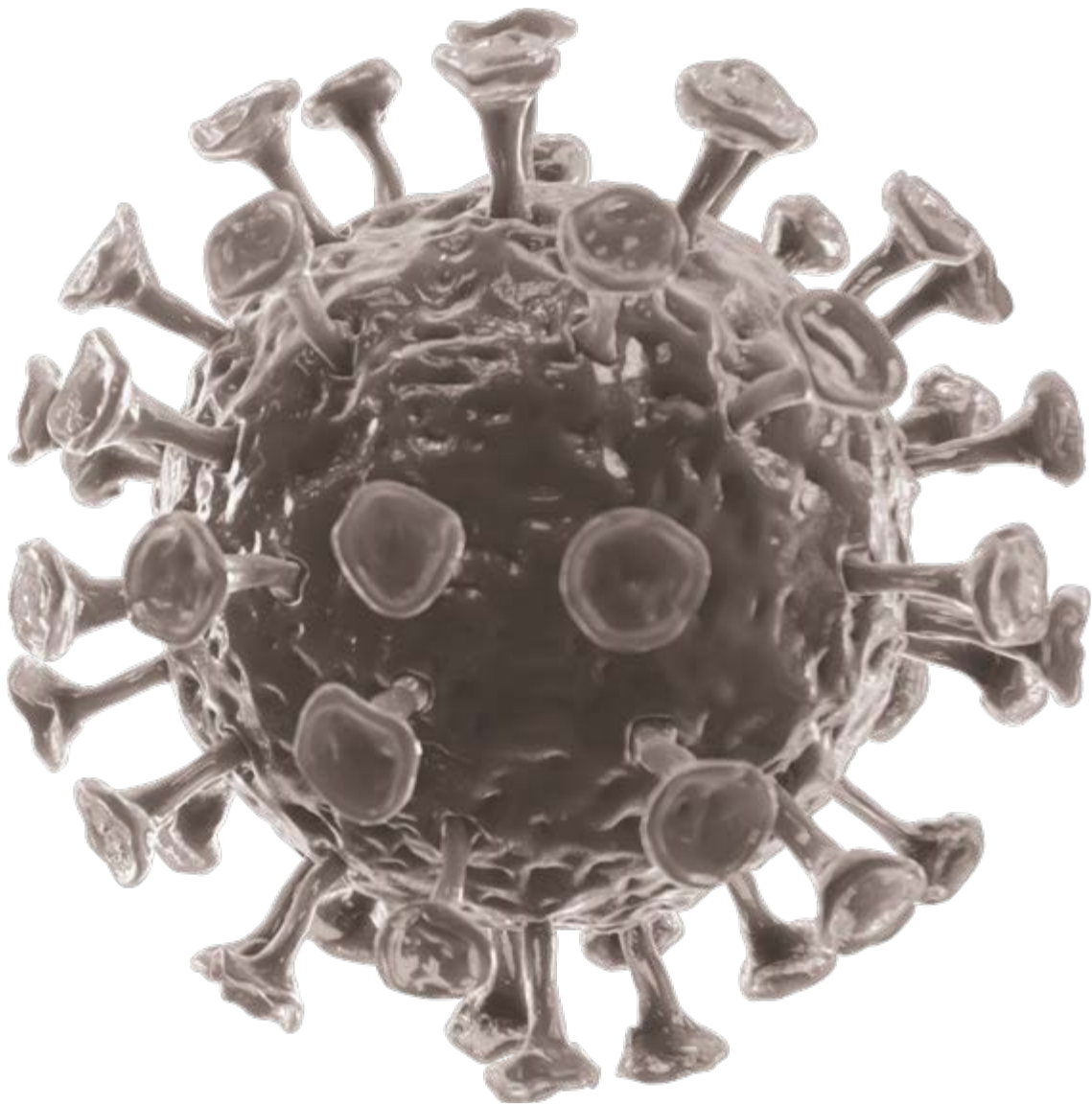COVID-19 VACCINES:

