarios:
    - maternal AEFIs not directly related to the pregnancy;
    - obstetric adverse events believed to be linked to COVID-19 vaccination during pregnancy; and
    - adverse events in the fetus (in the case of pregnancy loss), neonate or infant suspected to be associated with COVID-19 vaccination during pregnancy.
- Prompt investigations and causality assessment involving health care workers knowledgeable in maternal and neonatal health are needed to mitigate any adverse consequences for the mother-infant pair, as well as the vaccination programme itself.
- Currently, there is a lack of adequate data on the performance of COVID-19 vaccines in pregnant women. Therefore, both active and passive surveillance approaches are recommended.
- National AEFI monitoring programmes designed for routine childhood immunizations will need to be adapted to include COVID-19 vaccinations in adults, including pregnant women. For this the AEFI reporting forms, case investigation procedures, as well as causality assessment procedures will need to be adapted to take into account the specific characteristics of AEFIs following maternal immunization.
- There are challenges in assessing causality in individual cases of adverse birth outcomes due to the specific characteristics of pregnancy exposure to vaccine.
- Active surveillance approaches such as pregnancy exposure registries, cohort event monitoring studies, nested case-control and linkage studies may be used to assess the potential risks of adverse birth outcomes in vaccinated compared with unvaccinated women.
- Embedding AEFI surveillance for COVID-19 vaccines in existing surveillance programmes, such as pregnancy exposure registries for other medicines, may be an efficient way of harnessing existing resources for this purpose.
- Communication strategies for the AEFI programme need to be adapted to take into consideration the different stakeholders that need to be engaged when pregnant and breast-feeding women are vaccinated with COVID-19 vaccines.

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1. Introduction

1.1. COVID-19 disease and vaccination in pregnant and breastfeeding women

While there is no indication that pregnant women have an increased susceptibility to infection with SARS-CoV-2, there is evidence that pregnancy may increase the risk of severe illness and mortality from COVID-19 disease in comparison with non-pregnant women of reproductive age.[1] As seen with non-pregnant women, a high proportion of pregnant women have asymptomatic SARS-CoV-2 infection and severe disease is associated with recognized medical (e.g., high body-mass index (BMI), diabetes, pre-existing pulmonary or cardiac conditions[1,2,3,4]) and social (e.g., social deprivation, ethnicity) risk factors. Pregnant women with symptomatic COVID-19 appear to have an increased risk of intensive care unit admission, mechanical ventilation and death in comparison with non-pregnant women of reproductive age, although the absolute risks remain low.[1] COVID-19 may increase the risk of preterm birth, compared with pregnant women without COVID-19, although the evidence is inconclusive.[5]

SARS-CoV-2 has been observed in placenta and some case reports suggest that vertical transmission of the virus to infants born to infected women may occur (as opposed to postpartum infection).[3] However, congenital COVID-19 infections have not been reported so far during the pandemic.[4] The acute effects of the disease on neonates and infants have been secondary to complications arising from severe maternal illness and medically-indicated preterm delivery or caesarean delivery due to clinician concerns.

There is no evidence that SARS-CoV-2 can be transmitted via human breast milk. Consequently, WHO recommends that mothers continue to breastfeed their infants.[4,5,6,7]

Women of reproductive age represent an very large group of the categories of workers who have been prioritized to receive COVID-19 vaccination globally, i.e., health care workers, carers, educators and other front-line essential workers.[8] Several COVID-19 vaccines are under development using various technological platforms and some are already authorized for use under emergency use approval in response to the pandemic. For more information on each platform, and links to relevant, updated information on the status of development refer to the module, COVID-19 vaccines: description and general safety considerations for implementation in this manual.

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[1] Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320. doi: 10.1136/bmj.m3320.

[2] Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, et al. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine. 2020;25:100446. doi: 10.1016/j.eclinm.2020.100446.

[3] Fenizia C, Biasin M, Cetin I, Vergani P, Mileto D, Spinillo A, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. Nat Commun. 2020;11:5128. doi: 10.1038/s41467-020-18933-4.

[4] Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health. 2021; 5:113-21. doi: 10.1016/S2352-4642(20)30342-4.

[5] Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, Rayco-Solon P, Garcia-Casal MN, Rogers L, et al. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. Ann N Y Acad Sci. 2021 Jan;1484:32-54. doi: 10.1111/nyas.14477.

[6] World Health Organization. COVID-19 clinical management: living guidance, 25 January 2021. Available from: https://apps.who.int/iris/handle/10665/338882, accessed 26 March 2021.

[7] Rollins N, Minckas N, Jehan F, Lodha R, Raiten D, Thorne C, et al. A public health approach for deciding policy on infant feeding and mother–infant contact in the context of COVID-19. Lancet Glob Health. 2021;9:e552-7. doi.org/10.1016/S2214-109X(20)30538-6.

[8] World Health Organization. WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination, 14 September 2020. Available from: https://apps.who.int/iris/handle/10665/334299, accessed 26 March 2021.

To date, pregnant women have not been included in Phase II and III clinical trials of COVID-19 vaccines.[9] Hence data on COVID-19 vaccines in pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy, although studies are underway.[10] Section 1.2 summarizes WHO's current recommendations for COVID-19 vaccination in pregnant and lactating women.

Pregnant women may be exposed to COVID-19 vaccines in two ways:

1. inadvertent vaccination before the woman knows she is pregnant, i.e., at an early gestational stage; or
2. vaccination offered to a woman with confirmed pregnancy who is at high risk of COVID-19 exposure and infection or at risk of severe disease should they become infected, and who choose to be vaccinated.

The risks and benefits of COVID-19 vaccine exposure apply to both the pregnant woman and her fetus, and the timing of exposure during pregnancy may have an impact on the outcomes. It is important that vaccine safety monitoring programmes proactively include pregnant women that have been either inadvertently or knowingly exposed to COVID-19 vaccines, to collect information on associated obstetric and neonatal outcomes.

