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Commentary

Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data

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1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for low birth weight as an adverse event following maternal immunization

The birth weight of an infant is the first weight recorded after birth, ideally measured within the first hours after birth, before significant postnatal weight loss has occurred. Low birth weight (LBW) is defined as a birth weight of less than 2500 g (up to and including 2499 g), as per the World Health Organization (WHO) [1]. This definition of LBW has been in existence for many decades. In 1976, the 29th World Health Assembly agreed on the currently used definition. Prior to this, the definition of LBW was '2500 g or less'. Low birth weight is further categorized into very low birth weight (VLBW, <1500 g) and extremely low birth weight (ELBW, <1000 g) [1]. Low birth weight is a result of preterm birth (PTB, short gestation <37 completed weeks), intrauterine growth restriction (IUGR, also known as fetal growth restriction), or both.

The term low birth weight refers to an absolute weight of <2500 g regardless of gestational age. Small for gestational age (SGA) refers to newborns whose birth weight is less than the 10th percentile for gestational age. This report will focus specifically on birth weight <2500 g. Further details related to case definitions for PTB [2], IUGR and SGA are included in separate GAIA reports.

Globally, it is estimated that 15–20% of all births, or >20 million newborns annually, are low birth weight infants. Low- and middle-income countries account for a disproportionate burden of LBW;

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over 95% of the world's LBW infants are born in LMICs. There are marked global and regional variations in LBW rates. An estimated 6% of infants are born LBW in East Asia and the Pacific, 13% in Sub-Saharan Africa, and up to 28% in South Asia [3]. Up to half of all LBW infants are born in south Asia [4]. High-income regions report lower LBW rates, including 6.9% from UK [5]. Of concern is the estimated increase in LBW rates in certain middle-income countries such as Oman, where the LBW rate went from 4% in 1980 to 8.1% in 2000 [6].

One of the major challenges in monitoring the incidence of LBW is that more than half of infants in the LMICs are not weighed [7]. Population-based survey data often rely on modeled estimates, with statistical methods to adjust for underreporting and misreporting of birth weight. In the context of vaccine safety monitoring, accurate ascertainment of birth weight in LMICs will continue to require attention and investment to improve accuracy and reporting of this important health indicator.

1.1.1. Why are we concerned about low birth weight?

Low birth weight is a valuable public health indicator of maternal health, nutrition, healthcare delivery, and poverty. Neonates with low birth weight have a >20 times greater risk of dying than neonates with birth weight of >2500 g [8,9]. Additionally, low birth weight is associated with long-term neurologic disability, impaired language development [10], impaired academic achievement, and increased risk of chronic diseases including cardiovascular disease and diabetes. Preterm infants carry additional risk due to immaturity of multiple organ systems, including intracranial hemorrhage, respiratory distress, sepsis, blindness, and gastrointestinal disorders. Preterm birth is the leading cause of all under-5 child mortality worldwide [11].

In addition, economic studies in low-income settings have demonstrated that reducing the burden of low birth weight would have important cost savings both to the health system and to households [12].

1.1.2. What leads to low birth weight?

The underlying causes of both PTB and IUGR are multifactorial, and the biological pathways and preventive strategies for these two conditions are quite different [13–15]. The exact cause of PTB may be unknown in many cases, however numerous maternal, fetal and placental factors may contribute to PTB [13]. Significant maternal conditions include extra-uterine infection, chorioamnionitis, trauma and illness (e.g. pre-eclampsia/eclampsia). Significant fetal conditions include IUGR, fetal infection, death and anomalies. Placental pathologic conditions include placental abruption and placenta praevia [13].

In general, the causes of IUGR can be due to maternal, fetal, and placental factors. Although the etiologies are different, they often have the final common pathway of insufficient uterine-placental perfusion and fetal nutrition.

IUGR can be asymmetrical IUGR (where babies have features of malnutrition), symmetrical IUGR (hypoplastic small for dates) or mixed IUGR. Asymmetrical IUGR is the most common (70–80%) form of IUGR, resulting from an insult (often utero-placental insufficiency) later in pregnancy, which results in affected babies having normal length and head circumference (brain sparing), but reduced weight. Symmetrical IUGR on the other hand arises from an insult (often genetic, structural or infectious) occurring earlier in pregnancy leading to a reduction in all anthropometric parameters in fetus/newborn [15].

Insufficient perfusion, through abnormal placentation, aberrant placental vascularization, maternal hypertensive disorders, and tobacco use, all result in IUGR. Multiple gestation (i.e., twins, triplets) is associated with increased risk of both IUGR and PTB [16]. Infectious diseases, including intrauterine infections, HIV, and malaria, result in LBW due to both growth restriction and short gestation. Multiple maternal characteristics, risk behaviors, and social determinants are associated with both IUGR and PTB; these include maternal short stature, maternal malnutrition, low body mass index, poverty, black race, narrow child spacing, low maternal education, poor antenatal care, substance abuse, and emotional and physical stress [5,17–19]. How these factors are mediated biologically remains poorly understood.

Preterm birth may be spontaneous or medically-indicated, such as induction or cesarean section for maternal complications such as pre-eclampsia. Infectious and inflammatory processes are associated with increased risk for PTB, including chorioamnionitis, bacterial vaginosis, bacteriuria, and systemic or remote site infection such as sepsis and periodontal disease.

1.1.3. The importance of short gestation on immune function and vaccine efficacy

Transplacental antibody transfer is an active process mediated by Fc receptors in the placental syncytiotrophoblast [20], which increases from 30 weeks gestation. Small molecular weight particles (<600 Da) cross the placenta by passive mechanism including diffusion, however, larger molecular weight particles (>1000 Da) are transported across the placenta by and active receptor-mediated process [21]. Fetal IgG levels are approximately 50% of maternal antibody level at 32 weeks gestation and rises rapidly through the third trimester [22]. Preterm newborns have significantly lower antibody levels than term newborns [22]. LBW term newborns have significantly lower antibody concentrations to Herpes simplex virus type 1, respiratory syncytial virus ad varicella zoster virus than term newborns with birth weight >2500 g [23].

Maternal antibody levels, receptor density and functionality, avidity, antigen nature, and gestational age determine the efficiency of placental antibody transfer [24]. Diseases that are highly prevalent in some areas, such as malaria and human immunodeficiency virus (HIV), are known to cause placental damage, especially placental malaria [25,26]. Maternal HIV infection has been consistently associated with reduced placental passage of antibodies against several common viral and bacterial antigens [27,28]. Placental malaria has been associated with maternal hypergammaglobulinemia and reduced transfer of antibodies against measles virus, *Clostridium tetani*, *Streptococcus pneumonia*, and varicella-zoster virus in some studies [20,29–31]. The transfer during pregnancy of maternal antibodies to the fetus minimizes deficiencies in antibody production in the fetus and provides short-term passive immunity [32], conditioning the success of vaccination in newborns [33] which is especially important in preterm and IUGR newborns. Multiple comorbidities are associated with both LBW and immune suppression, such as malnutrition and infection, thereby further exacerbating diminished immune function in the compromised newborn.

1.1.4. Maternal immunization and birth weight

Maternal infections, including influenza, have been associated with increased risk of low birth weight newborns [34]. As a corollary, prevention of certain infections during pregnancy might have a protective effect against LBW. This has been observed in a maternal immunization trial conducted in Bangladesh [35], in which the mean birth weight of infants born to mothers who received an inactivated influenza vaccine during pregnancy was higher than of infants born to mothers who received a pneumococcal polysaccharide vaccine (3178 g vs. 2978 g, $p = 0.02$). This trend has not been observed in other maternal influenza immunization trials [36].