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Pathways to preterm birth: Case definition and guidelines for data collection, analysis, and presentation of 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 pathways to preterm birth as an adverse event following immunization

While immunizations confer protection against specific subtypes of infections, it is important to determine whether these interventions contribute to adverse maternal or neonatal outcomes in pregnancy. In particular, understanding the risk/benefit of immunizations with respect to pathways resulting in preterm birth is of particular interest. Preterm birth results from a variety of pathways ranging from idiopathic to spontaneous etiologies. Because there is a diverse spectrum of possible causes of preterm birth, it is

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important to determine whether some of the pathways to preterm birth can be activated by interventions, including immunizations.

The pathophysiology and pathways related to preterm birth represent diverse and complex processes. A critical principle is that spontaneous preterm births result from a spectrum of pathological processes that are initiated by specific molecular pathways, converging into a common pathway [1]. These molecular mechanisms are influenced by genetic, epigenetic, biological, behavioral, social, clinical, and environmental risk factors [1]. Different insults, such as stress, inflammation or infection, hemorrhage, uterine distention, and immune dysregulation can lead to uterine decidual and fetal membrane activation, which stimulate release of prostaglandins, cytokines, and matrix metalloproteinases that in turn lead to uterine contractions, cervical ripening, membrane rupture and subsequently, preterm birth [1]. In essence, it appears that the processes whereby term labor is initiated are implicated in preterm birth as well, with an important distinction being that term parturition results from physiologic activation of the components of the common pathway, while preterm labor arises from pathological processes that activate one or more of those components [1]. It is hypothesized that before 32 weeks gestation, the initiation of pathways to preterm birth requires a stronger stimulus than after 32 weeks, as later in the third trimester there is normal physiologic preparation of the uterus and cervix for delivery [1].

While preterm birth is being formally defined by another Brighton Collaboration working group and that definition will be incorporated into this document, the purpose of this exercise is to develop case definitions and guidelines for data collection, analysis, and presentation for the pathways to preterm birth. The etiologies of preterm birth can be grouped into four pathways that are considered the underlying events leading to preterm birth; they include: (1) premature preterm rupture of membranes (PPROM), (2) spontaneous preterm labor (PTL), (3) insufficient cervix (IC), and (4) provider-initiated preterm birth (PIPTB). Of note, the first three pathways are spontaneously occurring processes, while the fourth occurs when a decision is reached between a patient and her provider that iatrogenic initiation of labor is required for the health of the fetus, mother, or both. These four pathways are the adverse events of interest in this document, which will focus primarily on how researchers, in the context of vaccine trials, can determine that one of these four pathways has been activated, or an adverse event has occurred.

The diverse array of etiologies, coupled with obscured and/or overlapping clinical and scientific definitions has led to inconsistent definitions of pathways leading to preterm birth. Moving toward a consensus definition is critical for the purposes of monitoring adverse events in vaccine trials and to standardize terminology for improved data collection. Issues related to defining and classifying preterm birth include: relying on gestational age estimates based on a variety of approaches and validity, distinguishing between clinical versus etiologic phenotypes of preterm birth, considering whether to include or exclude multi-fetal gestations or stillborn infants, and deciding how to separate or combine different pathways to preterm birth [2]. Given that the term pathways to preterm birth has met with such difficulty in definition and classification previously, it is a crucial adverse outcome for the Brighton Collaboration to clarify for use in the context of vaccine related research.

Literature searches related to immunization in pregnancy were performed to identify existing definitions and contributing factors for premature preterm rupture of membranes, preterm labor, insufficient cervix, and provider-initiated preterm delivery; the four pathways to preterm birth. For premature preterm rupture of membranes, no data were published on the incidence of this outcome in association with immunizations in pregnancy. The same was true for insufficient cervix and provider-initiated preterm delivery; no published incidence of these outcomes related to immunization in pregnancy were available, even when similar terms were included in the search (incompetent cervix, iatrogenic preterm delivery/birth). In the case of preterm labor, while almost 100 studies were found based on the search terms preterm labor and immunization, only three of the articles mentioned preterm labor in the text of the articles, with only one reporting the incidence of preterm labor in the setting of an immunization. That paper reported that following administration of influenza A (H1N1) 2009 monovalent vaccine, 294 adverse events in pregnant women were reported to the Vaccine Adverse Event Reporting System; two women experienced preterm labor, or 1% of the immunized population in the United States [3]. There was no description of the definition used for preterm labor in this study or the long-term outcomes of those pregnancies; overall, however, it was determined that preterm labor was not likely due to the immunization itself [3].

Existing case definitions for the term, ‘pathways to preterm birth’, do not exist. Description of preterm birth as a syndrome, however, is a common finding, and attempts have been made at standardizing the pathways to preterm birth [1,2]. One classification system published in the American Journal of Obstetrics and Gynecology proposed a method based on clinical phenotypes defined by characteristics of the mother, fetus, placenta, signs of parturition, and the pathway to delivery [2]. This methodology involves detailed information on maternal, fetal, and placental conditions as well as information regarding the initiation of parturition and the pathway to delivery [2]. Under this system a particular patient may fall into one or more of the phenotypes allowing her case to be defined by all relevant conditions, instead of forced into one strictly defined pathway [2]. For example, maternal conditions include such clinical scenarios as intra-amniotic infection, trauma, pre-eclampsia/eclampsia, and uterine rupture [2]. Fetal and placental conditions as well as symptoms of parturition and the pathway to delivery also are listed in the document [2]. While this methodology has not been validated, the authors suggest that it be piloted in a population and evaluated for utility [2]. This methodology offers a very flexible approach to the concept of classifying pathways to preterm birth, but for the purposes of this document, the goal was to develop a better-defined set of pathways to preterm birth that can be measured and documented in vaccine research.

Each of the four pathways to preterm birth as presented in this document do have existing case definitions in the literature. For example, premature preterm rupture of membranes has been defined as, “rupture of the fetal membranes before term and outside of the context of labor” [4]. Preterm labor has previously been defined as “a syndrome attributable to multiple pathologic processes leading to uterine contractions that cause cervical change before term” [6]. Insufficient cervix has been defined as, “the inability of the uterine cervix to retain a pregnancy in the absence of the signs and symptoms of clinical contractions, or labor, or both in the second trimester” [7]. For the final pathway to preterm birth, a definition published regarding what was termed ‘iatrogenic preterm birth’ (which for the purposes of this document has been called, ‘provider-initiated preterm birth’) is, “nonspontaneous delivery before term” [8]. While some of these definitions are more specific than others, they are overall too general for use as outcomes of interest in vaccine-specific and other research, and would benefit from further development as broadly applicable and clinically specific definitions. As mentioned, the term ‘pathways to preterm birth’ suffers from the lack of a formal definition and represents a missed opportunity, as data comparability across trials or surveillance systems would facilitate data interpretation and promote the scientific understanding of the event.

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