1.2. WHO recommendations for COVID-19 vaccination in pregnant and breastfeeding women

At present (March 2021), the WHO Strategic Advisory Group of Experts on Immunization (SAGE) currently recommends that pregnant women may receive the vaccine if the benefits of vaccination outweigh the potential risks, such as occupational activities with unavoidable high risk of exposure, and pregnant women with co-morbidities which place them in a high-risk group for severe COVID-19 disease.[8] In other words, vaccination for pregnant women should be considered on an individual basis after consultation between the woman and her health care provider. As more data become available these guidelines will be updated. Routine testing for pregnancy before COVID-19 vaccination is not recommended.

Few vaccines are contra-indicated in breastfeeding women.[11] However, as of March 2021, there are no data available about the safety of COVID-19 vaccines in breastfeeding women and breastfed children. The lack of clinical data on the use of COVID-19 vaccines for breastfeeding women should be weighed against the potential benefits of breastfeeding including the passive transfer of antibodies from breast milk.[8] WHO does not recommend discontinuing breastfeeding after vaccination.[8]

In addition to WHO recommendations, other obstetric and gynaecologist networks recommend that women planning to become pregnant should complete their vaccination course before conception so that they are protected during pregnancy. There is no evidence that the COVID-19 vaccines affect fertility.

1.3. Pregnancy-and vaccine safety surveillance

Pregnant women require special considerations and this influences the design of surveillance systems.

[9] Taylor MM, Kobeissi L, Kim C, Amin A, Thorson AE, Bellare NB, et al. Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action. *Lancet Glob Health.* 2021; 9: e366-7. doi: 10.1016/S2214-109X(20)30484-8.
[10] For example, Clinicaltrials.gov, NCT04754594: Study to evaluate the safety, tolerability, and immunogenicity of SARS CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older.
[11] Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices. General best practice guidelines: special situations. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/special-situations.html, accessed 26 March 26, 2021.

Maternal and fetal/newborn/infant health needs to be monitored. Exposure to a vaccine can potentially affect both maternal and fetal health. The fetus can be affected:

- indirectly, if an event experienced by the mother, e.g., anaphylaxis, seizures with high fever, has an impact on her health and safety during pregnancy; or
- directly, e.g., theoretical risks of live-attenuated vaccines to the fetus.

Therefore, vaccinated pregnant women, systematic **reporting of both maternal and neonatal/infant adverse events following immunization (AEFIs)** must be incorporated into surveillance systems.

The timing of vaccination, other exposures and birth outcomes in relation to gestational age is critical: The **timing of exposure during the pregnancy** can affect the possible outcomes. Medicines and other teratogenic exposures can cause harm at any time during pregnancy. However, the period of organ and tissue development in the fetus, which typically occurs in the first eight weeks of gestation is critical.[12] For instance, a fetus exposed to an agent known to cause neural tube defects is at highest risk if exposed when the neural tube closes, which occurs at 3 to 6 weeks of gestation, whereas exposure occurring beyond the first trimester is unlikely to cause neural tube malformations.

Obtaining information about the **nature and timing of multiple potentially-confounding exposures,** including prescription, over-the-counter and traditional medicines, vitamins and supplements, and other vaccines, as well as substances such as alcohol, tobacco and illicit drugs, is therefore critical.

Gestational age at the time of vaccination is also important when characterizing birth outcomes such as preterm delivery, small for gestational age and certain congenital anomalies. Thus, relevant clinical data, such as last menstrual period, gestational dating using ultrasound or symphysis fundal height, and assessment of the neonate at birth are important. Standardized case definitions for gestational age assessment and adverse birth outcomes will ensure that data, including risk assessments, can be compared and harmonized across settings.

***Adverse effects may only be apparent sometime after exposure*:** The adverse effects of a potentially teratogenic exposure during pregnancy may only be apparent at the time of delivery, e.g., via surface examination of the neonate, particularly in settings where access to ultrasound services is limited, or later after birth, e.g., in the case of some congenital anomalies or neurodevelopmental delay.[13] Therefore, there can be a significant delay between the vaccine exposure and the identification and assessment of the outcome. Consequently, women who are exposed to COVID-19 vaccine during pregnancy should be followed up to establish the pregnancy outcome and assess the health of the neonate. In most countries, a facility-held or patient-held medical record which documents clinical data during the antenatal and perinatal period can be a useful source of information when investigating AEFIs. This may only be feasible through active surveillance approaches (see section 3.2 for active surveillance approaches).

Many potential contributing factors may coexist: Many suspected obstetric AEFIs have multiple potential causes and mediators including:

- comorbid infectious and non-infectious conditions, such as HIV, malaria, syphilis, diabetes, hypertension, anaemia, nutritional deficiencies;

[12] Vargesson N, Fraga L. Teratogenesis. 2017. In eLS, John Wiley & Sons, Ltd (Ed.). https://doi.org/10.1002/9780470015902.a0026056.

[13] Ajibola G, Zash R, Shapiro RL, Batlang O, Botebele K, Bennet K, et al. Detecting congenital malformations - lessons learned from the Mpepu study, Botswana. PLoS One 2017;12:e0173800. doi: 10.1371/journal.pone.0173800.

- environmental exposure, including radiation, medications, pollutants, alcohol, tobacco and recreational drugs; or
- genetic predisposition, as encountered with hereditary disorders and genetic mutations.

AEFI surveillance and investigations into the role of immunization in adverse obstetric outcomes should consider the possibility of alternative causes. In the case of active surveillance, particularly in pregnancy registries, assessment of these potential confounders requires systematic collection of data on common risk factors for adverse birth outcomes in both exposed and unexposed cohorts of pregnant women.