SAFETY
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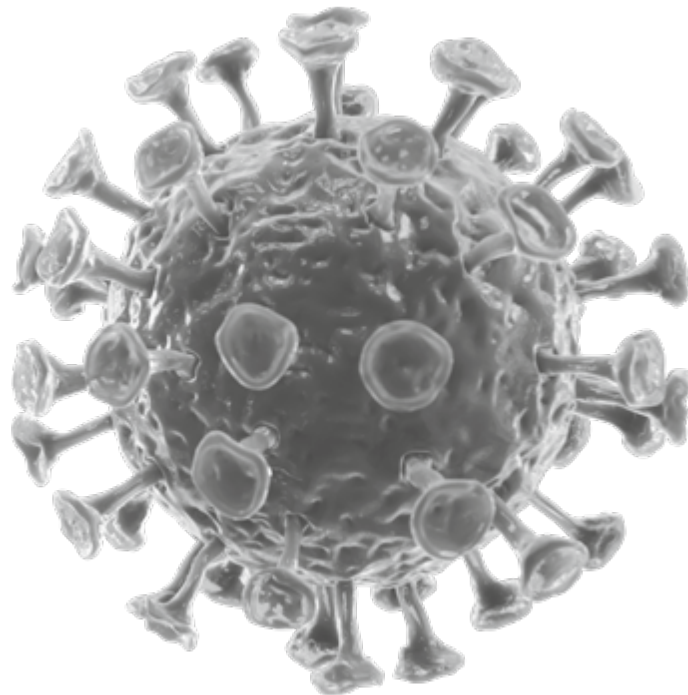## MODULE: SAFETY SURVEILLANCE OF COVID-19 VACCINES IN PREGNANT AND BREASTFEEDING WOMEN

World Health Organization

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

MODULE: SAFETY SURVEILLANCE OF COVID-19 VACCINES IN PREGNANT AND BREASTFEEDING WOMEN

World Health Organization

Contents

Key points

- Evidence suggests that pregnant women with COVID-19 are at higher risk of developing severe disease compared to non-pregnant women of reproductive age.
- 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, infant or child suspected to be associated with COVID-19 vaccination during pregnancy.
  - late/delayed adverse event in a child believed to be linked to 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 immunization 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.

01 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, evidence suggests that pregnant women with COVID-19 are at higher risk of developing severe disease compared to 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.[4,5,6,7]

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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   Raschetti R, Vivanti A.J, Vauloup-Fellous C. et al. Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun. 2020;11:5164. doi.org/10.1038/s41467-020-18982-9.

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.

Women of reproductive age represent a 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. 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.

To date, pregnant women have not been included in Phase II and III clinical trials of COVID-19 vaccines. 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. Section 1.2 summarizes WHO's current recommendations for COVID-19 vaccination in pregnant and breastfeeding 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 maternal and neonatal outcomes.

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

At present (April 2021), the WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends that pregnant women can receive COVID-19 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 a case by case basis after consultation between the woman and her health care provider. To help pregnant women decide, they should be provided with information about the risks of COVID-19 in pregnancy, the likely benefits of vaccination in the local epidemiological context, and the current limitations of the safety data for the vaccines in pregnant women.

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8 Strategic Advisory Group of Experts on Immunization (SAGE). COVID-19 vaccines technical documents. Available from: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials, accessed 26 May 2021.

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.[9] 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.[10] WHO does not recommend discontinuing breastfeeding after vaccination.

1.3   Pregnancy-and vaccine safety surveillance

Maternal immunization require special considerations which influence the design of surveillance systems.

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

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 critical **to *the assessment of the biological plausibility of an AEFI***. The **timing of exposure during the pregnancy** can affect the possible outcomes. Exposure to teratogens 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.[11] 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.

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

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9   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.

10   Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol. 2021 Published online ahead of print. doi:10.1016/j.ajog.2021.03.023

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

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.[12] Therefore, there can be a significant delay between the vaccine exposure and the identification and assessment of the outcome. Consequently, women exposed to COVID-19 vaccine should be followed up to establish the pregnancy outcome and assess the health of the neonate. 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;
- 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 maternal/neonatal/infant outcomes should consider the possibility of alternative causes. 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. 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.

