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# A systematic review of adverse events following immunization during pregnancy and the newborn period

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ABSTRACT

In 2013, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) requested WHO to develop a process and a plan to move the maternal immunization agenda forward in support of an increased alignment of data safety evidence, public health needs, and regulatory processes. A key challenge identified was the continued need for harmonization of maternal adverse event following immunization (AEFI) research and surveillance efforts within developing and developed country contexts. We conducted a systematic review as a preliminary step in the development of standardized AEFI definitions for use in maternal and neonatal clinical trials, post-licensure surveillance, and other vaccine studies. We documented the current extent and nature of variability in AEFI definitions and adverse event reporting among 74 maternal immunization studies, which reported a total of 240 different types of adverse events. Forty-nine studies provided explicit AEFI case definitions describing 35 separate types of AEFIs. We identified variability in how AEFIs were determined to be present, in how AEFI definitions were applied, and in the ways that AEFIs were reported. Definitions for key maternal/neonatal AEFIs differed on four discrete attributes: overall level of detail, physiological and temporal boundaries and cut-offs, severity strata, and standards used. Our findings suggest that investigators may proactively address these inconsistencies through comprehensive and consistent reporting of AEFI definitions and outcomes in future publications. In addition, efforts to develop standardized AEFI definitions should generate definitions of sufficient detail and consistency of language to avoid the ambiguities we identified in reviewed articles, while remaining practically applicable given the constraints of low-resource contexts such as limited diagnostic capacity and high patient throughput.

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## 1. Introduction

Since 1990, the world has experienced a dramatic decrease in early childhood mortality. In 2013, the global under-five mortality rate (U5MR) was 46 deaths per 1000 live births, nearly half the rate U5MR of 90 deaths per 1000 live births in 1990 [1]. However, the rate of this reduction in under-five mortality is still insufficient to reach the Millennium Development Goals' target of a two-thirds reduction of 1990 mortality levels by the year 2015 [2,3].

Compared to under-five mortality, declines in newborn mortality have been much slower to materialize. As of 2012, nearly 40% of all under-five child deaths occur in the neonatal period, i.e., babies in their first 28 days of life [4]. Additionally, in developing countries, nearly half of all mothers and newborns fail to receive skilled care during and immediately after birth. The World Health Organization (WHO) estimates that up to two-thirds of newborn deaths can be prevented if known, effective health measures are provided at birth and during the first week of life [4].

A potential strategy to address this global health need is the immunization of pregnant women to prevent diseases in

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their newborn children. Trans-placental transfer of antibodies has been demonstrated in several studies, and may confer protection against influenza during a newborn's first months of life [5]. This strategy is buoyed by the success of the global Maternal Neonatal Tetanus Elimination Initiative and recent vaccine studies demonstrating that immunization of pregnant women decreases newborn influenza [6,7]. However, there are challenges to introducing immunization programs in antenatal care in resource-poor settings, requiring careful consideration of existing regulatory processes and expansion of the evidence base to take into account local public health needs to inform maternal immunization programs and policy [8,9]. The WHO/PATH Maternal Influenza Immunization Project aims to address some of these challenges – specifically with respect to vaccine distribution, logistics, and potentially vaccine hesitancy and uptake – by promoting the integration of immunization into antenatal care platforms in low- and middle-income countries [10].

There are limitations to vaccine safety data in pregnant women as pregnant women are seldom included in clinical trials [11]. Most safety information comes from observational studies and analysis of post-licensure surveillance systems, such as those for influenza vaccines [12]. In 2014, the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed inactivated influenza vaccine safety in pregnancy and found no safety signals [13], and three recent systematic reviews of influenza vaccine safety in pregnancy have also been reassuring [14–16]. Nevertheless, the absence of global standard definitions for maternal immunization adverse events hinders comparisons of safety data across studies and geographic regions. For these reasons, the WHO and Brighton Collaboration are developing standardized adverse event definitions and reporting practices for use in clinical trials in pregnant women and other post-licensure vaccine safety monitoring.

