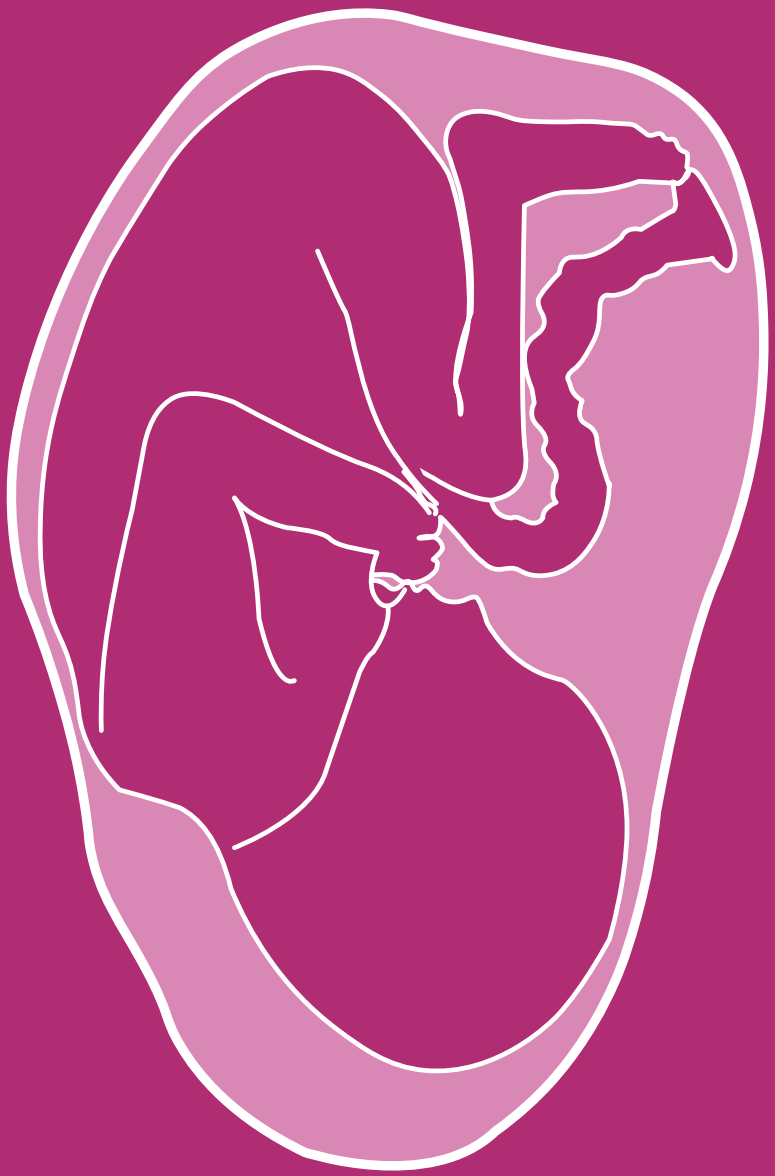
Estimation of background rates of adverse events of special interest in neonatal outcomes

Preterm births, stillbirths, neonatal deaths and low birthweight



World Health Organization

Estimation of background rates of adverse events of special interest in neonatal outcomes

Preterm births, stillbirths, neonatal deaths and low birthweight

World Health Organization

Estimation of background rates of adverse events of special interest in neonatal outcomes: preterm births, stillbirths, neonatal deaths and low birthweight

ISBN 978-92-4-011377-0 (electronic version)
ISBN 978-92-4-011378-7 (print version)

Suggested citation. Estimation of background rates of adverse events of special interest in neonatal outcomes: preterm births, stillbirths, neonatal deaths and low birthweight. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Contents

Acknowledgements

The development of this protocol was led by the Pharmacovigilance team at the World Health Organization (WHO) Department of Regulation and Prequalification. The following deserve special recognition for the roles played in the development of the protocol: Noha Iessa, who coordinated the drafting and oversaw development of the protocol, Annick Janin, Madhava Balakrishnan, Smaragda Lamprianou, Sujeet Jain and Shanthi Pal. The protocol was scripted by Kaatje Bollaerts, Mark Otiende and Somsuvro Basu, with technical input from Scott McDonald from the P95 – Excellence in Pharmacovigilance and Epidemiology team.

Special thanks are due to the WHO Global Advisory Committee on Vaccine Safety (GACVS, Switzerland), the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, Sweden), and other vaccine safety experts for their advice and significant technical contributions. Vaccines safety experts who contributed to the technical aspects of this publication include Steven Anderson (WHO GACVS, 2020–2024), NK Arora (INCLEN Trust International, India), Judith Brand (Uppsala Monitoring Centre), Sonali Kochhar (Global Health Consulting, United States of America), Niklas Norén (Uppsala Monitoring Centre) and Apoorva Sharan (WHO Headquarters consultant).

Thanks are due to WHO regional advisors Oleg Benes (WHO Regional Office for Europe (EURO)), Heeyoun Cho (WHO Regional Office for the Western Pacific (WPRO)), Adrien Inoubli (WHO Regional Office for South-East Asia (SEARO)) and Hitomi Kubota (WHO Regional Office for the Western Pacific (WPRO)), who provided feedback on how the protocol can be implemented in their respective regions.

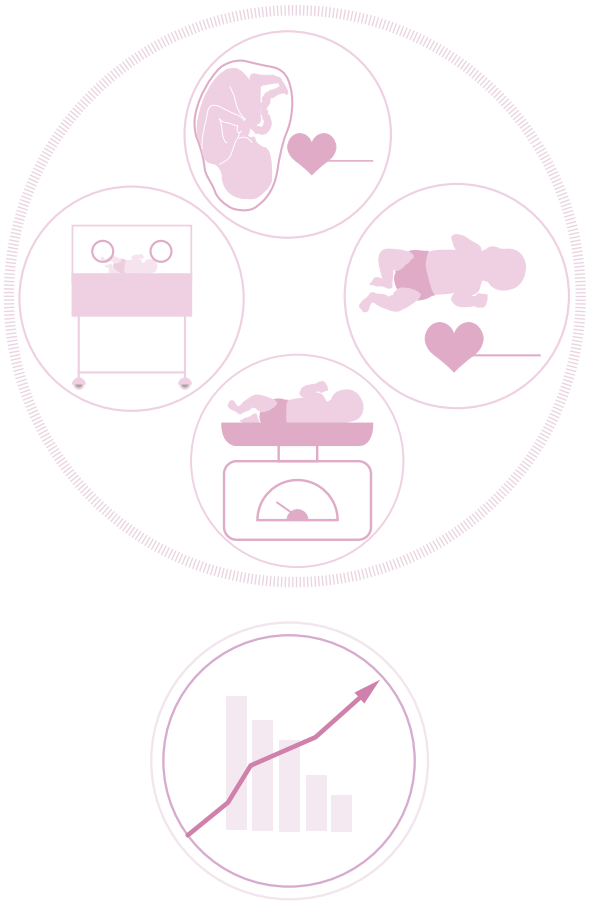
The extensive review by external reviewers Stephanie Dellicour (Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland), Viola Sarinic Macolic (European Medicines Agency, Netherlands) and Clare Cutland (University of the Witwatersrand, Johannesburg, South Africa) is much appreciated.

Before commissioning P95 to write the protocol, as part of WHO policy, written disclosures of potential conflicts of interest that might affect, or might reasonably be perceived to affect, objectivity and independence in relation to the protocol were reviewed. Additionally, all experts involved in the development and peer reviewers submitted a WHO declaration of interest, disclosing potential conflicts of interest. WHO reviewed each of the declarations and concluded that none could give rise to potential or reasonably perceived conflict of interest.

This work was partly supported by funds from the Center for Biologics Evaluation and Research, United States Food and Drug Administration (grant number 5U01FD005959-04).

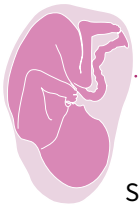
Abbreviations

AESI	**adverse event of special interest**
APGAR	**appearance, pulse, grimace, activity, respiration**
CI	**confidence interval**
GAIA	**Global Alignment of Immunization Safety Assessment in Pregnancy**
GDPR	**General Data Protection Regulation**
LMICs	**low- and middle-income countries**
LMP	**last menstrual period**
WHO	**World Health Organization**



1. Synopsis

Full title of study	Estimation of Background Rates of Adverse Events of Special Interest in Neonatal Outcomes. Preterm Births, Stillbirths, Neonatal Deaths and Low Birthweight.
Background and rationale	During pregnancy, women and infants are predisposed to specific infections due to various immunological and physiological changes. These infections can result in adverse outcomes. The risk and severity of these infections can be attenuated through maternal vaccination, whose benefits have been demonstrated before *(1–6)*. The World Health Organization (WHO) already recommends maternal vaccination against tetanus, pertussis and influenza to protect infants. The United States Food and Drug Administration has approved the first maternal respiratory syncytial virus vaccine, which may soon be introduced in low- and middle-income countries (LMICs) *(7)*. LMICs stand to benefit the most from these vaccines, because they have the highest burden of perinatal and infant mortality *(8, 9)*. It is crucial they develop safety monitoring beyond routine surveillance to inform current and future maternal vaccination programmes *(10–13)*. The aim of this project is to prospectively generate evidence on background rates of four adverse events of special interest (AESIs) in multiple countries *(14)* – preterm birth, stillbirth, neonatal death and low birthweight – before the introduction of novel vaccines such as maternal respiratory syncytial virus vaccine into national immunization programmes *(7, 15)*. The protocol will be piloted in LMICs with the potential for broader application.
Objectives	To estimate background rates of the following AESIs: • preterm birth • stillbirth • neonatal death • low birthweight.
Study design	This is a multisite prospective cohort study conducted in selected sentinel sites in LMICs. The study will collect data on all deliveries registered at participating sites, including deaths that occur within 28 days of birth. Preterm births, stillbirth and low birthweight will be ascertained only in participating health facilities. Neonatal deaths will be ascertained either in participating health facilities or at home on the 28th day of life.
Study period	The study will take place over at least one year.
Study population	The study population will comprise all deliveries (live and stillborn) at participating health facilities and their mothers from the day the study begins.



Study outcomes

The outcomes of interest, based on Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) case definitions, are:

- preterm birth
- stillbirth
- antepartum stillbirth
- intrapartum stillbirth
- timing of fetal death unknown
- neonatal death
- neonatal death in a non-viable birth
- neonatal death in a viable term live birth
- low birthweight.

Data sources

All deliveries (denominator data) and AESIs will be recorded by the study team in the selected health facilities for the duration of the study. The denominator data for calculating AESI rates and proportions for preterm births, neonatal mortality and low birthweight will be all live births recorded in the participating facility. The denominator data for calculating stillbirth rates will be all deliveries (live and non-live births). For neonates who will be discharged from the health facility before the 28th day of life, contact via telephone or home visit will be scheduled on the 28th day to ascertain the status (alive or dead) of the neonate. Measures will be taken to minimize the loss to follow-up.

Sample size

Sample sizes have been determined with the aim to estimate the quantity of interest with a prespecified precision.

Data analysis

Annual and (when feasible) monthly rates and proportions, with corresponding 95% confidence intervals (CIs), will be calculated.

All rates and proportions will be additionally stratified by site and country, as appropriate.

The preterm birth proportion (rate) will be calculated as the total number of preterm births identified in the participating site divided by the total number of live births, and expressed per 1000 live births.

The stillbirth proportion (rate) will be calculated as the total number of stillbirths identified in the participating site divided by the total number of live and non-live births, and expressed per 1000 births.

Neonatal mortality will be calculated as the total number of neonatal deaths on days 0–27 divided by the total number of live births recorded in the participating site, and expressed per 1000 live births.

The low birthweight proportion will be calculated as the total number of identified cases of low birthweight divided by the total number of live births, expressed as a percentage.

Ethics	The study will be conducted according to the International Ethical Guidelines for Health-related Research Involving Humans *(16)*, under the principles of the Declaration of Helsinki *(17)* and considering local legislation on medical research in humans and data sharing from clinical records beyond national or administrative borders. An opt-out process or oral consent will be required from all participants. All parties will ensure protection of personal data and will not include names or other identifying information (e.g. date of birth, address) on any study forms, reports or publications or in any other disclosures, except where required by law. Local data protection and privacy regulations will be observed in capturing, forwarding, processing and storing data. This protocol serves a dual purpose. Countries can implement the protocol independently without WHO involvement or use it as a master protocol supported by WHO for implementation. The protocol has been approved by the WHO Research Ethics Review Committee. Each participating site will be responsible for submission of the study protocol and any amendment to the respective local, national or independent ethics committees and/or institutional reviews boards according to local requirements.

2. Use of this protocol

This is a master protocol approved by the WHO Research Ethics Review Committee on 8 July 2025. It will be used by study sites that will submit a protocol to their national ethics review committee. The only country-specific changes that should be made are those needed to facilitate translation into the local language, and other changes that may be advised by the national ethics review committee.

Roles and responsibilities of the key stakeholders, such as the ministry of health and local community representatives, during the processes of implementation, study oversight, dissemination and follow-up should be assigned. The ministry of health will ensure adherence to health standards and facilitate dissemination of findings. Local community representatives will engage in the planning and execution, ensuring cultural sensitivities and practices are maintained and considered respectively.

Amended site-specific protocols developed for implementation in countries based on this WHO master protocol must be approved by the WHO Research Ethics Review Committee before implementation. Any third party that uses or follows this protocol does so at its sole discretion, and WHO will not have any responsibility or liability of any kind arising from or in connection with any use or following of this protocol by any third parties and/or the conduct of any studies by third parties that use or follow the protocol. Studies conducted by third parties pursuant to the protocol cannot be considered WHO studies, and third parties using or following this protocol for their studies will not label, characterize or otherwise represent such studies as “WHO studies”. All necessary and/or appropriate approvals at the local and/or national levels should be obtained before starting any such study.

3. Background and rationale

During pregnancy, various immunological and physiological changes occur that predispose the mother, fetus or infant to specific infections that can result in adverse outcomes *(5, 18–23)*. The risk and severity of these infections can be attenuated through maternal immunization, whose benefits have been demonstrated *(1–6)*. Maternal immunization protects the mother and the baby during pregnancy and early life by increasing the mother's antibodies against certain vaccine-preventable diseases. The protective antibodies are transferred to the infant during pregnancy, consequently protecting the infant who is too young to benefit directly from primary immunization and protecting the fetus from the effects of maternal infection *(24–26)*.

Despite evidence regarding the benefits of vaccination, one of the major barriers to vaccination during pregnancy (apart from lack of access) is the concern that vaccines may have adverse events on the mother and/or the fetus *(27, 28)*. Data from routine safety surveillance and a growing body of observational studies, including pregnancy registries and database studies, have demonstrated the safety of a selection of maternal immunization programmes, including the maternal tetanus toxoid and influenza vaccines *(26, 29)*.