It is particularly challenging to monitor the benefits and risks of immunization programmes in pregnant women and to communicate about this because several common health outcomes may be assessed as both benefits and risks and this assessment may change over time.[13] For example, the stillbirth rate could be reduced by immunization, if the vaccine reduces infections that lead to stillbirth. However, stillbirths will still occur and may be perceived and reported as AEFIs. The impact of immunization on mortality rates may not be detectable on the populational level, particularly early after immunization programme implementation, although pregnancy complications, such as stillbirth, will be registered. Hence, early benefit-risk analyses will be difficult and could lead to erroneous decision about the benefit-risk balance of an immunization programme, independently of any causal relationship between the complication and immunization.

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12 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.

13 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(49):5993-5997. doi: 10.1016/j.vaccine.2016.07.006. 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.

As a result of these unique conditions, attributing the cause of an AEFI to immunization in pregnancy for individual cases is extremely challenging, and often not possible. Characterization of safety concerns requires well-designed epidemiological studies to be conducted, hence the critical role of active surveillance systems for the safety assessment of maternal immunization in a given population. Ideally, active surveillance should aim to compare the risks of adverse maternal and birth outcomes, e.g., maternal morbidity, 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 safety signal that warrants further epidemiological study. Safety 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 (e.g., if the investigation suggests strong evidence against a causal association), and also informs the need for further investigation of the safety signal 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 (e.g. abscess at injection site) should be reported and processed through the routine AEFI reporting system, as recommended. The pregnancy should be noted in the reports. The guidance in this current module on pregnancy is for potential AEFIs relating to maternal 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 maternal or neonatal/infant serious AEFI or an adverse event of special interest (AESI), suspected to be related to the immunization 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 including cohort studies with longer durations of follow-up, in addition to routine spontaneous reporting. Section 3.2 provides an overview of different active surveillance methods that can be used to investigate AEFIs for maternal, neonatal and infant outcomes. Surveillance strategies adopted by individual countries will depend on local resources, infrastructure and diagnostic capacity.

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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.

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 and processes for the detection and reporting of 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 maternal or neonatal/infant outcomes are not systematically or routinely collected and therefore, these background rates are not known. In these countries, the risk of erroneously attributing adverse maternal 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 maternal and neonatal/infant outcomes of interest. Although national statistics for 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. Please refer to the Regulatory reliance and work-sharing module in this manual for safety surveillance specific considerations under different scenarios, i.e., Emergency Use Listing (EUL) product or licenced product.

02 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 <u>Adverse events following immunization (AEFI)</u> 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 designated authority and, if it is 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 modified standard AEFI reporting form (Appendix 5.1). This form has been modified to collect information on whether the vaccine recipient is pregnant or breast-feeding, and to indicate if the AEFI is related to a maternal/neonatal/infant outcome (Appendix 5.1).

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

In the case of inadvertent or intended exposure to a COVID-19 vaccine that is causing concern (e.g., anxiety in the pregnant woman/primary caregiver or other health care worker), exposure during pregnancy should be registered or reported as an adverse event using the standard AEFI reporting form, 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 (Fig 1). Proactive approaches, such as telephone follow-up or mobile health SMS alert systems are useful to obtain information about the outcome of pregnancies after vaccine exposure. All women of reproductive age should be informed about this mechanism so that they can report concerns and can be reached if they find out that they were pregnant at the time of receiving the COVID-19 vaccine.

