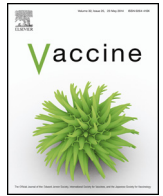




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## Hypertensive disorders of pregnancy: Case definitions & guidelines for data collection, analysis, and presentation of immunization safety data

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### 1. Preamble

#### 1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for the hypertensive disorders of pregnancy as adverse events following immunization

There is no universally accepted case definition of gestational hypertension, preeclampsia or eclampsia that occurs following immunisations. This is a missed opportunity, as data comparability across trials or surveillance systems would facilitate data interpretation and promote the scientific understanding of the event. As immunization is considered an essential element of care in pregnancy, the potential complications of this procedure should be understood. Additionally, vaccine studies may be conducted in a variety of settings, including those with fewer resources to perform the same diagnostic testing as in higher resource settings. It is important to provide definitions that can be utilized widely.

Around 10% of all pregnant women will be affected by a hypertensive disorder during pregnancy [1]. Hypertensive disorders of pregnancy are a significant contributor to maternal and neonatal morbidity and mortality, and are implicated in 10–15% of maternal deaths worldwide [1,2]. The exact mechanism responsible for hypertensive diseases of pregnancy, in particular preeclampsia, is not known. One leading hypothesis is that abnormalities in the development of the uteroplacental unit lead to increased hypoxemia and oxidative stress, which in turn lead to endothelial dysfunction and abnormalities in vascular tone and coagulation [3,4].

Hypertensive disease in pregnancy encompasses a spectrum of conditions, including gestational hypertension, preeclampsia (which can be further qualified as having severe features), eclampsia, chronic hypertension with superimposed preeclampsia and HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome. Because of differences among the guidelines issued by international societies, diagnosis can occasionally become confusing as terminology may vary. Nevertheless, it is important to differentiate hypertensive disorders that predate pregnancy from those that occur during pregnancy, as well as to categorize patients into more or less serious cases. Furthermore, the specific diagnosis has important treatment implications, such as timing of delivery.

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The definitive treatment for hypertensive diseases of pregnancy is delivery.

The association of vaccination with the hypertensive diseases of pregnancy has not been well studied and the exact incidence is not known. There are observational studies as well as case reports of hypertensive disease developing in women after vaccine administration but no causal link has been described. Furthermore, the case definitions for the observational studies are not well defined, with several studies relying solely on ICD-9 codes.

### 1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for the hypertensive disorders of pregnancy as adverse events following immunization

Following the process described in the overview paper [5] as well as on the Brighton Collaboration Website, <http://www.brightnocolaboration.org/internet/en/index/process.html>, the Brighton Collaboration Preeclampsia Working Group was formed in 2015 and included members with clinical, academic and public health 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.brightnocolaboration.org/internet/en/index/working\\_groups.html](http://www.brightnocolaboration.org/internet/en/index/working_groups.html).

To guide the decision-making for the case definition and guidelines, a literature search of publications in English was performed using Medline, Embase and the Cochrane Libraries, including the terms vaccines, vaccination, or immunization (or terms beginning with vaccin-, immuni-, inoculat-), and [hypertension AND pregnancy] or [preeclampsia or eclampsia] (or preeclam-, eclamp-). The search resulted in the identification of 516 references. All abstracts were screened for possible reports of preeclampsia, eclampsia or hypertension in pregnancy following immunization. Twenty-seven articles with potentially relevant material were reviewed in more detail, in order to identify studies using case definitions or, in their absence, providing clinical descriptions of the case material. Data collected from these 27 articles included information on the study type, the vaccine, the diagnostic criteria or case definition put forth, the time interval since time of immunization, and any other symptoms. References that lacked hypertensive diseases of pregnancy as an outcome were excluded.

Most publications were of observational studies, though there were also several publications from vaccine adverse event reporting groups. Only one publication [6] specified the criteria used to diagnose preeclampsia in study participants. Four of the publications reported using ICD-9 diagnostic codes to collect cases of preeclampsia/eclampsia or pregnancy related hypertension [2,7–9].

### 1.3. Rationale for selected decisions about the case definition of preeclampsia as an adverse event following immunization

#### 1.3.1. The terms for hypertension in pregnancy

The terms “eclampsia,” “preeclampsia,” “gestational hypertension” and “pregnancy-induced hypertension” are commonly used in clinical practice. “Pregnancy-induced hypertension” is a term referring to hypertensive disorders of pregnancy in general, but lacks the specificity of the other terms, and so the Brighton definitions will refer only to “eclampsia,” “preeclampsia,” and “gestational hypertension.” All of these disorders are characterized by elevations in blood pressure. Preeclampsia and eclampsia have additional diagnostic criteria based on laboratory findings by clinical physical exam or patient reported symptoms reflecting the systemic nature of the disease. The diagnosis of gestational hypertension is provisional, in that every woman with new blood

pressure elevation in pregnancy should be further evaluated for the development of preeclampsia. It is possible to move from a diagnosis of gestational hypertension to preeclampsia or eclampsia, but not from preeclampsia to gestational hypertension.

#### 1.3.2. Formulating a case definition that reflects diagnostic certainty: weighing specificity versus sensitivity

The number of symptoms and/or signs that will be documented for each case may vary considerably. The case definitions have been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, one additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 2, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of the hypertensive diseases of pregnancy can be captured.

It needs to be emphasized that the grading of definition levels is entirely about diagnostic certainty, not clinical severity of an event. Thus, a clinically very severe event may appropriately be classified as Level 2 rather than Level 1 if it could reasonably be ascribed to an etiology other than the hypertensive diseases of pregnancy. Detailed information about the severity of the event should additionally be recorded, as specified by the data collection guidelines.

#### 1.3.3. The timing of development of preeclampsia in the context of vaccine administration

Preeclampsia and gestational hypertension are conventionally defined as developing after 20 weeks gestation [10], but there can be great variability in exact timing of presentation of the disease. In one study, approximately 10% of the preeclampsia diagnoses were made before 34 weeks gestation [11]. Preeclampsia can develop up to 6 weeks postpartum and, in fact, 20–50% of eclampsia occurs in the postpartum period [12,13]. The progression from normal blood pressure to hypertension to preeclampsia can proceed rapidly, gradually, or not at all. Because of the unpredictability in development and progression of the disease, it is important for the purpose of vaccine trials to record the temporal relationship between immunization and development of any preeclampsia-related complication of pregnancy.

#### 1.3.4. Rationale for individual criteria related to the case definition

**1.3.4.1. Gestational hypertension.** Gestational hypertension refers to new onset hypertension after 20 weeks of gestation [10,14,15]. The use of “20 weeks gestation” as a diagnostic criterion is somewhat arbitrary, as there is no specific physiologic change known that occurs at this gestational age that permits the development of preeclampsia. However, given that this convention is widely used, the Brighton Collaboration will continue to utilize it for the sake of continuity.

Accurate blood pressure measurement is fundamental for the diagnosis of a hypertensive disorder of pregnancy. The WHO released a document in 2003 detailing the proper protocols and techniques that should be utilized when measuring blood pressure. While it is outside the scope of this document to present a comprehensive guide to accurate blood pressure measurement, several important points should be highlighted. Regardless of the type of device used to measure blood pressure, accuracy should be checked regularly by comparing the measurement device to a calibrated device, and health care providers should be properly trained in taking blood pressure measurements. Blood pressure should be measured with the patient in a seated position, with the arm at the level of the heart. An appropriate cuff size should be chosen based on the patient’s size (generally a length that is 1.5 times the circumference of the patient’s arm). The systolic blood pressure is the

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