An adverse event of special interest (AESI) is a prespecified medically significant event with the potential to be causally associated with a vaccine product and that needs to be carefully monitored and confirmed by further special studies. AESIs can have multiple potential causes and can occur independently from receipt of vaccine products. It is important to understand the rate of occurrence of AESIs before vaccine introduction, so there is a frame of reference with which to compare the rates of AESIs to identify any rate increase as a potential safety concern. Safety monitoring reduces vaccine hesitancy by providing clear evidence of vaccine safety and reassuring the public that potential risks are being monitored closely and addressed promptly. Implementing global safety monitoring in all settings promotes equitable access, ensuring no population is deprived of vaccines due to a lack of safety data.

WHO already recommends maternal immunization against tetanus, pertussis and influenza to protect children *(30–32)*. There are some maternal vaccine candidates currently under clinical evaluation that could potentially be licensed, such as vaccines that protect against cytomegalovirus and group B streptococcus *(33)*. There are also some vaccines that are licensed in high-income countries and are under regulatory review for registration in some LMICs, such as for protection against respiratory syncytial virus. LMICs stand to benefit the most from these vaccines, because they have the highest burden of perinatal and infant mortality *(8, 9)*. It is crucial, therefore, that LMICs have a baseline AESI rate so that any change in the observed number of AESIs is detected during routine safety surveillance. This then informs current and future maternal vaccination programmes *(11–13)*. Such data in high-income countries cannot be extrapolated to LMICs due to differences in health-care infrastructure, socioeconomic makeup, education levels, limited access to advanced medicines and higher incidence of infectious diseases. Many high-income countries have secondary data sources, such as electronic health records. The European Medicines Agency has published protocols to study background rates of certain AESIs, a need highlighted during the COVID-19 pandemic. These protocols use electronic health-care records, health registers and sales data *(34)*, which are increasingly being used for epidemiological research, but implementation in LMICs is not well established and remains limited and fragmented in many countries. Electronic health record systems in low-income countries are still in pilot stages and are often hindered by poor infrastructure, lack of management commitment, absence of standards, interoperability, limited technical support and poorly designed systems *(35–37)*. This necessitates the generation of primary data. Several studies have highlighted the limited epidemiologic data on maternal and neonatal outcomes in LMICs *(2, 3, 38, 39)*. In some settings, adverse outcomes in maternal and neonatal participants lack standardization in collection and interpretation, leading to variable data and affecting clinical trial outcomes. To address this, the Brighton Collaboration GAIA project was initiated in 2014 to develop standardized case definitions and guidance on data collection across the antenatal, intrapartum and postpartum periods *(40)*. WHO has previously conducted feasibility assessments to detect and classify perinatal and neonatal outcomes from retrospective data (archived records) using the GAIA definitions *(41)*. The feasibility study recommended a prospective design for future studies because it offers better prospects for improving data collection and recording systems within institutions, such as linkage of records between mothers and newborns.

This master protocol aims to prospectively generate evidence on background rates of four neonatal AESIs *(14)* – preterm birth, stillbirth, neonatal death and low birthweight – in preparation for the introduction of priority vaccines such as maternal respiratory syncytial virus vaccine in LMICs *(15)*. The study is designed to be piloted mainly in LMICs, with the potential for broader application in other settings.

4. Objectives

To estimate the background rates of the following AESIs using GAIA case definitions for:

- preterm births
- stillbirth
- neonatal death
- low birthweight.

5. Methodology

5.1 Study setting

The study will be conducted in LMICs, defined according to the World Bank classification *(14)*. In each country, one or more health facilities will be selected. The participating facilities will be selected according to data collected in the health facility screening questionnaire (Annex 1).

5.2 Study design

This will be a multisite prospective cohort study conducted in select sentinel sites in LMICs. A prospective study is the recommended design to collect good-quality AESI data in settings where electronic medical records are not available and physical archives are not accessible *(41)*. The study will collect data on all deliveries registered at participating sites for at least a year, including deaths that occur within 28 days of birth.

The countries and sites to be included in the study will be determined by WHO Headquarters and regional and country offices. The WHO Pharmacovigilance team will coordinate the study.

5.3 Study population

The study participants will comprise pregnant women[1] registered to deliver at participating health facilities and their newborns (live and stillborn) during the study period.

5.3.1 Inclusion criteria

- The participant must be registered or must have delivered at the participating health facility.
- Oral informed consent must be gained from the woman or legally acceptable representative or through an opt-out consent process.

5.3.2 Exclusion criteria

Women will be excluded if they cannot provide consent – for example, due to critical illness, acute emotional distress, a language barrier without an interpreter, or medical instability – and no legally authorized representative is available. Exclusion will occur after three attempts to obtain oral consent at different times. Study staff will note the number of women excluded and the reasons.

5.3.3 Country and site selection criteria

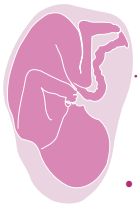
Country selection

- The country is a LMIC according to the World Bank classification *(14)*.
- The country has a functional national pharmacovigilance system willing to strengthen its capacity to monitor the safety of vaccines and medicines. The WHO Global Benchmarking Tool *(42)* will be used to assess the functionality of national regulatory authorities. The national pharmacovigilance system should be at a minimum of maturity level 2.

Preliminary health facility identification (initial screening for eligible health facilities)

- The health facility has an obstetrics department and maternity ward that manages at least 1000 deliveries per year. This threshold is based on a study assessing the feasibility of vaccine safety monitoring during pregnancy in LMICs *(41)* and the sample size requirement for obtaining reasonably precise estimates (see Section 5.7.1). This may vary on a site-by-site basis.

1 The terms “woman” and “mother” are intended to be inclusive of all people who identify as women and/or give birth. The majority of these are cisgender women (people who were born and identify as female), but our vision is also inclusive of the experiences of transgender men and other gender diverse people who have the reproductive capacity to give birth.



- The health facility has imaging facilities such as ultrasound or facilities that can access or verify metrics from affiliated centres where women can have ultrasound scans and other diagnostic services.
- The health facility has easily accessible medical records (electronic and/or paper) to supplement prospectively collected data.
- The health facility has qualified personnel and specialists, such as an obstetrician or paediatrician.

Health facilities that fulfil the initial screening criteria will proceed to complete the health facility screening questionnaire (Annex 1). The information gathered from this questionnaire will be used to evaluate the operational and diagnostic capabilities of the health facility. Questions cover the type of health facility (public or private), the qualification of staff to identify AESIs and complete case report forms, the availability of technical equipment (e.g. weighing scales), the availability of an obstetric department or maternity ward, and the mode of data collection and record-keeping (paper or electronic). The WHO regional office, in liaison with the WHO country office, will consult the ministry of health or national regulatory authority regarding the eligibility criteria of choosing participating sites.

When using health facility data, it is important to consider that deliveries occurring in the community may be excluded. This should be taken into account during data interpretation and communication of results. If information on patient demographics is available, a comparison of the broader population should be made to understand sample representation. If possible, study sites across diverse facilities and geographical areas should be selected for representation. If a poorly equipped health facility with low diagnostic capacity is selected, the variability between this facility and a better-equipped health facility should be considered to provide an indication of variability.

Appropriate caveats should be included when disseminating results to highlight the potential exclusion of community-based cases, differences between access to health facility-based care, and how well participants at the selected study sites represent the broader population.

5.4 Study period

The specific start and end dates of the study for each site will be decided by the site study team and the WHO Pharmacovigilance team. When the study concludes, data collection for neonatal deaths will continue for an additional 28 days to cover the neonatal period of the last live birth recorded.

5.5 Study outcomes

5.5.1 Birth outcomes

GAIA case definitions and suggested amendments for different settings will be used for the following newborn outcomes (see Annex 2) *(43)*:

- preterm births *(10)*
- stillbirth (adjusted to unknown timing of fetal death) *(11, 44)*
- neonatal death *(12)*
- low birthweight *(13)*.

5.5.2 Immunization history

Immunization history will be obtained by asking the pregnant or postpartum woman, checking medical records and checking vaccination cards (see Annexes 4–7). Some women will report that they have received the tetanus toxoid vaccine. This information will be collected as part of the clinical history of the woman. Only documented evidence of recent vaccination history will be used. Questions about recent vaccination include whether the woman was vaccinated in the past six weeks, the date of immunization, the disease targeted by the vaccine, and the name of the vaccine. The method in which the history was taken (e.g. through medical records or verbal history) will be documented.

5.6 Study flow: case identification and data collection

5.6.1 Recruitment

Recruitment of participants will take place at the health facility. It can be challenging to obtain consent from women during labour at health facilities with large sample sizes *(14–17)*. To avoid potential selection bias due to lack of consent and to ensure the consent process is practical and feasible, an opt-out consent or oral consent process will be used.

Pregnant women (and their parents or legal guardians if aged under 18 years) arriving at the health facility for delivery will be informed about the study. Study staff rather than staff treating the participants should seek consent to prevent applying any pressure to participate. It is important to approach the woman for consent during a calm moment, after she has been reviewed by medical staff, and ideally before labour is fully established.

For women and girls aged under 18 years presenting to the facility, local child protection services, where available, should be contacted to safeguard people from vulnerable populations. Special attention will be paid to people aged under 12 years, who are not permitted to participate in the study. Standard operating procedures will include clear protocols for conducting immediate safety assessments to ensure the well-being of any child aged under 12 years. For all girls and women aged under 18 years, the standard operating procedures will outline a step-by-step process for referral to appropriate local child and adolescent protection services, in accordance with mandatory reporting laws. All actions and communications with authorities will be thoroughly documented. Comprehensive orientation and training for study staff will be a priority, with particular emphasis on handling cases involving people aged under 15 years. This training will cover relevant child protection laws, mandatory reporting procedures, and strategies to ensure the privacy, safety and best interests of children and adolescents in potentially sensitive situations.

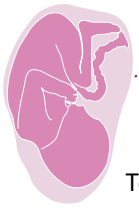
The study team will explain the study in the appropriate language. The woman (and her parent or guardian, if required) will be given an opportunity to discuss the study or ask questions at this point and at any time afterwards. Handouts or brochures can be given to the woman to review later. The study team will provide a contact name, telephone number and email address so the woman can ask any further questions or withdraw from the study. Study staff will clearly inform the woman that participation is voluntary and will not affect care in any way, regardless of whether she chooses to participate.

For oral consent, the woman (and her parent or guardian, if required) will be asked by the study team if she understands all parts of the consent and will be given another opportunity to ask any questions and seek clarification. Pregnant women and girls aged 12–18 years will be asked to provide written assent. The age at which a woman is considered an adult should be set in accordance with local law. Researchers should verify whether a minor has legal emancipation status before assigning an assent form together with parental consent. Legal emancipation warrants oral consent consistent with other adults in this study. Oral consent will be documented by the study staff. Participants will be informed during the consent process that they can withdraw at any time by contacting the study staff and expressing this wish, verbally or in writing.

Study staff obtaining consent should document that the woman was informed and understands the study objectives. If possible, consent should be obtained in front of a neutral witness and the opportunity provided for the woman to provide a thumbprint or mark consent.

For an opt-out process of consent, the woman (and her parent or guardian, if required) will be given a full oral explanation of the study in an appropriate language. Contact information will be provided in case the woman has further questions or chooses to opt out. The woman can continue to ask questions throughout the study and can contact the study staff at any time via telephone, email or in person to withdraw or address any concerns.

Both the oral consent and opt-out processes involve informing women about the study and their right to withdraw. Opt-out consent assumes participation unless potential participants actively decline. Provided it is approved by the local ethics board, the opt-out process is suitable for study sites with large numbers of people, where obtaining explicit written consent is impractical or can lead to bias.



To uphold participant autonomy and ensure an inclusive consent process that respects a diversity of literacy levels, oral consent is the preferred method when practical. Oral consent is crucial to accommodate acute clinical situations such as labour, and is adaptable to various cultural norms, ensuring that the method of obtaining consent facilitates rather than hinders a person's ability to make a fully informed decision.

Both consent methods are ethically justified when people are fully informed and autonomy is respected. For opt-out consent, documentation includes information materials detailing the study, the right to opt out, and the procedure for doing so. For oral consent, a neutral witness should be present, and an additional record of the woman's consent should be kept in a study staff attestation, detailing the date, witnesses, and confirmation of understanding and agreement. Staff should be trained to deliver consent effectively, maintain confidentiality, and provide points of contact for further questions or withdrawal.

Information collected on participants will include residential address and contact information to enable follow-up, in the case of newborns, for the neonatal period. This information is usually collected in medical records. Detailed study procedures will be described in specific manuals and standard operating procedures.

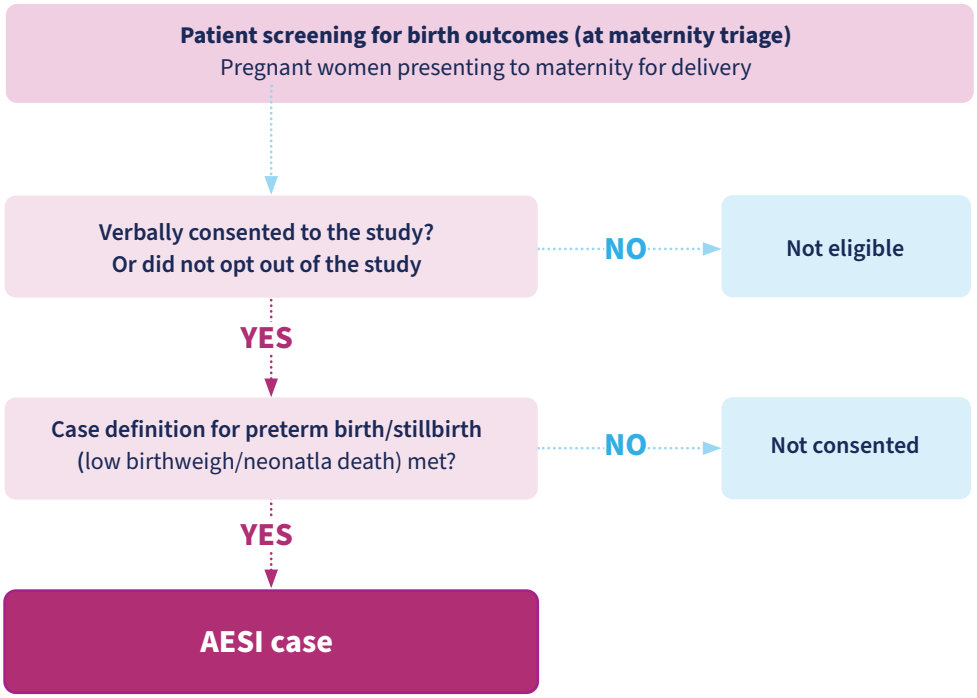
Considerations when seeking consent or follow-up after neonatal death

Approaching a woman after neonatal death requires sensitivity. Her well-being and grief must be prioritized. If consent is sought after neonatal death, initial contact should be delayed to allow for culturally appropriate mourning. The approach should include sincere condolences, clear options for participation, and information on bereavement support. Research staff should be trained in trauma-informed principles and effective communication. Support in some settings involves leveraging community resources and culturally relevant peer networks. Other settings may offer bereavement counselling and informational resources.

