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Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data

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ABSTRACT

Preterm birth is commonly defined as any birth before 37 weeks completed weeks of gestation. An estimated 15 million infants are born preterm globally, disproportionately affecting low and middle income countries (LMIC). It contributes directly to estimated one million neonatal deaths annually and is a significant contributor to childhood morbidity. However, in many clinical settings, the information available to calculate completed weeks of gestation varies widely. Accurate dating of the last menstrual period (LMP), as well as access to clinical and ultrasonographic evaluation are important components of gestational age assessment antenatally. This case definition assign levels of confidence to categorisation of births as preterm, utilising assessment modalities which may be available across different settings. These are designed to enable systematic safety evaluation of vaccine clinical trials and post-implementation programmes of immunisations in pregnancy.

1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for preterm birth as an adverse event following immunisation

Preterm birth has been defined as any birth before 37 weeks completed weeks of gestation. An estimated 15 million infants are

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born preterm, with resulting complications. It is the principal cause of an estimated one million neonatal deaths annually and a significant contributor to childhood morbidities. Low and middle income countries (LMIC) carry a higher burden of disease attributed to preterm birth.

The World Health Organisation (WHO) defines preterm birth as any birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of the woman's last menstrual period (LMP). This is further subdivided on the basis of gestational age (GA):

- extremely preterm (<28 weeks);
- very preterm (28–<32 weeks);
- moderate or late preterm (32–<37 completed weeks of gestation).

This is the most extensively used and accepted definition of preterm birth [1].

The ability to accurately determine the completed weeks of gestation varies widely between pregnancies, with the most precise assessment methods not uniformly available across different settings. Vaccination in pregnancy has been widely implemented to protect women and their babies from tetanus and pertussis in recent years, with an increasing number of vaccines being developed and trialled for use in pregnancy against a variety of bacterial and viral infections. As preterm birth is such an important pregnancy outcome that may represent an adverse event, it is important to establish a case definition for use across vaccine studies and post-licensure surveillance that is able to make use of all methodologies used to calculate gestational age, and that incorporates a hierarchy based upon the precision of the various methods used.

The nomenclature of GA is typically discussed in terms of the number of completed weeks (e.g., 33 weeks and 2 days, or 33 2/7 weeks). Defining GA has been considered useful in terms of neonatal outcome. In the past, three groups have been classified and utilised according to delivery following the onset of the last menstrual period. *Pre-term*: less than 259 days (37 weeks), *term*: 259–293 days (37–41 weeks). *Post-term*: 294 days (42 weeks) or more.

A term birth has been defined as between 37 and 42 weeks and used to describe the optimal timing for a good outcome for the mother and baby. The International Classification of Diseases defines term pregnancy as a delivery from 37 completed weeks to less than 42 completed weeks (259–293 days) of gestation. However, neonatal outcomes vary within this wide gestational age range, with a 2012 international stakeholder working group recommending sub-categorisation of term birth to more accurately describe deliveries and their outcomes. These sub-categories are: *early term* (37 0/7 weeks of gestation through 38 6/7 weeks gestation); *full term* (39 0/7 weeks of gestation through 40 6/7 weeks of gestation); *late term* (41 0/7 weeks of gestation through 41 6/7 weeks of gestation); and, *post term* (42 0/7 weeks of gestation and beyond). The American College of Obstetricians and Gynaecologists (ACOG) and the Society for Maternal–Foetal Medicine (SMFM) has endorsed this recommendation and encourages its use for categorising GA [2–5].

1.1.1. Pathophysiology of preterm birth

Causes of preterm birth are complex and the pathophysiology that triggers preterm birth is largely unknown, however, contributing maternal, foetal and placental predisposing factors have been identified. The most common of these include: antepartum haemorrhage or abruption; mechanical factors such as uterine over-distention and cervical incompetence; hormonal changes; and, bacterial infection and inflammation [6,7].

Over the past 20 years the access to assisted reproduction technology (ART) in many high income countries has contributed to the rise in the number of multiple births and an overall increase in the rates of preterm delivery. Infants born from multiple pregnancies are more likely to be born preterm due to spontaneous labour or premature rupture of membranes (PROM), or as a result of maternal conditions such as pre-eclampsia or foetal disorders [8,9]. Changes to policies which limit the number of embryos implanted as part of ART have led to a decline in the number of preterm births due to assisted fertility [10,11].

Epidemiologic studies have identified preterm birth risk factors as maternal age of less than 17 years or more than 35 years, being underweight, having an overweight pre-pregnancy body mass index, and short stature. Preterm birth rates vary geographically and within ethnic origins, with LMIC consistently having higher rates [7,12]. Physical and psychosocial stress and smoking have also been associated with higher preterm risk as does a previous preterm birth.

The assessment and diagnosis of preterm birth has remained problematic since it is not a defined disease and the WHO definition does not contain universally recognised reference standards. Different methodologies are used for assessing GA and because reporting rates vary widely between and within countries, accurate comparison of reporting rates of preterm birth and trending data is difficult to analyse [13–17].

1.1.2. Preterm birth categorisation

Preterm birth defined as less than 37 completed weeks encompasses a wide gestational age range with rates varying across countries. The WHO subcategories of 'extremely preterm', 'very preterm' and 'moderate or late preterm' are recommended to improve comparability of preterm birth data in relation to immunisation.

A limitation of the WHO definition is that there is no boundary between spontaneous abortion and a viable birth, complicating the assessment of preterm birth in the extremely preterm group of babies. A comparison between and within countries becomes complex with varying gestational lower limits of viability over time and across different settings. Determining a lower limit is complex as it is variably defined and arbitrary. It is often described in terms of risk factors and its causes, and is predominately developed according to postnatal viability and data quality in different settings [17–20].

Preterm births are reported only for live born infants. The pregnancy outcomes differ across countries where the upper limit for national or regional criteria for registration of a foetal death range from 16 weeks to 28 weeks, this impacting on the proportion of preterm births [21].

The registrations of births in LMIC often do not routinely record GA and the data on birthweight (BW) is often not recorded or compiled. It has been reported that 58% of babies in these countries are not weighed at birth and home based births are not represented [20,22,23].

1.1.3. Preterm birth following immunisation: what is known in literature?

Pregnant women are at increased risk of morbidity and mortality and adverse pregnancy outcomes, including preterm birth, due to vaccine preventable diseases. Vaccination in pregnancy is a recognised preventive measure for protecting the mother, foetus and infant [24–27].

Until the 1960s vaccines, including polio, influenza, diphtheria and tetanus toxoid vaccines, were routinely administered to pregnant women in maternal immunisation programmes. Studies in a variety of developed settings detected no increase in adverse consequences for the mother or foetus in vaccinated women [28,29]. However, the thalidomide teratogenicity disaster in pregnant women resulted in widespread concerns about the safety of all medicine use in pregnancy, including vaccines.

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