Fig 1: Routine surveillance with additional considerations for COVID-19 vaccine exposure during pregnancy
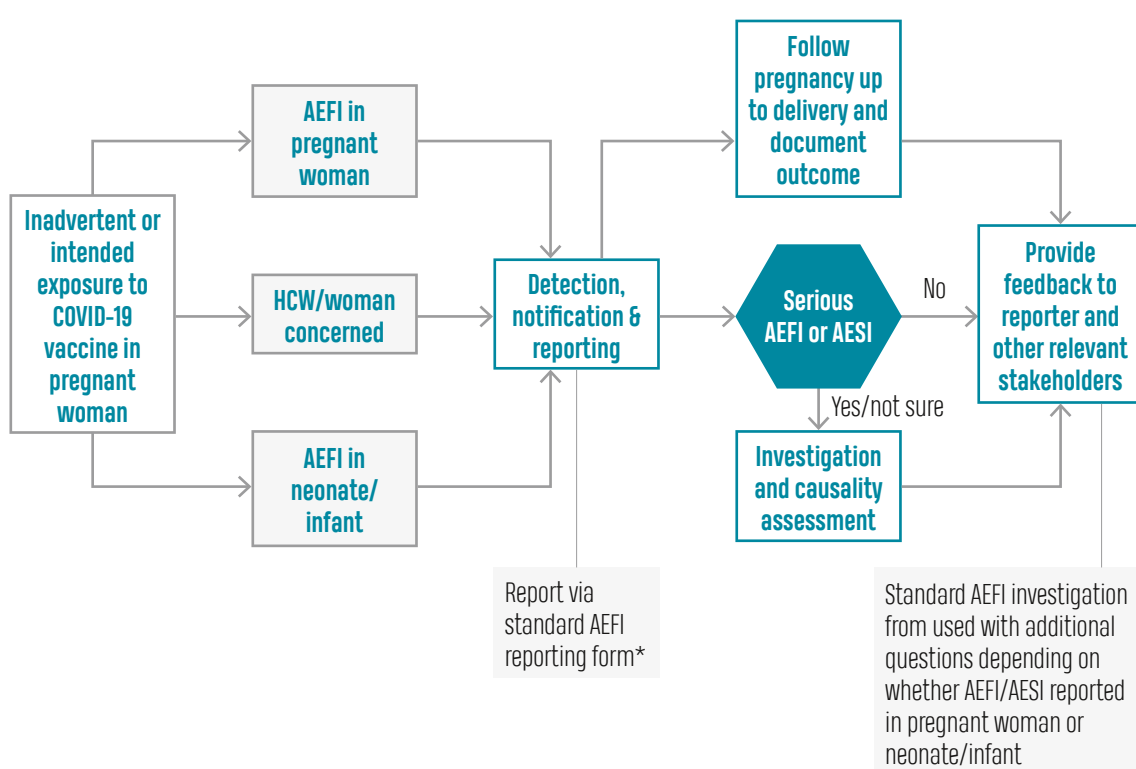
* Standard AEFI reporting form should be adapted to include checkboxes to specify if the AEFI reported after exposure during pregnancy occurred in:

☐ **Pregnant woman (obstetric outcome),**
☐ **Neonate, or**
☐ **Infant**

AEFI: adverse event following immunization; AESI: adverse event of special interest; HCW: health care worker

An AEFI should be reported if it is:

- an obstetric or non-obstetric adverse event that the pregnant woman/primary caregiver or the health care worker attributes to COVID-19 vaccination;
- any adverse event of concern observed in the neonate/infant that the pregnant woman/primary caregiver or the health care worker attributes to COVID-19 vaccination received by the woman during pregnancy.

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). For maternal and neonatal/infant AEFI and AESI, specific details are provided in section 2.2.

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, neonatal 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 maternal 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 suspected to be caused by COVID-19 vaccination of the mother during pregnancy 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 a **maternal adverse event** suspected to be associated with 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). Additional information that should be collected during the investigation of maternal and neonatal/infant AEFIs are listed in Appendix 5.2 and Appendix 5.3 respectively. 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 AESI
— 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 maternal, fetal and perinatal/neonatal death investigation processes. 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 experienced obstetricians, paediatricians and neonatologists as required, if available. It is also 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.

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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.

03 Active surveillance following COVID-19 immunization in pregnant women

Active vaccine safety surveillance is recommended in addition to the routine, passive surveillance or spontaneous reporting 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*[15] and the surveillance aspects are described in <u>monitoring and responding to adverse events of special interest (AESI)</u> module in this manual.

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.

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19 COVI-PREG: International COVID-19 and pregnancy registry. Available from: <u>https://www.chuv.ch/fr/dfme/dfme-home/recherche/femme-mere/materno-fetal-and-obstetrics-research-unit-prof-baud/covi-preg</u>, accessed 28 March 2021.