5.6.2 Study enrolment and withdrawal

Mother–infant pairs that meet the inclusion criteria (see Section 5.3.1) will be enrolled by study staff, who will then start the process of case identification. Participants may withdraw from the study at any time before publication. Participant data will be removed after withdrawal. Participants will be given a contact name, telephone number and email address to facilitate withdrawal. If a participant chooses to withdraw, the study staff will inform the participant about what will happen to any data already provided and address any concerns.

Fig. 1. Flow diagram of recruiting participants and identifying adverse events of special interest (AESIs) for neonatal outcomes



5.6.3 Case identification

GAIA definitions are provided in Annex 2. One of three levels of diagnostic certainty will be used to confirm an AESI. Before initiation of the study, clinicians and study staff will be trained extensively on GAIA case definitions to apply standard definitions for this study and beyond. Information needed to apply GAIA definitions will be collected in a case report form and in accordance with local processes and other WHO standards, such as the WHO Minimum Maternal and Neonatal Health Data Set *(45)*. Ideally, documentation of diagnosis and data observations should be in accordance with WHO standards and GAIA definitions. Any diagnosis not aligned with GAIA definitions and local variations should be communicated to study clinicians to inform future practices.

5.6.4 Identification of preterm birth, stillbirth, neonatal death and low birthweight

Preterm birth

Preterm birth is defined as birth before 37 weeks of gestation *(10)*. Preterm birth can be further stratified into extremely preterm birth (gestational age less than 28 weeks), very preterm birth (gestational age 28–<32 weeks), and moderate or late preterm birth (gestational age 32–<37 weeks).

Stillbirth

In accordance with GAIA definitions, stillbirth can be defined as early (occurring at 20–28 weeks of gestation) or late (occurring after 28 weeks of gestation) *(11)*. This project will describe the rates of stillbirth in which fetal death occurred antepartum (before the onset of labour) or intrapartum (at the time of delivery) and stillbirth in which the timing of fetal death is unknown.

Neonatal death

Neonatal death is defined as the death of a live-born child within 28 days (on days 0–27) after birth, per 1000 births *(12)*. This project will investigate neonatal deaths in non-viable live births and term live births.

Low birthweight

Low birthweight is defined as the first weight measured within 48 hours of birth at less than 2500 g. Low birthweight is further stratified into low birthweight (less than 2500 g), very low birthweight (less than 1500 g), and extremely low birthweight (less than 1000 g) *(13)*. Information on birthweight will be collected in accordance with local process and WHO standards (e.g. acknowledging survival for neonates as small as 500 g), and this information will be mapped in accordance with GAIA definitions.

5.6.5 Data sources

This will be a health facility-based study. All cases will be identified in the participating health facility. Denominator data for calculating AESI rates and proportions for preterm births, neonatal mortality and low birthweight will be all live births recorded in the participating health facility. Denominator data for calculating stillbirth rates will be all deliveries (live and non-live births).

5.6.6 Data collection and generation

If a woman meets the inclusion criteria, she is informed about the study and provides consent, data will be collected by study staff using standardized tools electronically (see Annexes 4–7). All infants born will be registered and linked to their mothers using unique identifiers. For infants with multiple outcomes under the study, such as low birthweight and neonatal death, data for both outcomes will be collected. Methods of data collection will be consistent across study settings.

In addition to outcome-specific information, the following information will be collected for all AESI outcomes:

- source of information of the report, including the date of reporting and the name of the person reporting;
- woman's age and sociodemographic data;
- relationship of the reporting person to the woman, if the woman is not self-reporting;
- date of delivery (obtained from the infant form);
- gestational age at the time of delivery, and method of assessing gestational age;
- labour and delivery details, such as mode of delivery and complications (e.g. fetal distress, antepartum/postpartum haemorrhage, assisted delivery);
- immunization history during pregnancy.

Preterm birth

Gestational age and clinical symptoms of the preterm birth will be collected alongside other information using the preterm birth case report form (see Annex 4).

Stillbirth

The following information will be collected for each stillbirth using the stillbirth case report form (see Annex 5):

- signs of life examined as per the described criteria, including spontaneous movement, umbilical cord pulse, heartbeat, respiration, crying and chest movement *(11)*;
- verbal history of the stillbirth by a medical or non-medical witness or the mother;
- timing of last fetal movement felt, observed or documented.

Harmonized data collection procedures will be described in a specific manual of study procedures for each setting.

Neonatal death

For newborns discharged before 28 days of life, the study staff will schedule appointments on the 28th day of life or communicate with the mother via telephone or a home visit to obtain information about the newborn's status, which will be recorded in the database. Other information that will be recorded includes the date of death, to calculate the duration of follow-up until death (see Annex 6). To minimize the likelihood of loss of participants to follow-up, the following measures will be implemented:

- The participant must be contactable via telephone or agree to home visits.
- If the participant provides a telephone number, call the number at the time it is given to ensure it is correct.
- If home visits are agreed, check the address through a utility bill or identification document if possible.
- Explain clearly that the participant will be contacted via telephone, at home or another form of contact. The telephone number of the caller will be provided beforehand by the study team for easy recognition by the participant.

Low birthweight

The following information will be collected for neonates born with low birthweight (see Annex 7):

- clinical description of signs and symptoms for establishing low birthweight as per the described criteria *(13)*;
- date of diagnosis to confirm date and time of first weight assessment of newborn (within 48 hours after birth);
- measurement details, including the units of routinely measured parameters (grams for birthweight), the method of measurement (e.g. type of scale used), information on routine calibration of the scale, and whether measurements are rounded.

5.6.7 Case report form completion

As much information as possible will be abstracted from routinely collected medical records at admission and filled in the case report forms. Any additional information not routinely collected by the participating facility will be collected separately according to the study procedures.

5.7 Statistical methods

5.7.1 Sample size calculation for preterm birth, stillbirth, neonatal death and low birthweight

The sample size required to estimate the proportion of preterm births, stillbirths, neonatal deaths and low birthweight (e.g. in one year) with a given level of precision for each site is as follows *(46)*:

$$n = \frac{N * Z^2 * P * (1 - P)}{Z^2 * P * (1 - P) + \mathrm{e}^2 * (N - 1)}$$

where:

n is the calculated sample size (number of births);

N is the total number of deliveries recorded in a year at the facility (obtained from past records);

Z is the critical value for the 95% confidence level;

P is the true proportion of the event (50% gives maximum possible sample size);

e is the precision (half-width of the confidence interval).

The resulting sample size will be the number of deliveries required to observe a proportion of, for example, 0.5 (50%) at the specified level of precision. Site selection will consider the number of births recorded in a health facility (e.g. annually) that will enable the estimation of AESI proportions with reasonable precision.

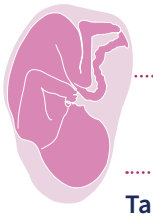


Table 1. Sample size considerations for newborn outcomes

Precision	2%		5%		10%		15%	
	Proportion (95% CI)	*n*	Proportion (95% CI)	*n*	Proportion (95% CI)	*n*	Proportion (95% CI)	*n*
0.50%	2.0 (1.5–2.5)	2618	5.0 (4.5–5.5)	5348	10.0 (9.5–10.5)	8177	15.0 (14.5–15.5)	9898
1%	2.0 (1.0–3.0)	726	5.0 (4.0–6.0)	1673	10.0 (9.0–11.0)	2948	15.0 (14–16)	3935
2%	2.0 (0.0–4.0)	187	5.0 (3.0–7.0)	447	10.0 (8.0–12.0)	829	15.0 (13–17)	1154
4%	–	–	5.0 (1.0–9.0)	114	10.0 (6.0–14.0)	214	15.0 (11–19)	302
8%	–	–	–		10.0 (2.0–18.0)	54	15.0 (7–23)	77

Cells are blank when the expected proportions and corresponding levels of precision result in confidence intervals that are negative in value.

5.7.2 Statistical analysis

The analysis will be fully described in a written and approved statistical plan. All analyses will be conducted using R statistical software *(47)*. Annual and, when feasible, monthly rates and proportions to assess seasonality of outcomes will be calculated with their corresponding exact binomial 95% CIs. All estimates will be additionally stratified by site, country, maternal age, gravidity, delivery mode, and multiple versus singleton deliveries (with type stated). The WHO Pharmacovigilance team will support selected sites to conduct the primary analyses. Any secondary outcomes or analyses, including pooled analyses, will be decided by study sites and the WHO Pharmacovigilance team.

Preterm birth

The proportion (rate) of preterm births will be calculated as the total number of identified cases divided by the total number of live births, expressed per 1000 live births.

Stillbirth

The proportion (rate) of stillbirths will be calculated as the total number of identified cases divided by the total number of live and non-live births, expressed per 1000 births.

Neonatal mortality

The neonatal mortality rate will be calculated as the total number of neonatal deaths (viable and non-viable live births occurring on days 0–27 of life) divided by the total number of live births, expressed per 1000 live births (relative to the total number of live births in the same period and location). A further sub-analysis of early neonatal mortality (deaths occurring within the first 7 days of life, on days 0–6) and late neonatal mortality (deaths occurring after the 7th day but before the 28th completed day of life, on days 7–27) can also be performed.

Low birthweight

The proportion of neonates with low birthweight will be calculated as the total number of identified cases of low birthweight divided by the total number of live births, expressed as a percentage.

5.8 Data management

The study will be implemented at the site level under the responsibility of the site principal investigator. A data management framework will be adopted to provide a consistent and integrated approach to managing data and ensuring data quality, security, compliance and effective use. Measures include encryption, secure storage, role-based access control, coding data, regular backups and clear data retention policies. Research staff will be trained in data security and ethical handling. Country-specific adaptations will comply with local laws and be reviewed by ethics committees. When handling identifiable data, confidentiality will be prioritized, including information on adverse neonatal outcomes, with restricted access and use coding early in the process. Identifiable data will be securely destroyed after the retention period, ensuring ethical management and valuable research.

A data management plan will be developed before initiation of the study. The data management plan will describe all the steps involved in data collection, cleaning and validation. Site-specific data management plans will be developed to allow for differences between study sites. The study sites will be responsible for collecting, cleaning and validating data. The study sites will also be responsible for managing the data in a local database or a database set up with the support of the WHO Pharmacovigilance team. The data collected by the study sites will be shared with the WHO Pharmacovigilance team, which will then conduct the primary statistical analyses. The data collected at each site will be owned by the respective site.

5.8.1 Data collection

Data can be collected via paper forms or electronically using an electronic data capture system. The system will consist of a module installed on a handheld device that will be synchronized with the site database in real time or at the end of each day. A unique identifier (provided by the health facility according to standard operating procedures) will be used to link the woman to her baby or babies. The system will have a web module for monitoring progress of the study. The software used in the handheld device will be developed using open-source technologies (PHP and MySQL). Comprehensive training on the use of the data collection forms, including the electronic data capture system if used, will be provided.

5.8.2 Data sources

The source documents required by the study will be the woman's and the infant's (for the first 28 days) medical records. All information needed about the woman and the infant from medical records will be identified before the start of the study. The source document required for each outcome being studied will be specified, and a request for access to medical records will be made to the study site in advance.

5.8.3 Data quality

Data quality will be assessed at all stages of the study, from the point of collection to analysis, including the time when the woman and infant are still in the health facility after birth. Immediately after data collection, the information collected will be verified for completeness by the study data manager. In sites that choose to use electronic case report forms, configurable checks will be built in to immediately detect missing data, out-of-range values, illogical entries and other potential errors. Manual cleaning processes will be used to detect anomalous data. Concurrent manual data review will be conducted. Any queries that arise will be reviewed and resolved.

5.8.4 Data security

The General Data Protection Regulation (GDPR) will apply *(48)*. To ensure compliance with GDPR and local data protection laws, the study will adopt a locally responsive and integrative approach that harmonizes internationally recognized data protection standards with jurisdiction-specific legal and ethical requirements. Core principles such as transparency law, confidentiality and accountability will guide all data related activities. Local regulations and cultural considerations will be carefully incorporated into site-specific protocols, which will outline tailored measures to address local obligations. These protocols will be reviewed and approved by the appropriate national ethics committee.

The study data management framework will be standardized, including procedures for collection, storage, processing and transfer of data, with regular audits and monitoring. Data collection tools, including web-based modules, will have secure login features to access data. The system will use a Secure Socket Layer (SSL) certificate with 256-bit SSL to secure data transfer. Study teams will be provided with login credentials with rights assigned for specific roles. Data collection will minimize directly identifiable information, with secure coding and storage methods. Access to identifiable information will be limited to authorized personnel, and data for analysis will be anonymized or coded. If electronic tools are used, site principal investigators and other designated study staff will have access to a supervisory online web module enabling them to view data pertaining to their respective sites and monitor the progress of the study in real time. Sharing of identifiable information will be avoided unless legally or ethically necessary, under strict agreements. Study sites will have access to only their study data and not data from other collaborating sites. Only authorized study staff and WHO Pharmacovigilance team members (e.g. software developers and database administrators) will have access to study data from all sites. A central data management team will oversee adherence to standards, providing guidance and support to local teams. Training for local staff will cover data protection principles, confidentiality and data privacy regulations, consent procedures, data security and handling of identifiable information, adapted to local languages and contexts.

Data storage

Data will be stored in a secure server complying with data safety regulations for personal health information.

File retention and archiving

GDPR will be applied to data storage and archiving. All original source documentation is expected to be stored at the site for a minimum of five years, or according to the local applicable regulations at the study site. Secure disposal methods will be implemented after expiration. Physical documents containing identifiable information will be stored in locked, access-controlled cabinets or rooms, protected from environmental damage, with access limited to authorized personnel. Electronic documents will be stored on secure servers with robust security measures, including encryption, role-based access controls, audit trails, firewalls, intrusion detection systems and regular backups. Access to all study documentation will be limited to trained and authorized personnel, with access logs maintained for physical storage areas where feasible.