As a result of these unique conditions, attributing cause to an immunization in pregnancy *for individual cases* is extremely challenging, and often not possible. The investigation and causality assessment of non-obstetric AEFIs in pregnant women themselves, i.e., not the fetus, are similar to the assessment done in any other adults. However, the role of active surveillance systems, such as pregnancy registries, for the evaluation of adverse obstetric outcomes in assessing the safety of vaccines in pregnant women, are important. Ideally, active surveillance should aim to compare the risks of adverse birth outcomes, e.g., stillbirth, neonatal death, low-birth weight, preterm delivery, and birth defects, in COVID-19 vaccine exposed pregnancies with the risks in an appropriate comparison group. This can be, for example, a cohort of unvaccinated pregnant women; or pregnant women who received another vaccine, such as a tetanus or influenza vaccine, or reliably estimated background risks of these outcomes.

1.4. Vaccine safety surveillance methods for COVID-19 vaccination in pregnant women

The aim of vaccine safety surveillance is to enable early detection and initial investigation of AEFIs to determine whether there is a signal that warrants further epidemiological study. Signal investigation allows a rapid response to mitigate any safety issues that could have a negative impact on both the individuals involved and the ongoing vaccine rollout, for instance, if the investigation suggests strong evidence against a causal association, as well as informing further investigation of the AEFI and management of the immunization programme. The specific objectives of vaccine safety surveillance are described in the *WHO Global Manual on Surveillance of Adverse Events following Immunization*.[14] Maternal AEFIs, notified to the health system that are not directly related to the pregnancy should be reported and processed through the routine AEFI reporting system, as recommended. The guidance in this current module on pregnancy is for potential AEFIs relating to obstetric and neonatal/infant outcomes following COVID-19 vaccination.

A combination of both passive and active surveillance methods is recommended for COVID-19 vaccines, which will be used on a large scale. After COVID-19 vaccines are licensed, routine surveillance systems (spontaneous reporting) will be helpful for detecting rare and delayed AEFIs throughout the product cycle.

Once a serious AEFI or an adverse event of special interest (AESI), suspected to be related to an obstetric or neonatal/infant outcome, is detected, additional information on the timing of the vaccine exposure during the pregnancy, presence of other potential causes for the AEFI or AESI and details of birth outcomes or adverse events will need to be collected for further investigation (Section 2.2). Some countries may choose to adopt active surveillance methods, in addition to routine, passive surveillance. Section 3.2 provides an overview of different active surveillance methods that can be

[14] World Health Organization. Global manual on surveillance of adverse events following immunization. Available at: https://www.who.int/vaccine_safety/publications/aefi_surveillance/en/, accessed 26 March 2021.

used to investigate AEFIs for obstetric, neonatal and infant outcomes. Surveillance strategies adopted by individual countries will depend on local resources, infrastructure and diagnostic capacity.

The rollout of COVID-19 immunization programmes will require close collaboration between the maternal and child health services, immunization services, and national pharmacovigilance programmes. Antenatal care providers, including obstetricians and midwives, may not be familiar with systems to detect and report AEFIs and may need training on AEFI surveillance before COVID-19 vaccines are introduced.

In many low- and middle-income countries (LMICs), information on background rates of adverse obstetric or neonatal/infant outcomes are not systematically or routinely collected and the rates are, therefore, not known. In these countries, the risk of erroneously attributing adverse obstetric or neonatal/infant outcomes to immunization is a concern, particularly in the context of high-profile, rapidly developed vaccines, such as the COVID-19 vaccines. Maternal and child health programme research groups, therefore, need to determine appropriate estimates of background rates for key adverse obstetric and neonatal/infant outcomes of interest. Although national statistics of key outcomes, such as stillbirth, neonatal death, maternal death, low birth weight and preterm births, may be available in most countries, rates of birth defects and other outcomes of interest may not. Furthermore, the accuracy and completeness of available data on background rates of pregnancy-related outcomes needs to be evaluated, particularly when the documentation may not be accurate and case ascertainment may be done in a different, non-standard manner.

Regulatory authorities need to be aware that **evidence on the safety profile of COVID-19 vaccines in pregnant women and fetuses/neonates/infants will be constantly evolving** as data are collected through research and the COVID-19 vaccination programme implementation processes. Therefore, regulators need to ensure that vaccine manufacturers and their representatives provide periodic updates on the international and regional safety profile of these vaccines in pregnancy, breastfeeding and infancy. Regulatory decisions relating to safety, made by regulatory authorities in other countries/regions may need to be reviewed for local relevance before being included in the local product information. Any changes made to the product information should be communicated to the immunization programme immediately as these may have programmatic and communications implications.

2. Routine (passive) AEFI surveillance following COVID-19 vaccination in pregnant women

Routine AEFI surveillance is the foundation of any vaccine safety surveillance system through the product cycle. The Adverse events following immunization (AEFI) module[15] in the COVID-19 vaccine safety surveillance manual outlines approaches for investigating AEFIs following COVID-19 vaccines in the general population. Chapter 6 of the *Global manual on surveillance of AEFI*[14] provides details on why AEFIs should be investigated, which AEFIs should be investigated, who should investigate, when and how to investigate AEFIs, specimens and laboratory testing, investigating AEFI clusters and the investigation of deaths following immunization under normal circumstances. The routine AEFI surveillance system should be adapted to accommodate surveillance in pregnant women, particularly if COVID-19 vaccination is offered routinely as standard care. Once an AEFI is suspected following exposure to a particular vaccine, a standard AEFI reporting form should be completed (Appendix 5.1). This will be reviewed by the national pharmacovigilance centre and, if found to be serious (death, hospitalization, disability, prolongation of hospitalization) or is of special interest, a detailed investigation by an investigation team will be conducted. Additional considerations that should be made at the reporting and investigation stages in the context of COVID-19 vaccine exposure in pregnant women are described below.

2.1. Considerations for reporting of AEFIs after administration of a COVID-19 vaccine to pregnant women

1) adjustment of the standard AEFI reporting form to indicate pregnancy (Appendix 5.1)
2) reporting an inadvertent exposure to a vaccine that is causing concern (e.g., anxiety) to the mother/primary caregiver or health care worker,
3) in the instance of an inadvertent pregnancy that is causing concern, the pregnancy should be followed up until delivery and the outcome documented.