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 maternal 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 maternal and neonatal events. 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 (April 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 systems are more complex and costly to implement than spontaneous reporting systems. They require leadership, clearly identified responsibilities for stakeholders, and resource commitment for regular active detection, reporting and 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.

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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.

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 *WHO 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.[21] These results may help to determine background rates at sentinel sites 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 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 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 practically be carried out without the waiver or alteration; and whenever appropriate, the participants will be provided with additional pertinent information after

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21 WHO Global Vaccine Safety Multi Country Collaboration (WHO GVS MCC). 2021. WHO GVS MCC Dashboard – minimum detectable risk. Available from: https://apps.p-95.com/WHO/, accessed 26 May 2021.

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, longer if possible. Prevalence and rates will have to be compared to historical data or concurrent data from women not exposed to the vaccine 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.

04 Communication

Ongoing communication between the various stakeholders, including the immunization programme, the maternal and child health programme, the national regulatory authority, and the different levels of the 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 COVID-19 vaccines to pregnant women and women of child-bearing age who may be or may become pregnant, women should be routinely informed about the benefits and anticipated potential and known risks of the vaccine versus, 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 to assess 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. 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.

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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.

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 address these 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 benefits and potential 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.

05 Appendices

Appendix 5.1

Standard reporting form for adverse events following immunization (AEFI)

AEFI reporting id number:

STANDARD REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFIs)

<table>
<tr><td colspan="2"></td><td colspan="2" align="right">**Dec 2020**</td></tr>
<tr><td colspan="2">*Patient name or initials*:</td><td colspan="2">*Reporter's Name*:</td></tr>
<tr><td colspan="2">*Patient's full Address*:</td><td colspan="2">Institution: _____</td></tr>
<tr><td colspan="2">Telephone: _____</td><td colspan="2">Designation & Department: _____</td></tr>
<tr><td colspan="2">Sex: ☐ M ☐ F</td><td colspan="2">Address: _____</td></tr>
<tr><td colspan="2">Pregnant – ☐ Yes ☐ No</td><td colspan="2">_____</td></tr>
<tr><td colspan="2">Breast-feeding: ☐ Yes ☐ No</td><td colspan="2">Telephone: _____</td></tr>
<tr><td colspan="2">*Date of birth (DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __</td><td colspan="2">E-mail:_____</td></tr>
<tr><td colspan="2">OR Age at onset : ☐☐ Years ☐☐ Months ☐☐☐ Days</td><td colspan="2">Date patient notified event to health care system (DD/MM/YYYY): __ __ / __ __ / __ __ __ __</td></tr>
<tr><td colspan="2">OR Age Group: ☐ 0 < 1 year ☐ 1- 5 years
☐ > 5 years - 18 years ☐ > 18 years – 60 years ☐ > 60 years</td><td colspan="2">Today's date (DD/MM/YYYY): __ __ / __ __ / __ __ __ __</td></tr>
</table>

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 reconstitution

<table>
<tr>
<td>
Adverse event (s):

☐ Severe local reaction | ☐ Abscess ☐ >3 days ☐ *beyond nearest joint*

☐ Seizures | ☐ Encephalopathy ☐ *febrile* ☐ *afebrile*

☐ Fever ≥38°C | ☐ Sepsis | ☐ Toxic shock syndrome

☐ Thrombocytopenia | ☐ Anaphylaxis

☐ Other (specify) _____

☐ Maternal / neonatal / infant adverse outcome (specify) _____

Date & Time AEFI started (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ ☐☐ Hr ☐☐ Min
</td>
<td>
Describe AEFI (signs and symptoms):
</td>
</tr>
</table>

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 incl. vaccinations and dates of administration (exclude those used to treat reaction), other relevant information (e.g. other cases). *Use additional sheet(s) if needed*:

First Decision making level to complete:

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

National level to complete:

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

*Compulsory field

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: │ │ └───┘

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

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

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

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; ☐ ate 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

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

World Health Organization