Monitoring and quality assurance

A site initiation visit will be conducted to ensure the site is ready to start data collection. Study staff will be trained on good clinical practices and the importance of confidentiality, study procedures, data collection and documentation. A training plan with routine refresher sessions will be maintained. Remote and, when possible, on-site monitoring of the study will be performed throughout the study to assess compliance with the protocol, adherence to the study procedures, and accuracy and completeness of the data.

6. Study management

6.1 Study implementation structure

6.1.1 Scientific advisory committee

A dedicated scientific committee (to be detailed in the site-specific protocol) will oversee the implementation and running of the study. The committee will provide scientific, statistical and technical expertise, as needed.

6.1.2 WHO Pharmacovigilance team

The WHO Pharmacovigilance team will support countries to implement the study, including site selection, study coordination and management, development of study protocols, use of data collection tools, use of operating procedures, study monitoring and data quality assurance, data analysis and dissemination of results.

6.1.3 National focal points

National focal points comprise representatives from national and local immunization programmes, national and local health management teams, national and local maternal and child health programmes, drug regulatory authorities and research ethics committee. National focal points are responsible for facilitating site selection, training, ethics, administrative clearance for study initiation, operating procedures, participating in study monitoring and quality assurance.

6.1.4 Site team

The site team will comprise a site principal investigator and co-principal investigator, staff from obstetrics, neonatology and community medicine, and research staff with the relevant expertise, who may be dedicated study or health facility staff. The study team will be responsible for ethics and approval at the site level, obtaining informed consent, data collection and monitoring study progress.

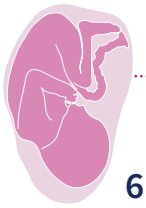
6.1.5 Changes to the protocol

Any changes to the protocol will be documented as amendments. Amendments that impact the study objectives, procedures or participant safety will require submission to the WHO Research Ethics Review Committee and all relevant local independent ethics committee or institutional review board for approval. Amendments will not be implemented until approval has been obtained. Minor amendments, such as a change of staff in the study site, will be intimated to the relevant independent ethics committee or institutional review board as appropriate. Any amendment that may have an impact on a participant's agreement to be part of the study will require re-consent (if verbal consent is obtained) or for the participant to be informed of the change (opt-out process).

6.2 Guiding principles

The study will be conducted according to the International Ethical Guidelines for Health-related Research Involving Humans *(16)*, under the principles of the Declaration of Helsinki *(17)*, and considering local legislation on medical research in humans and data sharing from clinical records beyond national or administrative borders.

This is an observational study that does not involve any medical interventions or modifications to clinical and diagnostic procedures. There are no direct benefits or risks to the participants. There are, however, significant potential societal advantages associated with this international study that intend to enhance safety monitoring of vaccination programmes. The long-term goal is to establish robust and sustainable public health surveillance systems in countries, with the capacity to consistently gather high-quality data to monitor vaccine safety.



6.3 Respecting participant autonomy

Participants will be informed during the oral consent process that their participation in the study is entirely voluntary, and they can withdraw consent at any time during the study. In facilities using the opt-out process, participants will be given contact information for study staff so they can ask questions or choose to opt out.

Given the varying practices and resources available, participating health facilities can choose to implement one or more of the following approaches to obtaining informed consent:

- Study-specific oral informed consent before case identification: pregnant women presenting to the health facility for term deliveries are approached for informed oral consent upon admission to the maternity ward.
- Opt-out consent upon registration at health facility: pregnant women presenting to the health facility for deliveries are informed of the study and given information on how to opt out if they choose.
- Broad informed consent upon registration at the health facility, as per the health facility's standard operation procedures: this option is available only to health facilities that routinely ask patients for informed consent to use their data for research purposes.
- Study-specific written informed consent before case identification: pregnant women presenting to the health facility for term deliveries are approached for informed consent upon admission to the maternity ward. Participants who cannot read or write can provide documented written consent with a thumbprint or signature.

6.4 Maintaining participant confidentiality

Data confidentially will be maintained at all times according to global and local regulatory requirements. Paper records will be kept in locked cabinets in the health facility. Electronic data will be stored in secure databases. Only authorized study team members will have access to study data with individual identifiers. Access to the study data will be controlled and will be limited to the principal investigators, people selected to perform quality and consistency checks, and the study statistician.

6.5 Data sharing and ownership

After the primary objectives of the study have been achieved and published, de-identified data will be shared upon reasonable request made to the study team and the WHO Pharmacovigilance team. Primary data ownership will reside with the local principal investigator's institution. Local authorities will have access to anonymized or aggregated data for oversight and public health initiatives. Any further research using data from the study must be approved as a collaboration between representatives from the study team, the principal investigators, the local or national regulatory authorities, and potentially the ethics and community representative to ensure the interests of participants and their communities are protected.

6.6 Independent ethics committee or institutional review board

WHO will ensure the master protocol and any amendments, with specific details about the study site, are submitted to the WHO Research Ethics Review Committee for review and approval. Each participating site will be responsible for submission of the study protocol and any amendment to the respective local, national or independent ethics committees or institutional reviews boards, according to local requirements. Any additional regulatory clearances, as required by the country law and regulations, will be adhered to in respect of each participating site.

7. Dissemination of study results

7.1 Study report

A study report with all the findings will be made available by the study team to the national health authorities within an agreed time period. The results will be communicated to the participating sites once the report is finalized.

7.2 Dissemination strategy

The dissemination actions will comprise at least the following:

- publication of scientific papers in an open-access format, consistent with good publication practices, with authorship and co-authorship agreed between the WHO Pharmacovigilance team and study sites;
- participation in scientific meetings with oral or poster presentations;
- a study report for the national health authorities with all the findings, made available by the study team within an agreed time period;
- engagement with the local community to communicate findings to the public in a sensitive and respectful manner.

7.3 Communicating findings to communities and participants

Findings will be disseminated at the community level, although individuals may still be informed via local clinical teams. A diverse approach will be used, including community meetings, visual aids, posters, printed materials in local languages, radio broadcasts, engagement with community leaders, and simplified written summaries. Before communications channels are used, key community stakeholders will be identified and engaged to ensure the communication methods and language are appropriate and culturally sensitive, and to obtain community-level permissions before implementation. Findings will be presented as aggregate trends within the context of local neonatal outcomes. Health-care professionals will share these findings with patients and families as part of their routine work, using factual and empathetic language. Communication around neonatal death will be framed with an understanding of local and cultural beliefs and practices, through trusted leaders and other people in the community. Communication with bereaved families will be handled individually, sensitively and supportively by trained and trusted people.

In general, the community will benefit from the study because findings will improve local health-care practices and raise awareness about neonatal outcomes informing policies and setting priorities. The study will also strengthen collaborations among stakeholders and build local capacity to diagnose AESIs and standardize practices, in preparation for introduction of new vaccines.

8. Study limitations

This study is based on deliveries that occur in facilities, due to facility-based diagnostic procedures required for AESI classification (for data accuracy and consistency) and does not include deliveries that occur at home. In settings where a significant proportion of deliveries take place at home, there is a risk of selection bias if the deliveries that occur in health facilities are systematically different from deliveries that occur at home due to factors such as limited physical access, education or cultural beliefs. In such settings, AESI estimates derived solely from health facility deliveries may not accurately reflect the occurrence in the overall study population. During interpretation of the study, it is crucial to emphasize that the reported rates are based solely on health facility submissions and may differ if community births are considered. The criterion of selecting higher-level health facilities with specific diagnostic capabilities is important to confirm pregnancy dating and gestational age needed for level diagnostic certainty of preterm births using GAIA definitions. Together with the expectation of mothers to have a telephone number, this could lead to a potential bias towards people who can afford to use or have access to better-equipped health facilities and telephone lines.

References

1 Sebghati M, Khalil A. Uptake of vaccination in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2021;76:53–65 (https://doi.org/10.1016/j.bpobgyn.2021.03.007, accessed 2 May 2025).

2 Brent RL. Risks and benefits of immunizing pregnant women: the risk of doing nothing. Reprod Toxicol. 2006;21(4):383–389 (https://doi.org/10.1016/j.reprotox.2005.09.009, accessed 2 May 2025).

3 Beigi RH, Krubiner C, Jamieson DJ, Lyerly AD, Hughes B, Riley L, et al. The need for inclusion of pregnant women in COVID-19 vaccine trials. Vaccine. 2021;39(6):868–870 (https://doi.org/10.1016/j.vaccine.2020.12.074, accessed 2 May 2025).

4 Misra RS, Nayak JL. The importance of vaccinating children and pregnant women against influenza virus infection. Pathogens. 2019;8(4):265 (https://doi.org/10.3390/pathogens8040265, accessed 2 May 2025).

5 Omer SB. Maternal immunization. N Engl J Med. 2017;376(13):1256–1267 (https://doi.org/10.1056/NEJMra1509044, accessed 2 May 2025).

6 Vojtek I, Dieussaert I, Doherty TM, Franck V, Hanssens L, Miller J, et al. Maternal immunization: where are we now and how to move forward? Ann Med. 2018;50(3):193–208 (https://doi.org/10.1080/07853890.2017.1421320, accessed 2 May 2025).

7 FDA approves first vaccine for pregnant individuals to prevent RSV in infants. Silver Spring, MD: United States Food and Drug Administration; 2023 (https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants, accessed 2 May 2025).

8 GBD 2015 Child Mortality Collaborators. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1725–1774 (https://doi.org/10.1016/S0140-6736(16)31575-6, accessed 2 May 2025). Erratum in Lancet. 2017;389(10064):e1 (https://doi.org/10.1016/S0140-6736(16)32608-3, accessed 2 May 2025).

9 Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. Lancet. 2021;398(10302):772–785 (https://doi.org/10.1016/S0140-6736(21)01112-0, accessed 2 May 2025).

10 Quinn JA, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Preterm birth: case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine. 2016;34(49):6047–6056 (https://doi.org/10.1016/j.vaccine.2016.03.045, accessed 2 May 2025).

11 Tavares Da Silva F, Gonik B, McMillan M, Keech C, Dellicour S, Bhange S, et al. Stillbirth: case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2016;34(49):6057–6068 (https://doi.org/10.1016/j.vaccine.2016.03.044, accessed 2 May 2025).

12 Pathirana J, Muñoz FM, Abbing-Karahagopian V, Bhat N, Harris T, Kapoor A, et al. Neonatal death: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6027–6037 (https://doi.org/10.1016/j.vaccine.2016.03.040, accessed 2 May 2025).

13 Cutland CL, Lackritz EM, Mallett-Moore T, Bardají A, Chandrasekaran R, Lahariya C, et al. Low birth weight: case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48 Pt A):6492–6500 (https://doi.org/10.1016/j.vaccine.2017.01.049, accessed 2 May 2025).

14 World Bank country and lending groups. Washington, DC: World Bank; 2023 (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519, accessed 2 May 2025).

15 Sobanjo-Ter Meulen A, Liljestrand J, Lawn JE, Hombach J, Smith J, Dickson KE, et al. Preparing to introduce new maternal immunizations in low- and lower-middle-income countries: a report from the Bill & Melinda Gates Foundation convening “Allies in Maternal and Newborn Care”; May 3–4, 2018. Vaccine. 2020;38(28):4355–4361 (https://doi.org/10.1016/j.vaccine.2020.04.075, accessed 2 May 2025).

16 International ethical guidelines for health-related research involving humans, fourth edition. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 2 May 2025).

17 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–2194 (https://doi.org/10.1001/jama.2013.281053, accessed 2 May 2025).

18 Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal immunological adaptation during normal pregnancy. Front Immunol. 2020;11:575197 (https://doi.org/10.3389/fimmu.2020.575197, accessed 2 May 2025).

19 Orefice R. Immunology and the immunological response in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2021;76:3–12 (https://doi.org/10.1016/j.bpobgyn.2020.07.013, accessed 2 May 2025).

20 Reiss JD, Peterson LS, Nesamoney SN, Chang AL, Pasca AM, Marić I, et al. Perinatal infection, inflammation, preterm birth, and brain injury: a review with proposals for future investigations. Exp Neurol. 2022;351:113988 (https://doi.org/10.1016/j.expneurol.2022.113988, accessed 2 May 2025).

21 Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–433 (https://doi.org/10.1111/j.1600-0897.2010.00836.x, accessed 2 May 2025).

22 Alberca RW, Pereira NZ, Oliveira LMDS, Gozzi-Silva SC, Sato MN. Pregnancy, viral infection, and COVID-19. Front Immunol. 2020;11:1672 (https://doi.org/10.3389/fimmu.2020.01672, accessed 2 May 2025).

23 Healy CM. Vaccines in pregnant women and research initiatives. Clin Obstet Gynecol. 2012;55(2):474–486 (https://doi.org/10.1097/GRF.0b013e31824f3acb, accessed 2 May 2025).

24 Maertens K, Orije MRP, Van Damme P, Leuridan E. Vaccination during pregnancy: current and possible future recommendations. Eur J Pediatr. 2020;179(2):235–242 (https://doi.org/10.1007/s00431-019-03563-w, accessed 2 May 2025).

25 Cinicola B, Conti MG, Terrin G, Sgrulletti M, Elfeky R, Carsetti R, et al. The protective role of maternal immunization in early life. Front Pediatr. 2021;9:638871 (https://doi.org/10.3389/fped.2021.638871, accessed 2 May 2025).

26 Chu HY, Englund JA. Maternal immunization. Clin Infect Dis. 2014;59(4):560–568 (https://doi.org/10.1093/cid/ciu327, accessed 2 May 2025).

27 MacDougall DM, Halperin SA. Improving rates of maternal immunization: challenges and opportunities. Hum Vaccin Immunother. 2016;12(4):857–865 (https://doi.org/10.1080/21645515.2015.1101524, accessed 2 May 2025).

28 Otieno NA, Otiato F, Nyawanda B, Adero M, Wairimu WN, Ouma D, et al. Drivers and barriers of vaccine acceptance among pregnant women in Kenya. Hum Vaccin Immunother. 2020;16(10):2429–2437 (https://doi.org/10.1080/21645515.2020.1723364, accessed 2 May 2025).

29 Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008;359(15):1555–1564 (https://doi.org/10.1056/NEJMoa0708630, accessed 2 May 2025). Erratum in N Engl J Med. 2009;360(6):648.

30 World Health Organization. Pertussis vaccines: WHO position paper, August 2015 – recommendations. Vaccine. 2016;34(12):1423–1425 (https://doi.org/10.1016/j.vaccine.2015.10.136, accessed 2 May 2025).

31 World Health Organization. Vaccines against influenza WHO position paper – November 2012. Wkly Epidemiol Rec. 2012;87(47):461–476.

32 World Health Organization. Tetanus vaccines: WHO position paper – February 2017. Wkly Epidemiol Rec. 2017;92(6):53–76.