All AEFIs are routinely reported through an established procedure using a standard AEFI reporting form (Appendix 5.1). This form has been modified to collect information on whether the vaccinee is pregnant or breast-feeding, the estimated trimester of gestational exposure and to indicate if the AEFI is related to an obstetric/neonatal/infant outcome (Appendix 5.1).

In the case of inadvertent exposure to a COVID-19 vaccine that is causing concern (e.g., anxiety in the mother/primary caregiver or health care worker), exposure in pregnancy should be registered or reported as an adverse event using the standard AEFI report, regardless of whether the pregnant woman experiences other AEFIs. The pregnant woman must be followed-up by health authorities to determine the outcome of the pregnancy (Figure 1). Proactive approaches, such as telephone follow-up by or mobile health SMS alert systems are useful to obtain information about the outcome of pregnancies after vaccine exposure.

A pregnant woman may also voluntarily opt for vaccination, if her risk-benefit assessment by her health care provider favours vaccination.

[15] World Health Organization. COVID-19 vaccines: safety surveillance manual. Available from: https://www.who.int/publications/i/item/10665338400, accessed 27 March 2021.

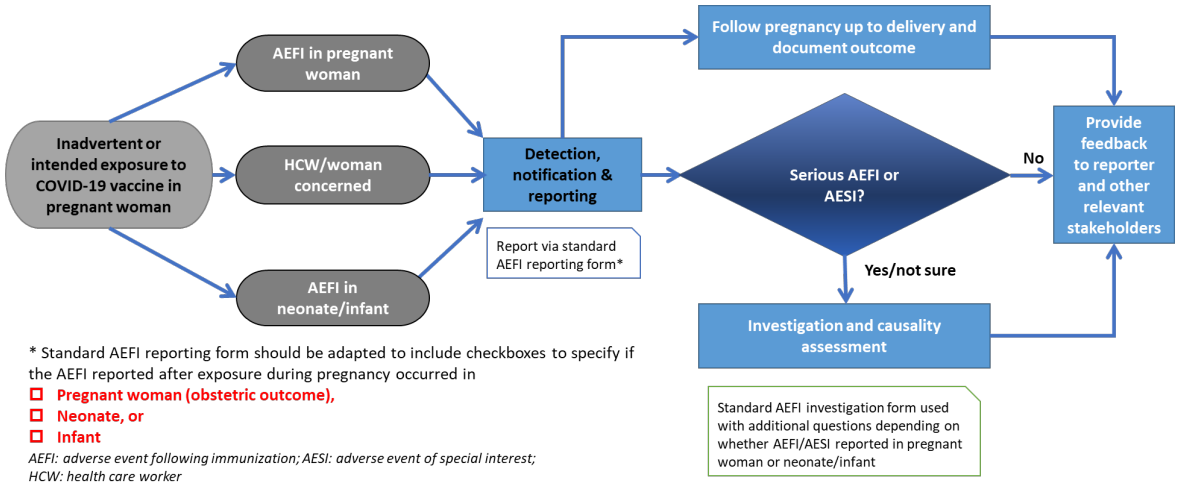

Figure 1: Routine surveillance with additional considerations for COVID-19 vaccine exposure during pregnancy

A healthy birth outcome will be reassuring and nothing more needs to be done. An adverse birth outcome should be investigated in detail promptly and assessed for causality. An AEFI should be reported if:

- the pregnancy outcome is other than a normal delivery;
- a non-pregnancy-related event occurs that the mother/primary caregiver or the health care worker attributes to COVID-19 vaccination;
- any event of concern is observed in the neonate or the mother postpartum;
- the mother/primary caregiver or the health care worker attributes any event to COVID-19 vaccination in the mother (postpartum) or the neonate/infant.

The standard AEFI reporting form should be completed and reviewed by the pharmacovigilance centre for any AEFI. A detailed investigation should be initiated for serious AEFIs and AESIs (information on investigation can be found in the Adverse events following immunization (AEFI) module[15]).

The immunization programme should collaborate with the maternal and child health services to ensure that relevant staff are familiar with reporting procedures for AEFIs, including when reporting is required. Services include primary, secondary and tertiary antenatal, perinatal and post-natal services and expanded programme on immunization (EPI) services. Once an adverse event is suspected by the mother/primary caregiver, or health care worker, the health services should be notified immediately.

2.2. Investigation of serious AEFIs and AESIs

Given that many adverse obstetric and neonatal/infant outcomes, e.g., maternal morbidity, miscarriage, stillbirth, low birth weight, are common and can have multiple aetiologies, routine investigation of all such events is not feasible. Hence, the notification and reporting of serious AEFIs events or AESIs should trigger a detailed investigation to obtain all relevant information about the patient, the vaccine and the vaccination to assess causality. On receipt of the initial AEFI report, the decision-making authority must determine whether the event:

- is a **maternal AEFI** not directly related to the pregnancy (e.g., severe injection-site reaction, anaphylaxis, Guillain-Barré syndrome);
- is an **obstetric adverse event** believed to be linked to the COVID-19 vaccination during pregnancy (see Table 1);

- Affects the **fetus (in the case of pregnancy loss), neonate or infant** suspected to be associated with vaccination during pregnancy.

In all cases the standard AEFI investigation form should be used (see Appendix 5.3 in module on AEFIs). For maternal and neonatal/infant related AEFIs additional information to collect during the investigation are listed in Appendix 5.2 and Appendix 5.3. The investigation form is also available as a software application and aide memoire which can be used to guide the investigation process. Data collected are used for causality assessment (see module on AEFIs).

Table 1: Suggested adverse events of special interest following exposure to COVID-19 vaccines in pregnancy. For standard case definition see the Brighton Collaboration website[16][17,18]

• Maternal death
• Maternal hospitalization
• Maternal thrombotic events
• Hypertensive disorders of pregnancy
• Miscarriage/spontaneous abortion
• Stillbirth
• Preterm birth
• Neonatal death
• Microcephaly
• Major congenital anomalies
• Infant death

In some countries all maternal, fetal and perinatal/neonatal deaths are investigated and reviewed through a confidential enquiry process. The immunization programme should ensure that their investigating procedures complement and support existing clinical surveillance systems. The immunization team may need to collaborate with the confidential enquiry team.

