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Commentary

Dysfunctional labor: Case definition & 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 dysfunctional labor as an adverse event following immunization

Vaccination during pregnancy is recommended for both maternal and neonatal benefit against a number of potential infections. The tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine is now routine recommended for pregnant women in each pregnancy not only for maternal benefit, but to confer passive antibody transfer to the newborn until infant immunizations can be given [1]. Influenza vaccinations are also strongly recommended for any pregnant woman, or women who might become pregnant during influenza seasons [2]. The safety of both these vaccinations has been well established. Efforts to develop new vaccinations for use during pregnancy represent a new opportunity to prevent common maternal and neonatal infections with severe morbidity and mortality. There is growing interest and research around maternal immunization against both Group B streptococcus (GBS) and Respiratory syncytial virus (RSV) as a public health strategy to prevent neonatal and infant infections worldwide [3,4].

Establishing the safety profile of any new vaccination requires careful surveillance of potential adverse effects and consistent terminology and definitions across context and time. The World Health Organization (WHO) defines an 'adverse event following immunization' (AEFI) as "any untoward medical occurrence which follows immunization and, which does not necessarily

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Table 1
Summary of professional guidelines.

Professional Organization	Year Published	First Stage		Second Stage	
		Nulliparous	Multiparous	Nulliparous	Multiparous
NICE [29]	2014	Normal: 8–18 h	Normal: 5–12 h	Birth expected within 3 h of start of active second stage	Birth expected within 2 h of start of active stage
		Suspected delay: <2 cm in 4 h, with delay confirmed with progress of less than 1 cm h later	Delay: <2 cm in 4 h OR slowing in progress of labor	Delay: 2 or more hours	Delay: 1 or more hours
ACOG/SMFM [11]	2014	Normal < 20 h	Normal < 14 h	No maximum time frame	No maximum time frame
		Arrest: 6 cm dilation and 4 h or more of adequate contractions or 6 h or more of inadequate contractions	Arrest: 6 cm dilation and 4 h or more of adequate contractions or 6 h or more of inadequate contractions	Permit at least 3 h of pushing	Permit at least 2 h of pushing
RANZCOG [30]	2014	Prolonged if: <1 cm/h in active phase	Prolonged if: <1 cm/h in active phase	>2 h	>1 h
WHO [31]	2014	<0.5 cm to 1 cm/h during the active phase	<0.5 cm to 1 cm/h during the active phase	N/A	N/A
SOGC [32]	1995	<0.5 cm/h over a 4 h period	<0.5 cm/h over a 4 h period	2 h if no regional anesthesia	N/A
FIGO [33]	2012	N/A	N/A	No more than 3 h of active pushing	No more than 2 h of active pushing

have a causal relationship with the use of the vaccine. The adverse event may be an unfavorable or unintended sign, an abnormal laboratory finding, a symptom or disease" [5]. Recognizing that vaccination is often temporally related to many events, abnormal findings or diseases, causality assessment between an AEFI and vaccination requires further rigorous assessment and study. Monitoring of a broad array of events, including those without established or suspected links to vaccine can therefore provide the initial basis for data with which such causality can be proven or disproven.

Dysfunctional labor is relatively common occurrence during the intrapartum stage of pregnancy. Incidence estimates vary due to differences in definitions, but approximately 20% of labors are thought to be affected by this condition [6]. Though there are no reported links between dysfunctional labor and immunization, the measurement of this potential complication in association with vaccination is important to establish vaccine safety. Despite being relatively common, there is a lack of consensus on the criteria for the diagnosis of dysfunctional labor. Guidelines from professional obstetric societies differ in both the criteria used to define this process and when intervention should occur (Table 1). The Brighton Collaboration has been developing standardized definitions for use in vaccine trials since 2001 [7]. To further consistent terminology and definitions of outcomes and adverse events typically reported in vaccine trials, specifically for maternal immunization, standardized definitions of common obstetric outcomes are needed. The goal of this working group was therefore to provide a case definition for this term to facilitate surveillance and case ascertainment in vaccine trials.

Labor is typically divided into three stages. The first stage of labor marks the onset of labor until full dilation of the cervix; the second stage, full dilation until delivery of the fetus, and the third, delivery of the placenta. In the 1950s, Friedman first described the first stage dividing this into latent and active phases of labor [8,9]. His work first demonstrated the broad range of labor duration experienced by women and until recently provided the basis for defining normal progress and length of labor limits of normal labor duration. Recent evidence, however, from a larger more diverse population of women have challenged these historical durations [10].

Dysfunctional or prolonged labor refers to prolongation in the duration of labor, typically in the first stage of labor. Diagnosis of delay in labor is dependent on careful monitoring of uterine contraction intensity, duration and frequency, cervical dilation and descent of the fetus through the pelvis. Dysfunctional labor can be an important contributor to maternal and perinatal mortality and morbidity if it remains unrecognized and untreated when needed. On the other hand, pre-emptive diagnosis of dysfunctional labor may lead to unnecessary interventions. Labor dysfunction is a leading indication for primary caesarean section and there is concern, that an over diagnosis may be a contributor to high and rising caesarean section rates [11].

The pathophysiology of dysfunctional labor is multifactorial and complex and yet to be fully elucidated. Often, the exact etiology of dysfunctional labor is unknown. Broadly, etiology can be categorized into uterine contractile dysfunctions and abnormalities in the cephalopelvic ratio (i.e. the relation of the fetal size, presentation and position to the maternal pelvis). Both these causes can be influenced by a number of genetic and environmental factors including but not limited to maternal and gestational age, pre-pregnancy body mass index, pregnancy weight gain, physical activity, medical co-morbidities, parity, and obstetric complications (pre-eclampsia, premature rupture of membranes, chorio-amnionitis, placental abruption) [12–15].

1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for dysfunctional labor as an adverse events following immunization

Following the process described in the overview paper [16] as well as on the Brighton Collaboration Website http://www.brightoncollaboration.org/internet/en/index/process.html, the Brighton Collaboration *Dysfunctional Labor Working Group* was formed in 2015 and included members of clinical, academic, public health and industry background. The composition of the working and reference group as well as results of the web-based survey completed by the reference group with subsequent discussions in the working group can be viewed at: http://www.brightoncollaboration.org/internet/en/index/working_groups.html.

To guide the decision-making for the case definition and guidelines, a literature search for publications in any language was performed using Medline, Embase and the Cochrane Libraries, including the terms dysfunctional, prolonged, delayed, obstructed, abnormal, augmented labor, arrest of dilation, labor dystocia AND 'vaccination' or 'vaccine' or 'immunization' OR 'immunize' OR 'inoculation'. The search resulted in the identification of 172 references. All abstracts were screened for possible reports of dysfunctional labor following immunization. Two full text articles with potentially relevant material were reviewed in more detail, in order to identify studies using case definitions or, in their absence,