33 Etti M, Calvert A, Galiza E, Lim S, Khalil A, Le Doare K, et al. Maternal vaccination: a review of current evidence and recommendations. Am J Obstet Gynecol. 2022;226(4):459–474 (https://doi.org/10.1016/j.ajog.2021.10.041, accessed 2 May 2025).

34 DARWIN EU® – background incidence rates of selected vaccine adverse events of special interest (AESIs) in Europe. Amsterdam: European Medicines Agency; 2024 (https://catalogues.ema.europa.eu/node/4155/methodological-aspects, accessed 21 May 2025).

35 Woldemariam MT, Jimma W. Adoption of electronic health record systems to enhance the quality of healthcare in low-income countries: a systematic review. BMJ Health Care Inform. 2023;30(1):e100704 (https://doi.org/10.1136/bmjhci-2022-100704, accessed 17 June 2025).

36 Colicchio TK, Cimino JJ, Fiol GD, Del Fiol G. Unintended consequences of nationwide electronic health record adoption: challenges and opportunities in the post-meaningful use era. J Med Internet Res. 2019;21(6):e13313 (https://doi.org/10.2196/13313, accessed 17 June 2025).

37 Tsai CH, Eghdam A, Davoody N, Wright G, Flowerday S, Koch S. Effects of electronic health record implementation and barriers to adoption and use: a scoping review and qualitative analysis of the content. Life (Basel). 2020;10(12):327 (https://doi.org/10.3390/life10120327, accessed 17 June 2025).

38 Balkus JE, Neradilek M, Fairlie L, Makanani B, Mgodi N, Mhlanga F, et al. Assessing pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe: results from a systematic chart review. PLoS One. 2021;16(3):e0248423 (https://doi.org/10.1371/journal.pone.0248423, accessed 21 May 2025).

39 Lokken EM, Mathur A, Bunge KE, Fairlie L, Makanani B, Beigi R, et al. Pooled prevalence of adverse pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe: results from a systematic review and meta-analyses to inform trials of novel HIV prevention interventions during pregnancy. Front Reprod Health. 2021;3:672446 (https://doi.org/10.3389/frph.2021.672446, accessed 21 May 2025).

40 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 (https://doi.org/10.1016/j.vaccine.2016.07.006, accessed 21 May 2025).

41 Stuurman AL, Riera M, Lamprianou S, Perez-Vilar S, Anderson SA, Mangtani P, et al. Vaccine safety surveillance in pregnancy in low- and middle-income countries using GAIA case definitions: a feasibility assessment. Vaccine. 2018;36(45):6736–6743 (https://doi.org/10.1016/j.vaccine.2018.09.033, accessed 2 May 2025).

42 WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems of medical products, revision VI. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/341243, accessed 2 May 2025).

43 Cutland CL, Sawry S, Fairlie L, Barnabas S, Frajzyngier V, Roux JL, et al. Obstetric and neonatal outcomes in South Africa. Vaccine. 2024;42(6):1352–1362 (https://doi.org/10.1016/j.vaccine.2024.01.054, accessed 2 May 2025).

44 Kochhar S, Clarke E, Izu A. Immunization in pregnancy safety surveillance in low and middle-income countries-field performance and validation of novel case definitions. Vaccine. 2019;37(22):2967–2974 (https://doi.org/10.1016/j.vaccine.2019.03.074, accessed 2 May 2025).

45 Supplement to mpox protocol section 3.7: Study flow – data sources and data collection. Geneva: World Health Organization (https://cdn.who.int/media/docs/default-source/medicines/pharmacovigilance/supplement-to-mpox-protocol--section-3.7.pdf?sfvrsn=6150985b_1&download=true, accessed 17 June 2025).

46 Naing L, Winn T, Rusli B. Practical issues in calculating the sample size for prevalence studies. Arch Orofacial Sciences. 2006;1:9–14.

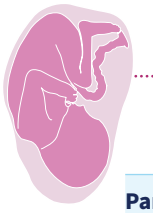
47 R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2021.

48 General Data Protection Regulation. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC. Brussels: European Commission; 2016 (https://eur-lex.europa.eu/eli/reg/2016/679/oj, accessed 2 May 2025).

Annex 1. Health facility screening questionnaire

Version 1, 24 March 2025: This questionnaire collects information on potential study site characteristics, how patient data are recorded, and resources available. The purpose of the data collected is to support the decision to select the health facility as a study site and to understand the baseline characteristics for interpretation of the findings. The form should be filled by potential site principal investigators expressing an interest in the study. The information can be obtained from health facility administration records. The questionnaire takes 10–20 minutes to fill.

	Part 1. General information		**Comments**
1	Health facility name and address		
2	Name and function of respondent		
3	Email address of respondent		
4	Country		
5	Full address		
6a	Is there an obstetrics department or maternity ward in your health facility?	Yes ☐ No ☐	
6b	Number of beds in maternity ward		
7	Number of deliveries per year		
8	Type of health facility	Primary ☐ Secondary ☐ Tertiary ☐	
9	Which of the following types of care are provided	Antenatal ☐ Maternity ☐ Paediatric ☐ Other ☐ *If other, specify:*	
10	Is the health facility public or private?	Public ☐ Private ☐	
11	Is the population served urban or rural?	Primarily urban ☐ Primarily rural ☐ Mixed ☐	
	Part 2. Patient data recording		
12	How are patient data recorded? *Check all that apply*	Electronically and stored in a database ☐ Paper-based and stored in a physical archive ☐	
13	Is internet access available in your health facility to allow for data entry?	Yes ☐ No ☐	
14	If there is a database or archive with patient data available (e.g. patient charts or discharge registry), can it be used for research purposes?	Yes ☐ No ☐	



Part 2. Patient data recording *(continued)*			
15	Is a unique identifier used for each patient?	Yes ☐ No ☐	
16	If unique identifiers are used, is the same identifier used across departments (e.g. antenatal, maternity, neonatal and paediatric wards)?	Yes ☐ No ☐	
17	Are individual patient charts easily accessible in the database or archive?	Yes ☐ No ☐	
18	Is a trained physician or nurse available to participate in the study to review medical records against case definition criteria and complete case report forms?	Yes ☐ No ☐	
19	If a trained physician or nurse is available to participate in the study, do they have experience in research, including data collection for research projects?	Yes ☐ No ☐	
Part 3. Newborn outcomes			**Comments**
20	Are live births recorded in maternity records, and/or elsewhere?	Maternity records: Yes ☐ Maternity records: No ☐ Elsewhere: Yes ☐ Elsewhere: No ☐ *If elsewhere, specify:*	
21	Are stillbirths (babies born without signs of life after 28 weeks of gestation) recorded?	Yes ☐ No ☐	
22	Are neonatal deaths (on days 0–28) that occur in the health facility recorded?	Yes ☐ No ☐	
23a	Is gestational age routinely ascertained?	Yes ☐ No ☐	
23b	If yes to Question 23a, how is gestational age usually ascertained?	Ultrasound scan in first trimester ☐ Ultrasound scan in second trimester ☐ Ultrasound scan in third trimester ☐ Last menstrual period from interview with mother ☐ Fundal height ☐ Other ☐ *If other, specify:*	
24a	Are newborns routinely weighed at birth?	Yes ☐ No ☐	

Part 3. Newborn outcomes *(continued)*			**Comments**
24b	What type of scale is available? How often is the scale calibrated?	Digital ☐ Mechanical ☐ Hanging ☐ *Calibration:*	
25	Are APGAR scores routinely assessed, including for suspected stillbirths?	Yes ☐ No ☐	
26a	Does your health facility have a resident obstetrician?	Yes ☐ No ☐	
26b	Does your health facility have a resident paediatrician?	Yes ☐ No ☐	

Annex 2. Global Alignment of Immunization Safety Assessment in Pregnancy case definitions

The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) case definitions were established to standardize definitions of key neonatal outcomes to enhance the safety monitoring of maternal immunization programmes. They contain detailed criteria and introduce levels of diagnostic certainty. The case report forms in Annexes 4–6 should be used to collect information needed to define neonatal outcomes using the GAIA definitions. Diagnosis and level of certainty should be carried out by trained specialist paediatricians and obstetricians. The time taken to make a diagnosis depends on the amount of data available and the experience of using the definitions. Completed questionnaires in Annexes 4–6 should be used with this to confirm the diagnosis and level of certainty. Levels of certainty have been revised in accordance with findings in studies aimed to assess applicability and utility *(1)*.

Preterm birth

- **Level 1 of diagnostic certainty:**

  i certain last menstrual period (LMP) or intrauterine insemination date or embryo transfer date with confirmatory first trimester scan (≤13 weeks and 6 days);

  or

  ii first trimester scan (≤13 weeks and 6 days).

- **Level 2A of diagnostic certainty:**

  i certain LMP with second trimester scan (14 weeks to 27 weeks and 6 days); if LMP and ultrasound do not correlate, default to ultrasound gestational age assessment;

  or

  ii certain LMP with first trimester physical examination.

- **Level 2B of diagnostic certainty:**

  i uncertain LMP with second trimester scan (14 weeks to 27 weeks and 6 days).

- **Level 3A of diagnostic certainty:**

  i certain LMP with third trimester scan (28 weeks or more);

  or

  ii certain LMP with confirmatory second trimester fundal height;

  or

  iii certain LMP with birthweight;

  or

  iv uncertain LMP with first trimester physical examination.

- **Level 3B of diagnostic certainty:**

  i uncertain LMP with fundal height;

  or

  ii uncertain LMP with newborn physical assessment;

  or

  iii uncertain LMP with birthweight.

- **Level 3C of diagnostic certainty:**

  i uncertain LMP with third trimester fundal height.

- **Level 3D of diagnostic certainty:**

  i uncertain LMP with third trimester ultrasound.

Stillbirth (unknown timing of fetal death)

Antepartum stillbirth

- **Level 1 of diagnostic certainty:**

  i delivery of infant with no signs of life at birth (no spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, APGAR score of 0 at one and five minutes) determined by physical examination after delivery (with or without electronic monitoring of heart rate, respiratory rate and pulse oximetry);

  and

  ii prenatal ultrasound examination documenting lack of fetal cardiac activity or movement before the onset of labour;

  or

  iii auscultation for fetal heart tones (using electronic devices or non-electronic devices) documenting lack of fetal heartbeat;

  and

  iv maternal report of lack of fetal movement for 24 hours or more;

  or

  v maternal physical examination confirming lack of fatal movement;

  or

  vi radiology findings consistent with intrauterine fetal death;

  and

  vii attended delivery followed by fetal physical examination after birth consistent with antepartum death by obstetrician, neonatologist, paediatrician, maternal-fetal medicine specialist or pathologist, or (in settings where access to a specialist is not feasible) diagnosis by a health-care provider trained or experienced to make the diagnosis (e.g. general practice physician, midwife, nurse practitioner, physician's assistant, or other qualified trained practitioner);

  or

  viii fetal/placental pathology report consistent with antepartum death;

  and

  ix gestational age within predefined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (level 1 or 2 in gestational age assessment algorithm) *(2)*.

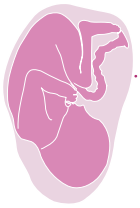
- **Level 2A of diagnostic certainty:**

  i delivery of an infant with no of signs of life at birth (no spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, APGAR score of 0 at one and five minutes) determined by physical examination after delivery;

  and

  ii maternal report of lack of fetal movement for 24 hours or more;

  or



iii maternal physical examination confirming lack of fetal movement;

or

iv auscultation for fetal heart tones (using electronic or nonelectronic devices) documenting lack of fetal heartbeat;

and

v attended delivery followed by physical examination after birth consistent with antepartum death, by specialist or qualified trained practitioner appropriate to the setting;

or

vi fetal/placental pathology report consistent with antepartum death;

and

vii gestational age within predefined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (level 1–2 in gestational age assessment algorithm) *(2)*.

- **Level 2B of diagnostic certainty:**

i delivery of an infant reported to have no of signs of life at birth (no spontaneous movements, no umbilical cord pulse, no heartbeat, no cry or spontaneous respirations, no chest movement and whole-body cyanosis);

and

ii maternal report of lack of fetal movement for 24 hours or more before delivery;

or

iii report of auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat;

and

iv attended delivery followed by physical examination of the fetus after birth consistent with antepartum death by a health-care professional appropriate to the level of standard of care in the setting;

or

v verbal history by a trained health-care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth and with physical features consistent with antepartum death;

and

vi gestational age within predefined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (level 2–3 in gestational age assessment algorithm) *(2)*.

- **Level 3 of diagnostic certainty:**

i delivery of an infant reported to have no of signs of life at birth (no spontaneous movements, no umbilical cord pulse, no heartbeat, no cry or spontaneous respirations, no chest movement and whole-body cyanosis);

and

ii maternal report of lack of fetal movement for 24 hours or more before delivery;

or

iii report of auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat;

and

iv non-attended delivery followed by physical examination of the fetus after birth consistent with antepartum death by a health-care professional appropriate to the level of standard of care in the setting;

or

v verbal history by a trained health-care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth and with physical features consistent with antepartum death;

and

vi gestational age within predefined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (level 2–3 in gestational age assessment algorithm) *(2)*.

- **Level 4 of diagnostic certainty:**

  i report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made);

  ii maternal information insufficient to assess gestational age.

Intrapartum stillbirth

- **Level 1 of diagnostic certainty:**

  i delivery of an infant with no signs of life at birth, including: no spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, and APGAR score of 0 at one and five minutes;

  and

  ii determination of the absence of signs of life made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate and pulse oximetry;

  and

  iii evidence of live fetus before the onset of labour (documentation of fetal movement and of fetal heart tones by ultrasound before the onset of labour) (note: in the absence of evidence of a live fetus before the onset of labour, the fetal death should be reported as a stillbirth or antepartum stillbirth);

  and

  iv attended delivery followed by physical examination after birth consistent with intrapartum death by an obstetrician, neonatologist, paediatrician, maternal-fetal medicine specialist or pathologist, or (in settings where access to a specialist is not feasible) diagnosis by a health-care provider trained or experienced to make the diagnosis (e.g. general practice physician, midwife or another qualified trained practitioner);

  and

  v gestational age within predefined range for selected stillbirth definition as assessed by maternal and/or fetal-neonatal parameters (level 1 in gestational age assessment algorithm) *(2)*.