2.3. Profile of the AEFI investigation team

The profile of investigators who conduct the AEFI field investigations will be determined by the operational structure and the expertise available to the surveillance system in the country. In addition to the regular members, the investigation team should have access to obstetric, paediatric and neonatal expertise as required. It is important to include health care workers such as nurses/midwives or others with obstetric and neonatal/infant experience. If expert or additional assistance is required for investigation at the district, province or national level, such assistance should be solicited.

[16] Brighton Collaboration. COVID-19 relevant Brighton Collaboration resources and tools. Available from: https://brightoncollaboration.us/covid-19/, accessed 28 March 2021.

[17] Bonhoeffer J, Kochhar S, Hirschfeld S, Heath PT, Jones CE, Bauwens J, et al. Global alignment of immunization safety assessment in pregnancy – The GAIA project. Vaccine. 2016;34:5993-7. doi: 10.1016/j.vaccine.2016.07.006.

[18] Munoz FM, Eckert LO, Katz MA, Lambach P; Ortiz JR, Bauwens J, et al. Key terms for the assessment of safety of vaccines in pregnancy: Results of a global consultative process to initiate harmonization of adverse event definitions. Vaccine. 2015; 33: 6441-52. doi: 10.1016/j.vaccine.2015.07.112.

3. Active AESI surveillance following COVID-19 immunization in pregnant women

Active vaccine safety surveillance is recommended in addition to the routine, passive surveillance systems discussed above because there is currently a lack of data available on COVID-19 vaccine safety in pregnant women and because of the difficulty of assessing causality of adverse events at the individual level.

Active surveillance aims to detect adverse events on an ongoing basis within a defined group; e.g., pregnant women and their offspring. The events detected can be used to determine the rate of specific adverse events within the group, e.g., pregnant women exposed to vaccine, and to identify any trends or changes via a continuous pre-organized process. In some approaches, e.g., pregnancy exposure registries, the rates of these events can be compared with those in a concurrent or historical cohort of unexposed pregnant women, facilitating the assessment of risk associated with the vaccination.

Active surveillance involves the systematic collection, analysis, and interpretation of data and is especially useful in enhancing passive safety surveillance following the introduction of new vaccines. The specific objectives of immunization safety surveillance are described in the *WHO global manual on Surveillance of adverse events following immunization*[14] and the monitoring and responding to adverse events of special interest (AESI) module in this guide.

Pregnancy exposure registries and prospective cohorts of pregnant women that include women receiving antimalarial, antiretroviral, or antiepileptic treatment, that are already in place could be adapted or expanded to collect information on COVID-19 vaccine exposure. Where conditions and resources allow, a dedicated COVID-19 vaccine pregnancy exposure registry could be implemented. Multinational surveillance consortia involved in COVID-19 infection surveillance in pregnancy could be expanded to include COVID-19 vaccine safety surveillance.[19] In addition, data sharing and data pooling across multiple countries can create larger cohorts that are needed to assess the risk of rare events. If data are going to be pooled there should be a common data exchange standard with standardized definitions for key outcomes (see section 3.1) and the analyses must take into consideration the heterogenicity of data from different settings.

3.1. Standardized case definitions.

It is important that comparable data are collected in the different programmes to enable data harmonization and comparisons. This is necessary at every level of assessment. When a case definition is not available, a standardized definition should be developed and used. This is particularly relevant for rare events (e.g., major congenital anomalies) where combined cohort data may be necessary to ensure analyses are sufficiently powered. Standardized case definitions for obstetric and neonatal events for safety monitoring of vaccines in pregnant women have been developed by the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project, managed by Brighton Collaboration (www.brightoncollaboration.org).[17] Definitions are available for some identified AESI for COVID-19 vaccines.[20].The guidance below relates to the surveillance of obstetric and neonatal events.

[19] COVI-PREG: International COVID-19 and pregnancy registry. Available from: https://www.chuv.ch/fr/dfme/dfme-home/recherche/femme-mere/materno-fetal-and-obstetrics-research-unit-prof-baud/covi-preg, accessed 28 March 2021.
[20] Safety Platform for Emergency Vaccines. D2.3.1 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes. Available from https://brightoncollaboration.us/wp-content/uploads/2020/11/SO2-D2.3.1_Tier-1-AESI-ICD-9-10-CM-and-MedDRA-Codes-.pdf, accessed 28 March 2021.

The surveillance for general AESI are described in the monitoring and responding to adverse events of special interest (AESI) module in this guide.

At present (March 2021) there is insufficient evidence from animal studies and clinical trials to guide the definition of AESI specific to pregnant women vaccinated with a COVID-19 vaccine. A suggested list based on expert opinion is given in Table 1. It may not be feasible to monitor all of them. In any active surveillance system, it will be necessary to prioritize surveillance based on relevant elements that are routinely documented and collected during clinical care, many of which are already recorded in delivery or labour ward registers, or as programme indicators. Case detection must be compatible with the diagnostic capacity of the setting, while remaining sensitive and specific. As data accumulate with the increased use of COVID-19 vaccines, AESIs relating to maternal exposure may be identified and this guidance will be updated accordingly.

3.2. Methods for active safety surveillance

Active surveillance is more complex and costly to implement than spontaneous reporting systems. It requires leadership, clearly identified responsibilities for stakeholders, and resource commitment for regular active assessment of outcomes. There are several methods that can be used for active surveillance of COVID-19 vaccine exposure in pregnant women, and the choice will depend on the local availability of resources and existing infrastructure. Resources made available for the COVID-19 vaccination programmes may present opportunities for strengthening systems, training and capacity building (particularly infrastructure/systems for standardized quality data collection) and for encouraging collaboration between programmes. Ideally, active surveillance systems for COVID-19 vaccine safety monitoring should be integrated into existing public health and pharmacovigilance platforms.