The objective of this systematic review is to determine the extent and nature of variability in AEFI definitions and adverse event reporting among maternal immunization studies. The review aims to characterize the heterogeneity of AEFI definitions and reporting methods, which will directly inform ongoing vaccine safety standardization efforts for the purposes of clinical trial design as well as vaccine pharmacovigilance after licensing. These efforts will enhance collection, reporting, and comparison of clinical and post-marketing surveillance safety data—advancing our collective understanding of vaccine safety in pregnancy, and contributing to the harmonization of vaccine pharmacovigilance.

## 2. Methods

### 2.1. Eligibility criteria and assessment

#### 2.1.1. Types of studies

We included randomized controlled trials and observational studies that define one or more AEFIs for the purpose of safety monitoring. We also included reviews of maternal immunization studies; reviews were thought to potentially contain abstracted information on AEFI definitions that may not have existed, either at all or at the same level of detail, in the source publications. Maternal immunization reviews were therefore included to ensure that this content was not overlooked. We did not include unpublished studies.

#### 2.1.2. Types of participants

Studies chosen for review included pregnant women of all ages. Studies that did not explicitly include pregnant women, either exclusively or as part of an at-risk demographic, were excluded.

#### 2.1.3. Types of interventions

Eligible interventions included all vaccines evaluated in pregnant women.

#### 2.1.4. Types of comparisons

We included studies making any relevant comparisons of vaccines against a control, such as placebo, unexposed or untreated group, or alternate vaccine formulation.

#### 2.1.5. Types of outcome measures

Acceptable outcome measures included intervention efficacy, effectiveness, or safety. Specifically, studies that did not evaluate vaccine safety as a primary outcome were included if maternal, childbirth, or neonatal safety or adverse event data were reported.

#### 2.1.6. Other selection criteria

Study setting had no impact on inclusion. We included studies conducted in any country or region, in rural, urban, or mixed contexts, and in any participant setting such as in-hospital or in-community. Five studies published in languages other than English were considered for inclusion, but none were included in the final review due to lack of translation capacity. There was no constraint on date of publication.

### 2.2. Search strategy

We conducted a comprehensive and systematic search of published literature potentially containing data on maternal and neonatal adverse events following maternal immunization (Fig. 1).

Sources included all published maternal immunization studies conducted to date (randomized controlled trials and observational studies), identified via searches of PubMed, EMBASE, Web of Science, and the Cochrane Database. The search strategy used for this review was derived from prior work by Bonhoeffer et al including a systematic review of vaccine safety data reporting [17]. Publications citing key papers that evaluated or attempted to establish immunization study reporting standards (e.g. Bonhoeffer et al. [17]) were also included in the search process. Supplementary Table 1 details our maternal AEFI search strategy on PubMed and EMBASE; Fig. 1 indicates the total number of results from all searches.

### 2.3. Screening and data extraction

The initial screening was conducted by one reviewer; a two-reviewer system was employed throughout the remainder of the review workflow. We imported search results into Endnote X5, and one reviewer (T.R.F.) screened titles and abstracts for eligibility. We discarded articles if their titles and abstracts clearly bore no relevance to this review. We retrieved full texts of eligible studies, and discarded inaccessible studies (six articles published prior to 2000, were inaccessible). Consensus and/or discussion with a second reviewer (D. N.) resolved uncertainty during the screening process with regard to inclusion/exclusion of studies. We recorded the rationale for study exclusion as part of the screening process.

The objective of our review was to determine the variance in AEFI definitions across all maternal immunization literature irrespective of study design, rigor, outcome, or potential bias. Therefore, a methodological study quality assessment (e.g., a Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis) was not required for the purposes of this review. Studies included in this review were neither assessed for, nor ranked on the basis of, limitations in design or possible bias.

We abstracted data from all research studies and publications meeting the inclusion criteria into an Excel workbook (Supplemental Table 2). We compiled additional data required

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