- **Level 2 of diagnostic certainty:**

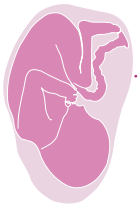
  i delivery of an infant with no of signs of life at birth, including no spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations and APGAR score of 0 at one and five minutes;

  and

  ii determination of the absence of signs of life made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate and pulse oximetry or documentation of lack of response to resuscitation efforts;

  and

  iii evidence of live fetus before the onset of labour (maternal report of fetal movement before the onset of labour and documentation of fetal heart tones by auscultation or handheld doppler) (note: in the absence of evidence of a live fetus before the onset of labour, the fetal death should be reported as a stillbirth or antepartum stillbirth);



and

iv attended delivery followed by physical examination after birth consistent with intrapartum death by a health-care professional appropriate to the level of standard of care in the setting;

and

v gestational age within predefined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (level 1–2 in gestational age assessment algorithm) *(2)*.

- **Level 3 of diagnostic certainty:**

  i delivery of an infant reported to have no of signs of life at birth, including no spontaneous movements, no umbilical cord pulse, no heartbeat, no cry, no spontaneous respirations or chest movement and whole-body cyanosis;

  and

  ii evidence of live fetus before the onset of labour (maternal report of fetal movement before the onset of labour or auscultation of fetal heart tones) (note: in the absence of evidence of a live fetus before the onset of labour, the fetal death should be reported as a stillbirth or antepartum stillbirth);

  and

  iii non-attended delivery followed by physical examination of the fetus after birth consistent with intrapartum death by a health-care professional appropriate to the level of standard of care in the setting or verbal history by a trained health-care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth;

  and

  iv gestational age within predefined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (level 2–3 in gestational age assessment algorithm) *(2)*.

- **Level 4 of diagnostic certainty:**

  i report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made);

  and

  ii maternal information insufficient to assess gestational age.

Neonatal death

Neonatal death in a non-viable live birth

- **Level 1 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age <22 weeks (gestational age level of certainty = 1) *(2)*;

  or

  iii birthweight <500 g;

  and

  iv death of infant in first 28 days of life;

  and

  v medically confirmed death.

- **Level 2 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age/size of newborn assessed as at least one of:
  - **gestational age <22 weeks (gestational age level of certainty = 1 or 2)** *(2)*
  - **birthweight <500 g;**

  and

  iii death of infant in first 28 days of life;

  and

  iv medically confirmed death or non-medically confirmed death.

- **Level 3 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age <5 months according to parent/family member/delivery attendant (gestational age level of certainty = 2 or 3);

  and

  iii death of infant in first 28 days of life;

  and

  iv medically confirmed death or non-medically confirmed death.

Neonatal death in an extremely preterm live birth

- **Level 1 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age between ≥22 and <28 weeks (gestational age level of certainty = 1);

  or

  iii birthweight between ≥500 g and <1000 g;

  and

  iv death of infant in first 28 days of life;

  and

  v medically confirmed death.

- **Level 2 of diagnostic certainty:**

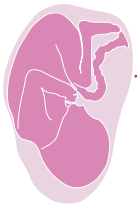
  i live born infant;

  and

  ii gestational age/size of newborn assesses as one or more of:
  - gestational age between ≥22 weeks and <28 weeks (gestational age level of certainty = 1 or 2) *(2)*
  - birthweight between ≥500 g and <1000 g;

  and

  iii death of infant in first 28 days of life;



and

iv medically confirmed death or non-medically confirmed death.

- **Level 3 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age between ≥5 months and <7 months according to mother/father/family member/delivery attendant (gestational age level of certainty = 2 or 3) *(2)*;

  and

  iii death of infant in first 28 days of life;

  and

  iv medically confirmed death or non-medically confirmed death.

Neonatal death in a preterm live birth

- **Level 1 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age between ≥28 weeks and <37 weeks (level of certainty = 1) *(2)*;

  or

  iii birthweight between ≥1000 g and <2500 g;

  and

  iv death of infant in first 28 days of life;

  and

  v medically confirmed death.

- **Level 2 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age/size of newborn assessed as one or more of:

  - gestational age between ≥28 weeks and <37 weeks (gestational age level of certainty = 1 or 2) *(2)*
  - birthweight between ≥1000 g and <2500 g;

  and

  iii death of infant in first 28 days of life;

  and

  iv medically confirmed death or non-medically confirmed death.

- **Level 3 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age between ≥7 months and <9 months according to parent/family member/delivery attendant (gestational age level of certainty = 2 or 3) *(2)*;

  and

iii death of infant in first 28 days of life;

and

iv medically confirmed death or non-medically confirmed death.

Neonatal death in a term live birth

- **Level 1 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age ≥37 weeks (gestational age level of certainty = 1);

  and

  iii birthweight >2500 g;

  or

  iv documented intrauterine growth retardation if birthweight ≤2500 g;

  and

  v death of infant in first 28 days of life;

  and

  vi medically confirmed death.

- **Level 2 of diagnostic certainty:**

  i live born infant;

  and

  ii gestational age/size of newborn assessed as one or more of:

  - gestational age ≥37 weeks (gestational age level of certainty = 1 or 2) *(2)*
  - birthweight ≥2500 g;

  and

  iii death of infant in first 28 days of life;

  and

  iv medically confirmed death or non-medically confirmed death confirmed by examination by (at least) a non-medically trained attendant (e.g. undertaker, community member).

- **Level 3 of diagnostic certainty:**

  i live born infant;

  and

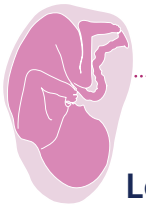
  ii gestational age ≥9 months according to parent/family member/delivery attendant (gestational age level of certainty = 2 or 3);

  and

  iii death of infant in first 28 days of life;

  and

  iv medically confirmed death or non-medically confirmed death.



Low birthweight

- **Level 1 of diagnostic certainty:**

  i newborn infant weighed within 24 hours of birth;

  and

  ii electronic scale graduated to 10 g used;

  and

  iii scale calibrated at least once a year;

  and

  iv scale placed on a level, hard surface;

  and

  v scale tared to zero grams;

  and

  vi weight recorded as <2500 g;

  or

  vii birthweight recorded as <2500 g;

  and

  viii birthweight assessed as per the health facility's standard operating procedure, which fulfils the first five criteria of level of certainty 1.

- **Level 2 of diagnostic certainty:**

  i newborn infant weighed within 24 hours of birth;

  and

  ii scale (electronic or spring) graduated to at least 50 g;

  and

  iii scale calibrated at least once a year, or more often if moved;

  and

  iv scale tared to zero grams or 0.00 kg;

  and

  v weight recorded as <2500 g;

  or

  vi birthweight recorded as <2500 g;

  and

  vii birthweight assessed as per the health facility's standard operating procedure, which fulfils the first four criteria of level of certainty 2.

- **Level 3 of diagnostic certainty:**

  i newborn infant weighed on day 1 or 2 of life (first 48 hours of life);

  and

  ii weight measured using dial, spring or colour-coded scale;

  and

  iii weight assessed as <2500 g.

- Level 4 of diagnostic certainty:

  i newborn infant weight assessed on day 1 or 2 of life (first 48 hours of life);

  and

  ii proxy measure of birthweight used;

  and

  iii weight category assessed as <2500 g.

Reference

1 Cutland CL, Sawry S, Fairlie L, Barnabas S, Frajzyngier V, Roux JL, et al. Obstetric and neonatal outcomes in South Africa. Vaccine. 2024;42(6):1352–1362 (https://doi.org/10.1016/j.vaccine.2024.01.054, accessed 2 May 2025).

2 Quinn JA, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Preterm birth: case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine. 2016;34(49):6047–6056 (https://doi.org/10.1016/j.vaccine.2016.03.045, accessed 21 May 2025).

Annex 3. Baseline information

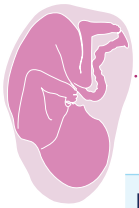
Version 1, 24 March 2025: The following baseline information should be collected for all deliveries. The questionnaire should be administered by trained and authorized study staff and data mangers. Information sources include face-to-face, telephone, virtual or electronic interview with the woman and medical notes. The questionnaire takes less than five minutes to complete. Medical notes should be accessed only by people authorized to do so.

	Maternal information	If interviewing a representative of the woman, check this box ☐
	Please ask the woman presenting to the maternity ward or a legally acceptable representative of the woman the following questions	Relationship of representative to woman: .....
1	Age of woman in completed years at time of delivery	..... years
2	Place of residence *Give closest town centre*	.....
	Newborn characteristics	
3	Date of delivery	dd/mm/yyyy ...../...../..... Unknown ☐
4a	Who attended the delivery?	Midwife ☐ Obstetrician ☐ Maternal-fetal medicine specialist ☐ Other ☐ *If other, specify:* ..... Unknown ☐
4b	What was the mode of delivery	Vaginal ☐ Caesarean section ☐
4c	Were there any delivery complications?	Yes ☐ No ☐ Unknown ☐
4d	If yes to Question 4c, what was the complication? *Select all that apply*	Fetal distress ☐ Antepartum/postpartum haemorrhage ☐ Assisted vaginal delivery ☐ Other ☐ *If other, specify:* .....
4e	What was the delivery outcome of the mother?	Alive ☐ Dead ☐

Annex 4. Preterm birth case report form

Version 1, 24 March 2025: This case report form is designed to collect structured information needed to diagnose preterm births using Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) definitions. Information on the woman, pregnancy, fetal growth, maternal immunization and delivery relevant to the preterm birth diagnosis will be collected. The questionnaire should be administered by trained and authorized study staff and data mangers. Information sources include face-to-face, telephone, virtual or electronic interview with the woman, interview with health-care professionals that cared for the woman and medical notes. The questionnaire usually takes about 20 minutes to complete, but longer if information needs to be supplemented from medical notes. Medical notes should be accessed only by people authorized to do so**.**

Part 1		
	Maternal information	If interviewing a representative of the woman, check this box ☐
	Please ask the woman presenting to the maternity ward or a legally acceptable representative of the woman the following questions	Relationship of representative to woman: ....
1	Age of woman in completed years at time of delivery	..... years
2	Place of residence *Give closest town centre*	.....
	Newborn characteristics	
3	Date of delivery	dd/mm/yyyy...../...../..... Unknown ☐
4a	Who attended the delivery?	Midwife ☐ Clinical officer/clinical associate ☐ Medical officer/junior doctor ☐ Obstetrician ☐ Maternal-fetal medicine specialist ☐ Other ☐ *If other, specify:* Unknown ☐
4b	What was the mode of delivery?	Vaginal ☐ Caesarean section ☐
4c	Were there any delivery complications?	Yes ☐ No ☐ Unknown ☐



Part 1 *(continued)*

4d	If yes to Question 4c, what was the complication? *Select all that apply*	Fetal distress ☐ Antepartum/postpartum haemorrhage ☐ Assisted vaginal delivery ☐ Other ☐ *If other, specify:* .....
4e	What was the delivery outcome of the mother?	Alive ☐ Dead ☐

Part 2. Gestational age at birth

Woman's last menstrual period (LMP)

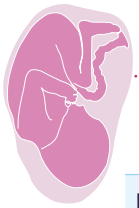
5a	Is the woman's LMP known?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 6*
5b	What is the date of the LMP reported by the woman?	dd/mm/yyyy ...../...../..... Unknown ☐
5c	Is the woman certain or uncertain about the LMP?	Certain ☐ Uncertain ☐ Unknown ☐

Assisted reproduction technology (highly unlikely in low- and middle-income countries)

6a	Was the conception natural (i.e. without the use of assisted reproduction technology)?	Yes ☐ No ☐ Unknown ☐ *If yes or unknown, go to Question 7*
6b	Did intrauterine insemination take place for this pregnancy? *Intrauterine insemination is a procedure in which a fine catheter is inserted through the cervix into the uterus to deposit a sperm sample directly into the uterus, to achieve fertilization and pregnancy*	Yes ☐ No ☐ Unknown ☐
6c	What was the date of intrauterine insemination?	dd/mm/yyyy ...../...../..... Unknown ☐
6d	Did embryo transfer take place for this pregnancy? *Embryo transfer is a procedure in which one or more embryos are placed in the uterus or fallopian tube*	Yes ☐ No ☐ Unknown ☐

Part 2. Gestational age at birth *(continued)*

6e	What was the date of embryo transfer?	dd/mm/yyyy ...../...../..... Unknown ☐
	Ultrasound during pregnancy	
7a	Was an ultrasound scan done during pregnancy?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 8a*
7b	When was the first ultrasound scan done during the pregnancy?	Gestational age ..... weeks and ..... days
7c	What was the date of the first ultrasound scan?	dd/mm/yyyy ...../...../..... Unknown ☐
7d	What was the estimated gestational age based on the first ultrasound scan?	..... weeks and ..... days
7e	What was the expected delivery date based on the first ultrasound scan?	dd/mm/yyyy ...../...../..... Unknown ☐
	Physical examination of woman in first trimester (defined as ≤13 weeks + 6days)	
8a	Was a physical examination of the woman done in the first trimester?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 9a*
8b	What was the date of the physical examination in the first trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
8c	If yes to Question 8a, did a pelvic bimanual examination confirm an enlarged uterus?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 9a*
8d	What was the estimated gestational age based on the physical examination in the first trimester?	..... weeks and ..... days
8e	What was the expected delivery date based on the physical examination in the first trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
	Fundal height of woman in second trimester (defined as 14 weeks to 27 weeks + 6 days)	
9a	Was the fundal height measured in the second trimester? *If more than one measurement was done in the second trimester, report the first measurement*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 102a*
9b	What was the fundal height?	.....



Part 2. Gestational age at birth *(continued)*		
9c	What was the measurement unit of the fundal height?	Centimetres ☐ Inches ☐ Other ☐ *If other, specify:* ..... Unknown ☐
9d	What was the date of the fundal height measurement?	dd/mm/yyyy ...../...../..... Unknown ☐
Part 3. Birthweight		
10a	Was the newborn weighed within 48 hours of birth?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 11a*
10b	What was the measurement unit of the birthweight?	Grams ☐ Kilograms ☐ Pounds ☐ Other ☐ *If other, specify:* ..... Unknown ☐
10c	What was the birthweight?	.....
10d	What was the date of the birthweight measurement?	dd/mm/yyyy ...../...../..... Unknown ☐
Part 4. Immunization during pregnancy		
11a	Did the mother receive any vaccine(s) during pregnancy? *Please answer "yes" or "no" only if there is documented evidence; otherwise please answer "unknown"*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, end of questionnaire*

Part 4. Immunization during pregnancy *(continued)*		
11b	If yes to Question 11a, which vaccines were administered, and when? *Enter more than one item if the woman was vaccinated with more than one vaccine type and/or more than one dose*	**Vaccine 1:** Type: ..... Dose number: ..... Date: (dd/mm/yyyy): ...../...../..... Date unknown ☐ **Vaccine 2:** Type: ..... Dose number: ..... Date: (dd/mm/yyyy): ...../...../..... Date unknown ☐ **Vaccine 3:** Type: ..... Dose number: ..... Date: (dd/mm/yyyy): ...../...../..... Date unknown ☐ **Vaccine 4:** Type: ..... Dose number: ..... Date: (dd/mm/yyyy): ...../...../..... Date unknown ☐

Form completed by: ..... (staff member) ..... (sign) .