3.2.1. General principles

The use of **sentinel sites** for focussed data collection may address some logistical and resource challenges. Sentinel sites are treatment/health care facilities identified for data collection, selected for their geographical location and ability to diagnose accurately and report high-quality data. These sentinel sites should be located in a range of regions, and cover different target populations as well as different COVID-19 vaccine platforms.

It will be important to collect **data prospectively** to minimize recall and reporting bias, and to enable the calculation of event rates.

Knowledge of **background rates** of adverse events is desirable. This information is often lacking or incompletely collected, and the available knowledge will vary across settings. The Safety in Pregnancy: the *Global Vaccine Safety Multi-Country Collaboration* project completed data collection for the assessment of the applicability of GAIA case definitions for selected neonatal outcomes (congenital microcephaly, low birth weight, neonatal death, neonatal infection, preterm birth, small for gestational age and stillbirth) in August 2020 and the results will be available soon.[21] These results may help to determine background rates and provide tested methodology to determine these rates (including definition of denominators). Active surveillance strategies at sentinel sites can be designed to include data collection for unvaccinated pregnant women to enable rates in vaccine-exposed and -unexposed groups to be calculated and compared.

Outcome events must have **standardized definitions** and **ascertainment should be optimized,** although it is possible that the vaccination and the outcome will be recorded in different health care

[21] World Health Organization. 2021. Safety in Pregnancy: the Global Vaccine Safety Multi-country Collaboration Project. Available from: https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/pregnancy-and-lactation/mcc, accessed 28 March 2021.

services, e.g., vaccination in primary care or as part of a mass vaccination campaign and outcome events presenting to obstetric or other health care services.

The exposed group will be all pregnant women with a date of conception before or within 30 days of vaccination.

3.2.2. Prospective cohort studies

3.2.2.1. Pregnancy exposure registries

Pregnancy exposure registries (PERs) are prospective surveillance systems in which women are enrolled at their first antenatal care visit, and then followed through to pregnancy outcome and beyond. Information on vaccination during pregnancy, and outcomes, is actively collected in a standardized and systematic manner. If possible, *all* women presenting for antenatal care at the sentinel site should be considered for inclusion to determine event rates in both vaccinated and unvaccinated women. Individual consent for the use of the data for the purposes of research and surveillance is encouraged, although in certain situations, the need for informed consent can be waived. Such situations include when the research poses minimal risk to the participants; where the rights and welfare of the participants are not compromised; where the research could not practicably be carried out without the waiver or alteration; and whenever appropriate, the participants will be provided with additional pertinent information after participation. The conditions for such a waiver would need to be discussed with the relevant ethics committee(s) with a clear explanation to justify the request for a waiver.

Primary care sentinel sites representing a population from a defined geographical area, with a clear referral pathway are preferred. The cohort should be as diverse as possible and not limited by maternal age, maternal health status, or gestational age at presentation.

Depending on resources and the quality of existing record keeping, various data elements can be considered for collection in a pregnancy exposure registry, or data collection can be limited to a few selected clinical variables. Training to improve clinical record-keeping and outcome ascertainment using standardized case definitions should be conducted. All live and stillborn neonates should be examined and weighed, and any external major congenital anomalies noted by surface examination, and, if possible, photographed or referred for expert review (with consent). Common adverse birth outcomes such as low-birth weight, preterm birth and small for gestational age should be recorded and their rates compared between exposure groups to identify any differences in risk.

PERs can be used to assess data quality, describe the epidemiology of exposure and outcomes in the cohort, and to determine and compare event rates, if the numbers are appropriate for this. It could be possible to incorporate COVID-19 vaccine safety surveillance in existing PERs for other health interventions, such as antiretrovirals, antimalarials and other vaccines.

3.2.2.2. Cohort event monitoring exposure during pregnancy

Cohort event monitoring involves enrolling pregnant women who have received a COVID-19 vaccine into a prospective cohort, and systematically recording data on all adverse events that occur over a given period. Importantly, there is no direct control or comparator group. The length of the period, or risk window, will depend on the characteristics of the defined endpoints. For example, if obstetric outcomes are of interest, they will be followed until the end of their pregnancy; and if delayed maternal events and infant events, including their growth and development, are of interest, they will be followed up to 12 months postpartum. Prevalence and rates will have to be compared to historical data or background rates seen in other studies in similar populations. The event rates can be calculated because the numerator, i.e., number of cases, and the denominator, i.e., number vaccinated; will be available.

3.2.2.3. Nested case-control studies

Within an existing enumerated cohort, e.g., Vaccine Safety Datalink or a PER, women with an outcome of interest can be identified, together with a specified number of matched controls who did not present the event of interest. The vaccination status of the cases and controls will then be determined. This study design is useful when the outcomes are rare or when the exposure of interest is difficult to ascertain. Measures of association between exposure and outcome can then be determined, but the risk or event rates cannot.

3.2.3. Record linkage studies – retrospective cohorts

Electronic record linkage studies, for example using a unique patient identifier, offer many advantages. First, encounters and events per individual can be linked across sites, time periods, and services. This addresses the challenge that patients may present to a health care site for the outcome event that is different from the health care site where they were exposed (vaccinated). Second, if it is possible to link the records for mothers and their infants, exposure data in the mother (vaccination) can be linked to outcome data for their infant (hospital admission, death, developmental delay). Established health information systems can facilitate the definition of large cohorts with data for multiple outcome events. Even where individual-level data are unavailable, aggregate data can be used to compare outcome event rates in exposed or unexposed groups. Systems with the capacity to link records are, therefore, needed to successfully implement sustainable vaccine safety monitoring systems.

The use of novel technologies, such as 'mHealth' and mobile devices, can be explored to facilitate data collection in countries with limited health information systems.

Further information on data sharing, repositories and timelines are discussed in the data management module in this manual.

4. Communication

Ongoing communication between various programmes, including the immunization programme, the maternal and child health programme, the national regulatory authority, and the different levels of government is vital to ensure that there is a coordinated approach to maintaining confidence in the immunization programme. A communication strategy for addressing safety concerns around COVID-19 vaccination will require input from relevant communication experts and should be informed by research into public knowledge, attitudes, beliefs and practices.[22]

Before offering vaccines to pregnant women and women of child-bearing age who may be or may become pregnant, they should be routinely informed about the benefits and anticipated potential risks of the vaccine, the risks of the disease the vaccine is trying to prevent. In addition, they should be asked about their pregnancy status, trimester of pregnancy, as well as other information about the presence of any contra-indications.

The importance of employing the key principles of clarity, empathy, openness and transparency, when communicating about COVID-19 vaccine safety to women who are intentionally or inadvertently vaccinated during pregnancy cannot be over-emphasised. The safety communication module in this manual provides useful recommendations and resources for supporting good communication practices.[15] Pregnant women need to take into consideration the risks of COVID-19 disease, as well as the risk of vaccination, not just for themselves, but also for their unborn child. The communication strategy for pregnant women should also solicit the support of antenatal care providers, women's rights and gender equity advocates, midwifery and nursing associations, as well as other relevant civil society organizations.

Both immunization and maternal and child health staff need to be trained on how to counsel women who are inadvertently exposed to COVID-19 vaccines while pregnant. This should be based on the most up-to-date information available on the safety profile of the particular COVID-19 vaccine received. Information resources for pregnant women and clinicians, such as medicine and teratology information centres, poison control centres and COVID-19 hotlines, need to be prepared to provide accurate and up-to-date information on the safety of available vaccines.

As with all vaccinees, counselling women at the time of vaccination on the expected common minor (usually self-limiting) reactions they may experience after vaccination, will provide them with the information they need to prepare for such events should they occur. It will also help them to recognise events that are unexpected or that may require further clinical care. Communication materials that address frequently asked questions around the potential benefits and risks of the vaccines, specifically targeting pregnant women, could be made available on social media platforms as well as at facilities where pregnant women, and women of child-bearing age who are planning a pregnancy, are likely to receive a COVID-19 vaccine.

[22] World Health Organization. (2016). How to implement influenza vaccination of pregnant women: An introduction manual for national immunization programme managers and policy makers. Available from: https://apps.who.int/iris/handle/10665/250084, accessed 29 March 2021.

5. Appendices

5.1. Appendix 5.1

Standard reporting form for adverse events following immunization (AEFI)

AEFI reporting ID number: **Dec 2020**

STANDARD REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFIs)

***Patient name or initials*:** ***Patient's full Address*:** Telephone: Sex: ☐ M ☐ F Pregnant – Yes / No If pregnant – Trimester: I ☐ II ☐ III; ☐ Breast-feeding: Yes No ☐) ***Date of birth (DD/MM/YYYY)*: _ _/_ _/_ _ _ _** *OR Age at onset:* ☐☐*Years* ☐☐ *Months* ☐☐ ☐ *Days* *OR age Group:* ☐ 0 <1 year ☐ 1-5 years ☐ >5-18 years ☐ >18–60 years ☐ >60 years	***Reporter's Name*:** Institution: Designation & Department: Address: Telephone: E-mail: Date patient notified event to health care system (DD/MM/YYYY): _ _/_ _/_ _ _ _ Today's date (DD/MM/YYYY): _ _/_ _/_ _ _ _

Health care facility (or vaccination centre) name:									
Vaccine							***Diluent***		
Name of vaccine (Generic)	**Brand name incl. name of manufacturer*	**Date of vaccination*	**Time of vaccination*	Dose (1st, 2nd, etc.)	**Batch/ lot number*	Expiry date	**Batch/ lot number*	Expiry date	Time of recon sti-tution

Adverse event(s): ☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint* ☐ Seizures ☐ *febrile* ☐ *afebrile* ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever≥38°C ☐ Other (specify)..... ☐ Obstetric/ neonatal/infant adverse outcome (specify)_____ Date & time AEFI started (DD/MM/YYYY): __ __/__ __/__ __ __ __ __ ☐☐ h ☐☐min	Describe AEFI (signs and symptoms):
Serious: Yes / No: If Yes ☐ death ☐ life-threatening ☐ disability ☐ hospitalization ☐ congenital anomaly ☐ Other important medical event (Specify_____) ***Outcome:*** ☐ recovering ☐ recovered ☐ recovered with sequelae ☐ not recovered ☐ unknown ☐ Died: if checked, date of death (DD/MM/YYYY): __ __/__ __/__ __ __ __ Autopsy done: ☐ yes ☐ no ☐ unknown	
Past medical history (including history of similar reaction or other allergies), concomitant medication and dates of administration (exclude those used to treat reaction), other relevant information (e.g. other cases)***.*** *Use additional sheet(s) if needed:*	

501

502 *First Decision making level to complete:*

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

503 *National level to complete:*

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

504 **Compulsory field*

505

5.2. Appendix 5.2

Recommended additional information to collect for investigations of an obstetric-related AEFI following vaccination of a pregnant woman

Oct 2020

Additional information to collect for investigations of an obstetric-related AEFI following vaccination of a pregnant woman

Aim of the investigation: To determine if there is an association between the reported obstetric AEFI and the vaccine administered during pregnancy.