...../...../.....(date, dd/mm/yyyy)

Form checked by: ..... (staff member) ..... (sign) .

...../...../.....(date, dd/mm/yyyy)

Annex 5. Stillbirth case report form

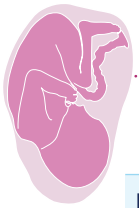
Version 1, 24 March 2025: This case report form is designed to collect structured information needed to diagnose stillbirth using Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) case definitions. Information on signs of life at birth, fetal heart tones and movement before labour, clinical examinations during pregnancy and maternal immunization relevant to stillbirth diagnosis will be collected. The questionnaire should be administered by trained and authorized study staff and data mangers. Information sources include face-to-face, telephone, virtual or electronic interview with the woman, interview with health-care professionals that cared for the mother and baby, pathology reports and medical notes. The questionnaire usually takes 30–60 minutes to complete, but longer if information such as pathology reports are not readily available. Medical notes and pathology reports should be accessed only by people authorized to do so.

Part1		
	Maternal information *Please ask the woman presenting to the maternity ward or a legally acceptable representative of the woman the following questions*	If interviewing a representative of the woman, check this box ☐ Relationship of representative to woman: ....
	Age of woman in completed years at time of delivery	..... years
	Place of residence Give closest town centre	.....
	Newborn characteristics	
	Date of delivery	dd/mm/yyyy ...../...../..... Unknown ☐
	Who attended the delivery?	Midwife ☐ Obstetrician ☐ Maternal-fetal medicine specialist ☐ Other ☐ *If other, specify:* ..... Unknown ☐
	What was the mode of delivery?	Vaginal ☐ Caesarean section ☐
	Were there any delivery complications?	Yes ☐ No ☐ Unknown ☐
	If yes to Question 4c, what was the complication? Select all that apply	Fetal distress ☐ Antepartum/postpartum haemorrhage ☐ Assisted vaginal delivery ☐ Other ☐ *If other, specify:* ..... Unknown ☐
	What was the delivery outcome of the woman?	Alive ☐ Dead ☐

Part1 *(continued)*

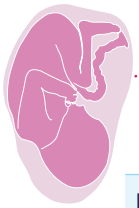
Absence of signs of life at birth

1a	Was a physical examination of the fetus or infant performed after delivery?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 11a
1b	By whom was the physical examination performed?	General practice physician ☐ Maternal-fetal medicine specialist ☐ Midwife ☐ Neonatologist ☐ Nurse practitioner ☐ Obstetrician ☐ Pathologist ☐ Paediatrician ☐ Physician's assistant ☐ Midwife ☐ Other qualified practitioner ☐ *If other qualified practitioner, specify:* .... Other ☐ *If other, specify:* ..... Unknown ☐
2	Which of the following signs were present at birth? *To be obtained from health-care professional present at the birth or from medical notes*	Spontaneous movement ☐ Umbilical cord pulse ☐ Heartbeat ☐ Respiration ☐ Crying ☐ Chest movement ☐ Other unspecified sign of life ☐ *If other, specify:* .....
3	Was the APGAR score 0 at one and five minutes?	Yes ☐ No ☐ Unknown ☐
4	Was there whole-body cyanosis?	Yes ☐ No ☐ Unknown ☐
5	Was there a response to resuscitation?	Yes ☐ No ☐ Unknown ☐



Part1 *(continued)*		
6a	Was the physical examination after birth consistent with antepartum death (e.g. maceration, meconium staining, tissue injury, oedema)?	Yes ☐ No ☐ Unknown ☐
6b	Was the physical examination after birth consistent with intrapartum death?	Yes ☐ No ☐ Unknown ☐
	Verbal history	
7a	Is a verbal history of stillbirth by a trained health-care provider, a non-medical witness or the woman documented?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 8a
7b	Is the verbal history consistent with a fetus born with no signs of life or unresponsive to resuscitation?	Yes ☐ No ☐ Unknown ☐
7c	Is the verbal history describing fetal physical features consistent with antepartum death?	Yes ☐ No ☐ Unknown ☐
	Pathology report	
8a	Was a fetal/placental pathology report available?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 9a
8b	Was the fetal/placental pathology report consistent with antepartum death?	Yes ☐ No ☐ Unknown ☐
	Presence of fetal heart tones and fetal movement before onset of labour	
9a	Was there a prenatal ultrasound examination?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 10a
9b	Did the prenatal ultrasound examination document fetal heart tones before the onset of labour?	Yes ☐ No ☐ Unknown ☐
9c	Did the prenatal ultrasound examination document fetal movement before the onset of labour?	Yes ☐ No ☐ Unknown ☐
10a	Was auscultation for fetal heart tones performed before the onset of labour?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 11a

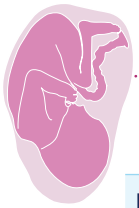
Part1 *(continued)*		
10b	Were fetal heat tones documented by auscultation before the onset of labour?	Yes ☐ No ☐ Unknown ☐
11a	Was a handheld Doppler used for fetal heart tones performed before the onset of labour?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 12a
11b	Were fetal heart tones documented by a handheld Doppler before the onset of labour?	Yes ☐ No ☐ Unknown ☐
12a	Did the woman report fetal movement before the onset of labour?	Yes ☐ No ☐ Unknown ☐
12b	Did the woman report a lack of fetal movement for 24 hours or more before the onset of labour?	Yes ☐ No ☐ Unknown ☐
12c	Did a physical examination of the woman confirm lack of fetal movement?	Yes ☐ No ☐ Unknown ☐
13	Are radiology findings consistent with intrauterine fetal death?	Yes ☐ No ☐ Unknown ☐
Part 2. Gestational age at stillbirth		
	Woman's last menstrual period (LMP)	
14a	Is the woman's LMP known?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 15
14b	What is the date of the LMP reported by the woman?	dd/mm/yyyy ...../...../..... Unknown ☐
14c	Is the woman certain or uncertain about the LMP?	Certain ☐ Uncertain ☐ Unknown ☐
	Assisted reproduction technology	
15	Was the conception natural (i.e. without the use of assisted reproduction technology)?	Yes ☐ No ☐ Unknown ☐ If yes or unknown, go to Question 18



Part 2. Gestational age at stillbirth *(continued)*		
16a	Did intrauterine insemination take place for this pregnancy? *Intrauterine insemination is a procedure in which a fine catheter is inserted through the cervix into the uterus to deposit a sperm sample directly into the uterus, to achieve fertilization and pregnancy*	Yes ☐ No ☐ Unknown ☐
16b	What was the date of intrauterine insemination?	dd/mm/yyyy...../...../..... Unknown ☐
17a	Did embryo transfer take place for this pregnancy? *Embryo transfer is a procedure in which one or more embryos are placed in the uterus or fallopian tube*	Yes ☐ No ☐ Unknown ☐
17b	What was the date of embryo transfer?	dd/mm/yyyy...../...../..... Unknown ☐
	Ultrasound during pregnancy	
18	Was an ultrasound scan done during pregnancy?	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 22a
19a	Was an ultrasound scan done during the first trimester? *The first trimester is defined as <13 weeks + 6 days*	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 20a
19b	What was the date of the ultrasound scan in the first trimester? If more than one scan was done, use the date of the scan closest to week 9 of gestation	dd/mm/yyyy...../...../..... Unknown ☐
19c	What was the estimated gestational age based on the ultrasound scan in the first trimester?	..... weeks and ..... days
19d	What was the expected delivery date based on the ultrasound scan in the first trimester?	dd/mm/yyyy...../...../..... Unknown ☐
20a	Was an ultrasound done during the second trimester? *The second trimester is defined as 14 weeks to 27 weeks + 6 days*	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 21a
20b	What was the date of the ultrasound scan in the second trimester?	dd/mm/yyyy...../...../..... Unknown ☐
20c	What was the estimated gestational age based on the ultrasound scan in the second trimester?	..... weeks and ..... days

Part 2. Gestational age at stillbirth *(continued)*

20d	What was the expected delivery date based on the ultrasound scan in the second trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
21a	Was an ultrasound done during the third trimester? *The third trimester is defined as ≥28 weeks*	Yes ☐ No ☐ Unknown ☐
21b	What was the date of the ultrasound scan in the third trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
21c	What was the estimated gestational age based on the ultrasound scan in the third trimester?	..... weeks and ..... days
21d	What was the expected delivery date based on the ultrasound scan in the third trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
	Physical examination of woman in the first trimester	
22a	Was a physical examination of the woman done in the first trimester?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 23a*
22b	What was the date of the physical examination in the first trimester?	dd/mm/yyyy...../...../..... Unknown ☐
22c	If yes to Question 22a, did a pelvic bimanual examination confirm an enlarged uterus?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 23a*
22d	What was the estimated gestational age based on the physical examination in the first trimester?	..... weeks and ..... days
22e	What was the expected delivery date based on the physical examination in the first trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
	Fundal height of woman in second trimester	
23a	Was the fundal height measured in the second trimester? *If more than one measurement was done in the second trimester, report the first measurement*	Yes ☐ No ☐ Unknown ☐ If no or unknown, go to Question 24a
23b	What was the fundal height?	.....
23c	What was the measurement unit of the fundal height?	Centimetres ☐ Inches ☐ Other ☐ *If other, specify:* ..... Unknown ☐



Part 2. Gestational age at stillbirth *(continued)*		
23d	What was the date of the fundal height measurement?	dd/mm/yyyy ...../...../..... Unknown ☐
Part 3. Immunization during pregnancy		
24a	Did the woman receive any vaccine(s) during pregnancy? *Please answer "yes" or "no" only if there is documented evidence; otherwise answer "unknown"*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, end of questionnaire*
24b	How many vaccines did the woman receive?	.....
24c	Against which disease(s) was the woman immunized?	Disease 1: ..... Disease 2: ..... Disease 3: ..... Unknown ☐
24d	What is/are the dates of immunization of the woman? *Enter more than one date if the woman was vaccinated more than once*	Date 1 (dd/mm/yyyy): ...../...../..... Date 2 (dd/mm/yyyy): ...../...../..... Date 3 (dd/mm/yyyy): ...../...../..... Unknown ☐
24e	What is/are the name(s) of the vaccine(s)?	Vaccine 1: ..... Vaccine 2: ..... Vaccine 3: ..... Unknown ☐

Form completed by: ..... (staff member) ..... (sign) .

...../...../.....(date, dd/mm/yyyy)

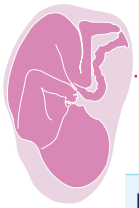
Form checked by: ..... (staff member) ..... (sign) .

...../...../.....(date, dd/mm/yyyy)

Annex 6. Neonatal death case report form

Version 1, 24 March 2025: This case report form is designed to collect structured information needed to diagnose neonatal death using Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) case definitions. Information on the newborn characteristics, birthweight, death, gestation, clinical examination during pregnancy and maternal immunization will be collected. The questionnaire should be administered by trained and authorized study staff and data mangers. Information sources include face-to-face, telephone, virtual or electronic interview with the woman, interview with health-care professionals that cared for the woman and the baby or babies, pathology reports and medical notes. The questionnaire usually takes 30–60 minutes to complete, but longer if information needs to be supplemented from pathology reports and medical notes. Pathology reports and medical notes should be accessed only by people authorized to do so.

Part 1		
	Maternal information *Please ask the newborn's mother or a legally acceptable representative the following questions*	If interviewing a representative of the newborn's mother, check this box ☐ Relationship of representative to newborn's mother: ....
1	Age of newborn's mother in completed years at time of delivery	..... years
2	Place of residence *Give closest town centre*	.....
	Newborn characteristics	
3a	Date of birth	dd/mm/yyyy ...../...../..... Unknown ☐
3b	Sex	Male ☐ Female ☐ Indeterminate ☐ Unknown ☐
	Birthweight	
4a	Was the newborn weighed within 48 hours of birth?	Yes ☐ No ☐ Unknown ☐
4b	What are the units of the birthweight measurement?	Grams ☐ Kilograms ☐ Pounds ☐ Other ☐ *If other, specify:* ..... Unknown ☐
4c	What was the birthweight?	.....



Part 1 *(continued)*

4d	What was the date of the birthweight measurement?	dd/mm/yyyy ...../...../..... Unknown ☐
4e	Was the birthweight low?	Yes ☐ No ☐ Unknown ☐
4f	Was there a medical confirmation of the low birthweight by a physician or other health worker?	Yes ☐ No ☐ Unknown ☐
4g	By whom was the medical confirmation given?	General practice physician ☐ Nurse practitioner ☐ Obstetrician ☐ Paediatrician ☐ Physician's assistant ☐ Other qualified practitioner ☐ *If other qualified practitioner, specify:* ..... Other ☐ *If other, specify:* ..... Unknown ☐
	Newborn death	
5a	Date of death	dd/mm/yyyy ...../...../..... Unknown ☐
5b	Was the death medically confirmed by a suitable qualified medical or allied medical professional, such as a medical doctor, nurse or paramedic?	Yes ☐ No ☐ Unknown ☐
5c	Was the death non-medically confirmed by a non-medically qualified person, such as an undertaker, community member, parent, family member or caregiver?	Yes ☐ No ☐ Unknown ☐
5d	Indicate that all of the following were not present at birth: *To be obtained from a health-care professional present at the birth or medical notes*	Spontaneous movement ☐ Umbilical cord pulse ☐ Heartbeat ☐ Respiration ☐ Crying ☐ Chest movement ☐ Other unspecified sign of life ☐

Part 2. Gestation

Gestational age at birth

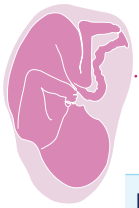
6a	Was the gestational age reported by a parent, family member or delivery attendant?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 7a*
6b	What was the gestational age reported by a parent, family member or delivery attendant?	..... weeks and ..... days

Mother's last menstrual period (LMP)

7a	Is the mother's LMP known?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 8*
7b	What is the date of the LMP reported by the mother?	Yes ☐ No ☐ Unknown ☐
7c	Is the mother certain or uncertain about the LMP?	Certain ☐ Uncertain ☐ Unknown ☐