Additional relevant information from the mother prior to immunization:

Confirmation of the pregnancy by test ☐ Yes/ ☐ No

Gestational age at the time of immunization: _____ weeks or trimester ☐ 1st / ☐ 2nd / ☐ 3rd

Gestational age assessed by:

☐ history (LMP) / ☐ early US (before 24 weeks) / ☐ late US (after 24 weeks) / ☐ fundal height

Past obstetric history:

Parity / obstetric score, Y/N and number:

gravidity _____ parity _____live_____ miscarriage_____termination of pregnancy _____ stillbirth_____ preterm _____

Maternal medical complications in prior pregnancies: ☐ hypertensive disorders [e.g. eclampsia/HELLP syndrome], ☐ gestational diabetes, ☐ premature delivery, ☐ LBW or SGA infants, ☐ neonatal death ☐ other, specify _____

Current pregnancy

Conditions that increase the risk for obstetric complications during this pregnancy: ☐ incompetent cervix, ☐ placenta previa, ☐ oligo-polyhydramnios ☐ Other, specify _____

Maternal nutritional status: ☐ well-nourished ☐ undernourished ☐ overweighed/obese

Maternal health status at the time of vaccination: ☐ normal, ☐ morbidity present (specify)- _____ ; document maternal vital signs and presence/absence of signs and symptoms of acute or active disease in the box below:

Maternal vital signs and presence/absence of signs and symptoms:

Fetal health status at the time of vaccination: normal, ☐ morbidity present (specify)- _____ ; document live fetus, and presence/absence of fetal anomalies (based on obstetric examination, prenatal testing and obstetric ultrasound when available) in the box below:

Live fetus, and presence/absence of fetal anomalies:

Past history of prior adverse reactions to vaccines before pregnancy ☐ yes/ ☐ no

Details of adverse reactions to past vaccination:

Administration of other vaccines during pregnancy ☐ yes/ ☐ no. If yes, specify _____

Administration of concomitant medications, including immunomodulatory agents during pregnancy ☐ yes/ ☐ no.

If Yes, indication/ drug names/ dates:

Existing medical conditions (prior to pregnancy) _____

Active/recent maternal infection with HIV, Hep B, Hep C, TB, malaria, STI, maternal group B Streptococcus, other chronic infections (results of prenatal testing for these) ☐ yes/ ☐ no. If yes, specify _____

Maternal use/abuse of alcohol, drugs, use of nutritional or other supplements ☐ yes/ ☐ no. If yes, specify _____

Receipt of blood products one month before or after vaccination ☐ yes/ ☐ no. If yes, specify _____

Rh isoimmunization ☐ yes/ ☐ no/ ☐ unknown

Other nonmedical events that could have led to the adverse event, e.g., trauma, occupational or environmental factors. ☐ yes/ ☐ no. If yes, specify _____

Additional findings to be verified on clinical examination of the woman (Add additional sheet(s), if necessary):

Vital signs:

- Complete physical examination

Examination of injection site for oedema, induration, fluctuance, necrosis, and regional lymphadenopathy

Obstetric examination:

- Doppler or ultrasound fetal heart beat
- Fundal height

Clinical signs and symptoms consistent with active/new medical condition including infectious and non-infectious conditions: ☐ yes/ ☐ no. If yes, specify _____

Additional laboratory tests to be done to assist with diagnosis and identify possible cause of the AEFI during pregnancy or postpartum **(Add additional sheet(s), if necessary)**:

- Basic haematology, peripheral smear, chemistries (hepatic and renal function), urine
- Serologies for specific pathogens
- Other immunologic tests (antibody response to vaccine, cellular immunity, cytokines, inflammatory markers, etc)
- Viral and bacterial pathogen identification from pertinent sources by appropriate stains, cultures, molecular techniques or serologies as available
- Histopathology of relevant tissues, including the placenta

If autopsy is conducted – special forensic tests recommended (Add additional sheet(s), if necessary):

For the mother:

- Gross anatomy
- Histopathology
- Pathogen identification through appropriate stains, cultures, or molecular methods

For the fetus/neonate/infant:

- Gross anatomy
- Histopathology
- Pathogen identification through appropriate stains, cultures, or molecular methods

510 HELLP: haemolysis, elevated liver enzymes, low platelet count; LBW: low birth weight; LMP: last
511 menstrual period; SGA: small for gestational age; STI: sexually transmitted disease; US: ultrasound

512

5.3. Appendix 5.3:

Recommended additional investigations for AEFI in a neonate/ infant following vaccination of the mother during pregnancy or breastfeeding

Recommended additional investigations for AEFI in a neonate/infant following vaccination of the mother during pregnancy or breastfeeding
Aim of the investigation: To determine if there is an association between the adverse event reported in the neonate/infant when vaccine administered to mother during pregnancy or lactation.
Additional relevant information on the neonate/infant Date of delivery: Type of delivery: Place of delivery (home/institutional): Delivery conducted by: Complications during labour/ delivery: Birth weight (grams): Birth length (cm): Head circumference (cm): Gestational age at birth (weeks): Method of assessing gestational age at birth: ☐LMP; ☐ early ultrasound <24 weeks; ☐ late ultrasound >24 weeks; ☐ Ballard / Dubowitz / other gestational as per dating scan APGAR Score: 1 min ☐ 5 min☐

Additional findings to be verified on clinical examination of the infant (Add additional sheet(s), if necessary):

- Vital signs
- Physical examination of the neonate/infant (standard full system check noting any major or minor anomalies)
- Complete physical examination

Special test(s) done:

e.g. full blood count for thrombocytopenia if petechial rash, bilirubin if jaundiced.

Clinical signs and symptoms consistent with active/new medical condition including infectious and non-infectious conditions

Additional laboratory tests to be done to assist with diagnosis and identify possible cause of the adverse event during pregnancy or postpartum (Add additional sheet(s) if necessary):

- Basic haematology, peripheral smear, chemistries (hepatic and renal function), urine
- Serologies for specific pathogens
- Humoral and cellular responses to vaccine (antibodies, cytokines, inflammatory markers, etc)
- Viral and bacterial pathogen identification from pertinent sources by appropriate stains, cultures, molecular techniques or serologies, as available
- Histopathology of relevant tissues, including the placenta

If autopsy is conducted – special forensic tests recommended (Add additional sheet(s) if necessary):

For the neonate/infant

- Gross anatomy
- Histopathology
- Pathogen identification through appropriate stains, cultures, or molecular methods