Assisted reproduction technology

8	Was the conception natural (i.e. without the use of assisted reproduction technology)?	Yes ☐ No ☐ Unknown ☐ *If yes or unknown, go to Question 11*
9a	Did intrauterine insemination take place for this pregnancy? *Intrauterine insemination is a procedure in which a fine catheter is inserted through the cervix into the uterus to deposit a sperm sample directly into the uterus, to achieve fertilization and pregnancy*	Yes ☐ No ☐ Unknown ☐
9b	What was the date of intrauterine insemination?	dd/mm/yyyy ...../...../..... Unknown ☐
10a	Did embryo transfer take place for this pregnancy? *Embryo transfer is a procedure in which one or more embryos are placed in the uterus or fallopian tube*	Yes ☐ No ☐ Unknown ☐
10b	What was the date of embryo transfer?	dd/mm/yyyy ...../...../..... Unknown ☐



Part 2. Gestation *(continued)*

Ultrasound during pregnancy

11	Was an ultrasound scan done during pregnancy?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 15a*
12a	Was an ultrasound scan done during the first trimester? *The first trimester is defined as <13 weeks + 6 days*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 13a*
12b	What was the date of the ultrasound scan in the first trimester? *If more than one scan was done, use the date of the scan closest to week 9 of gestation*	dd/mm/yyyy ...../...../..... Unknown ☐
12c	What was the estimated gestational age based on the ultrasound scan in the first trimester?	..... weeks and ..... days
12d	What was the expected delivery date based on the ultrasound scan in the first trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
13a	Was an ultrasound done during the second trimester? *The second trimester is defined as 14 weeks to 27 weeks + 6 days*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 14a*
13b	What was the date of the ultrasound scan in the second trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
13c	What was the estimated gestational age based on the ultrasound scan in the second trimester?	..... weeks and ..... days
13d	What was the expected delivery date based on the ultrasound scan in the second trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
14a	Was an ultrasound done during the third trimester? *The third trimester is defined as ≥28 weeks*	Yes ☐ No ☐ Unknown ☐
14b	What was the date of the ultrasound scan in the third trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
14c	What was the estimated gestational age based on the ultrasound scan in the third trimester?	..... weeks and ..... days
14d	What was the expected delivery date based on the ultrasound scan in the third trimester?	dd/mm/yyyy ...../...../..... Unknown ☐

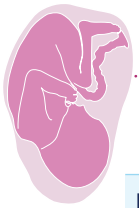
Part 2. Gestation *(continued)*

Physical examination of woman in the first trimester (defined as ≤13 weeks + 6 days)

15a	Was a physical examination of the woman done in the first trimester?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 16a*
15b	What was the date of the physical examination in the first trimester?	dd/mm/yyyy ...../...../..... Unknown ☐
15c	If yes to Question 15a, did a pelvic bimanual examination confirm an enlarged uterus?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 16a*
15d	What was the estimated gestational age based on the physical examination in in the first trimester?	..... weeks and ..... days
15e	What was the expected delivery date based on the physical examination in the first trimester?	dd/mm/yyyy ...../...../..... Unknown ☐

Fundal height of woman in second trimester (defined as 14 weeks to 27 weeks + 6 days)

16a	Was the fundal height measured in the second trimester? *If more than one measurement was done in the second trimester, report the first measurement*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, go to Question 17a*
16b	What was the fundal height?	.....
16c	What is the measurement unit of the fundal height?	Centimetres ☐ Inches ☐ Other ☐ *If other, specify:* ..... Unknown ☐
16d	What was the date of the fundal height measurement?	dd/mm/yyyy ...../...../..... Unknown ☐



Part 3. Immunization during pregnancy

17a	Did the woman receive any vaccine(s) during pregnancy? *Please answer "yes" or "no" only if there is documented evidence; otherwise please answer "unknown"*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, end of questionnaire*
17b	How many vaccines did the woman receive?	.....
17c	Against which disease(s) was the woman immunized?	Disease 1: ..... Disease 2: ..... Disease 3: ..... Unknown ☐
17d	What is/are the dates of immunization of the woman? *Enter more than one date if the woman was vaccinated more than once*	Date 1 (dd/mm/yyyy): ...../...../..... Date 2 (dd/mm/yyyy): ...../...../..... Date 3 (dd/mm/yyyy): ...../...../..... Unknown ☐
17e	What is/are the name(s) of the vaccine(s)?	Vaccine 1: ..... Vaccine 2: ..... Vaccine 3: ..... Unknown ☐

Form completed by: ..... (staff member) ..... (sign) .

...../...../.....(date, dd/mm/yyyy)

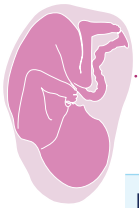
Form checked by: ..... (staff member) ..... (sign) .

...../...../.....(date, dd/mm/yyyy)

Annex 7. Low birthweight case report form

Version 1, 24 March 2025: This case report form is designed to collect structured information needed to diagnose low birthweight using Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) case definitions. Information on the newborn characteristics and maternal immunization will be collected. The questionnaire should be administered by trained and authorized study staff and data mangers. Information sources include face-to-face, telephone, virtual or electronic interview with the woman, interview with health-care professionals that cared for the woman and the baby or babies, and medical notes. The questionnaire usually takes 20 minutes to complete, but longer if information needs to be supplemented from medical notes. Medical notes should be accessed only by people authorized to do so.

Part 1		
	Maternal information *Please ask the newborn's mother or a legally acceptable representative the following questions*	If interviewing a representative of the newborn's mother, check this box ☐ Relationship of representative to newborn's mother: ....
1	Age of newborn's mother in completed years at the time of delivery	..... years
2	Place of residence *Give closest town centre*	.....
	Newborn characteristics	
3	Date of birth	dd/mm/yyyy ...../...../..... Unknown ☐
4	Sex	Male ☐ Female ☐ Indeterminate ☐ Unknown ☐
	Birthweight	
5a	Was the newborn weighed within 24 hours of birth?	Yes ☐ No ☐ Unknown ☐
5b	What are the units of the birthweight measurement?	Grams ☐ Kilograms ☐ Pounds ☐ Other ☐ *If other, specify:* ..... Unknown ☐



Part 1 *(continued)*

5c	What type of scale was used to measure weight?	Electronic scale with graduations of 10 g, 5 g or 1 g ☐ Electronic scale with graduations of 50 g ☐ Mechanical or spring scales ☐ Bathroom scales ☐
5d	When was the scale last graduated?	.....
5e	During the weighing process: • was the scale placed on a hard surface? • was the scale tared to zero?	....
5f	What was the birthweight?	.....
5g	What was the date of birthweight measurement?	dd/mm/yyyy ...../...../..... Unknown ☐
5h	Was there a medical confirmation of the low birthweight by a physician or other health worker?	Yes ☐ No ☐ Unknown ☐
5i	By whom was the medical confirmation given?	General practice physician ☐ Nurse practitioner ☐ Obstetrician ☐ Paediatrician ☐ Physician's assistant ☐ Other qualified practitioner ☐ *If other qualified practitioner, specify:* ..... Other ☐ *If other, specify:* ..... Unknown ☐

Immunization during pregnancy

6a	Did the woman receive any vaccine(s) during pregnancy? *Please answer "yes" or "no" only if there is documented evidence; otherwise please answer "unknown"*	Yes ☐ No ☐ Unknown ☐ *If no or unknown, end of questionnaire*
6b	How many vaccines did the woman receive?	.....
6c	Against which disease(s) was the woman immunized?	Disease 1: ..... Disease 2: ..... Disease 3: ..... Unknown ☐

Part 1 *(continued)*

6d	What is/are the dates of immunization of the woman? *Enter more than one date if the woman was vaccinated more than once*	Date 1 (dd/mm/yyyy): ...../...../..... Date 2 (dd/mm/yyyy): ...../...../..... Date 3 (dd/mm/yyyy): ...../...../..... Unknown ☐
6e	What is/are the name(s) of the vaccine(s)?	Vaccine 1: ..... Vaccine 2: ..... Vaccine 3: ..... Unknown ☐

Form completed by: ..... (staff member) ..... (sign)

...../...../.....(date, dd/mm/yyyy)

Form checked by: ..... (staff member) ..... (sign)

...../...../.....(date, dd/mm/yyyy)

Annex 8. Oral informed consent information sheet

The following oral informed consent/opt-out information sheet is for pregnant women and women after delivery. It should be translated into the local language. This informed consent is for adults only.

[set the following as an information sheet]

You have received care from this health facility.

This health facility is part of an observational research study, which means we observe patients without changing their care. The health facility is conducting a study that aims to understand how often certain birth complications occur, such as preterm birth (babies born early), stillbirth, neonatal deaths and low birthweight. This rate is called the background rate and helps monitor the safety of new medicines or vaccines. By knowing how often these complications happen before introducing new treatments, researchers can spot any changes in their frequency.

This research will be conducted in [NUMBER OF SITES] health facilities across [NUMBER OF COUNTRIES] countries, and information will be collected for [NUMBER OF YEARS] years. Your admission details, collected as part of routine care, may be used for this study. The types of data collected include your vaccination history, information on your delivery, results of routine monitoring tests and examinations on how your baby is growing (e.g. ultrasound scans) during your pregnancy, routine markers tested for at birth, and use of assisted reproductive technology (e.g. IVF). Participating in this study will not change (increase or decrease) the health care that you or your baby receive, and you will not receive any direct benefit from this research. Information gathered from many people will be transferred safely and confidentially to a database studied by the World Health Organization (WHO). The study will support future research and help detect and report important health events before and after new vaccines are introduced. It will also improve data-collection and recording practices, benefiting other people in the future.

All research information will be anonymized, meaning it will not include your name, address or any personal details that could identify you or your child. The health facility will assign someone to securely store and manage the research data. The anonymized data will be stored in a secure database located in [WHERE DATA WILL BE STORED]. It may also be added to research databases for future use by WHO and other collaborators to enhance research and improve the detection and reporting of important health events. Your personal data will always be handled according to data protection and privacy laws and will be shared only with authorized people, including WHO and its representatives. The study will be conducted over the course of one year, and the results will be disseminated in scientific publications. The study staff will inform you of the results of the study at the time of publication.

The study sponsor is [NAME OF STUDY SPONSOR], and the principal investigators are [TO BE COMPLETED BY COUNTRY TEAMS].

If you decide to take time to reflect, please inform us of your decision to participate in the study at your next hospital facility or health visit. If you are willing to allow the information about you collected in the health facility as part of routine care to be used for this research, please provide oral consent.

You are free to contact [STUDY PRINCIPAL INVESTIGATOR, CONTACT EMAIL/PHONE NUMBER] to understand how your information has been used. If at any point you do not wish to share your information, you are free to contact [STUDY PRINCIPAL INVESTIGATOR] and withdraw from the study at any time for any reason, up until publication of the findings, and information collected from you will not be used. Additionally, the [RESEARCH ETHICS COMMITTEE] can be contacted if you have any concerns about how the study is being conducted. The name, email address and telephone number of the research staff to contact have been provided to you.

Study findings will be communicated in many ways, such as visual aids, posters and printed materials. The results will help inform other families about how common certain neonatal outcomes such as preterm birth are. At the end of the study, we will share the overall findings with all participants. You can hear about the study results from the clinical team, community workers and trusted community leaders. You will receive a summary of the results via [METHOD OF COMMUNICATION, e.g. EMAIL, MAIL, WEBSITE]. This summary will provide an overview of the study's outcomes and any significant discoveries.

We know that talking about baby health can be very sensitive. To make sure we share the results in a caring way, we will work with community leaders to find the best way to communicate our findings.

You also have the choice to opt out of this research. By doing so, rest assured that your care in the health facility will not be affected in any way.

Annex 9. Oral informed assent form

Hello! You have received care from this health facility.

This facility is part of a study where we observe patients without changing their care. We want to understand how often certain birth complications happen, such as babies born early, stillbirths, neonatal deaths and low birthweight. This helps us monitor the safety of new medicines or vaccines. By knowing how often these complications happen before introducing new treatments, researchers can spot any changes.

This study will be conducted in [NUMBER OF SITES] health facilities across [NUMBER OF COUNTRIES] countries, and information will be collected for [NUMBER OF YEARS] years. Your admission details, collected as part of routine care, may be used for this study. We will collect information such as your vaccination history, details about your delivery, results from tests and ultrasound scans during pregnancy, and any use of assisted reproductive technology such as IVF. Participating in this study will not change the health care you or your baby receive, and you will not get any direct benefit from the research. However, the information gathered from many people will be safely and confidentially transferred to a database studied by the World Health Organization (WHO). This will support future research and help detect and report important health events before and after new vaccines are introduced. It will also improve data collection and recording practices, benefiting other people in the future.

All research information will be anonymized, meaning it will not include your name, address or any personal details that could identify you or your child. The facility will assign someone to securely store and manage the research data. The anonymized data will be stored in a secure database located in [WHERE DATA WILL BE STORED]. It may also be added to research databases for future use by WHO and other collaborators to enhance research and improve the detection and reporting of important health events. Your personal data will always be handled according to data protection and privacy laws and will be shared only with authorized people, including WHO and its representatives. The study will be conducted over the course of one year, and the results will be shared in scientific publications. The study staff will inform you of the results of the study at the time of publication.

The study sponsor is [NAME OF STUDY SPONSOR], and the principal investigators are [TO BE COMPLETED BY COUNTRY TEAMS].

If you decide to take time to reflect, please inform us of your decision to participate in the study at your next hospital or health visit. If you are willing to allow the information about you collected in the health facility as part of routine care to be used for this research, please sign and date this form.

You are free to contact [STUDY PRINCIPAL INVESTIGATOR, CONTACT EMAIL/PHONE NUMBER] to understand how your information has been used. If at any point you do not wish to share your information, you are free to contact [STUDY PRINCIPAL INVESTIGATOR] and withdraw from the study at any time for any reason, up until publication of the findings, and information collected about you will not be used. Additionally, the [RESEARCH ETHICS COMMITTEE] can be contacted if you have any concerns about how the study is being conducted. The name, email address and telephone number of the research staff to contact have been provided to you.

We will share the study results using things such as pictures, posters and handouts. This information will help other families understand how often certain baby health issues, such as being born early, happen. At the end of the study, we will share the overall findings with all participants. You can hear about the study results from the clinical team, community workers and trusted community leaders. You will receive a summary of the results via [METHOD OF COMMUNICATION, e.g. EMAIL, MAIL, WEBSITE]. This summary will provide an overview of the study's outcomes and any significant discoveries.

We understand that talking about baby health can be very sensitive. To make sure we share the results in a thoughtful way, we will work with community leaders to find the best way to communicate our findings.

You also have the choice to refuse and to opt out of this research. By doing so, rest assured that your care in the health facility will not be affected in any way.

For more information, please contact:

Regulation and Prequalification Department (RPQ)
Regulation and Safety (REG)
Pharmacovigilance (PVG)
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland

Email: pvsupport@who.int