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Congenital anomalies: 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 congenital anomalies as an adverse event following immunization

Congenital anomalies, also commonly referred to as birth defects, congenital disorders, congenital malformations, or congenital abnormalities, are conditions of prenatal origin that are present at birth, potentially impacting an infant's health, development and/or survival. We will use the term congenital anomalies in this report. Congenital anomalies encompass a wide array of structural and functional abnormalities that can occur in isolation (i.e., single defect) or as a group of defects (i.e., multiple defects). Multiple defects may occur as part of well-described associations, such as the non-random co-occurrence of Vertebral anomalies, Anal atresia, Cardiac defects, Tracheoesophageal fistula, and/or Esophageal atresia, Renal and Radial anomalies, and Limb defects (VACTERL) [1].

Congenital anomalies vary substantially in severity. Some congenital anomalies are associated with spontaneous abortion, stillbirth, or death in the early postnatal period. Global deaths due to congenital anomalies decreased from 750.6 thousand in 1990 to 632.1 thousand in 2013, with respective age-standardized death rates of 11.0 and 8.7 per 100,000 [2]. Subtypes of fatal congenital anomalies (with estimated number of global deaths in 2013 in thousands) are congenital heart anomalies (323.4), neural tube defects (68.9), Down's syndrome (36.4), and chromosomal unbalanced rearrangements (17.3) [2]. Other congenital anomalies may have little impact on survival. Anomalies which affect an infant's life expectancy, health status, physical or social functioning may be described as "major" anomalies. In contrast, "minor" anomalies are those with little or no impact on health or short-term or long-term function [3]. We have chosen to focus on major anomalies for this case definition due to their impact on public health and pre-existing structure for surveillance and reporting by large national and international organizations.

The causes of congenital anomalies are wide-ranging, with many anomalies remaining of undetermined etiology. Structural anomalies are often due to errors in embryogenesis occurring at critical periods of fetal development. Critical exposure periods during pregnancy can vary by organ system or type of anomaly. However, first trimester (gestational age 1–13 weeks) is generally considered the highest risk period. Medications, infectious agents, and environmental toxins have all been implicated as teratogens; illicit drugs and other maternal exposures can also disrupt fetal development and increase the risk for one or more congenital abnormalities [1]. Some structural and many functional defects are attributed to underlying genetic defects or chromosomal abnormalities. These defects may be due to one or both parents being genetic carriers, one or both parents sharing the disease state, or the occurrence of de novo mutations [4]. The timing of clinical recognition of major anomalies varies both by type of defect and by access to health care.

To date, multiple studies have investigated congenital anomaly outcomes following maternal vaccination, for both recommended and inadvertent vaccination.

1.1.1. Vaccinations routinely recommended during pregnancy

1.1.1.1. Influenza vaccine, including seasonal and pandemic vaccines. Many countries routinely recommend that pregnant women receive influenza vaccine at any time during pregnancy [5,6]. Thus, studies evaluating the potential for these vaccines to impact embryogenesis or risks for congenital anomalies are of critical importance. Maternal immunization during pregnancy with inactivated influenza vaccine is associated with a brief increase in maternal inflammatory biomarkers [7,8]. At the time of publication, there was no data to support an association between the maternal inflammatory response to vaccination and fetal development and risk for congenital anomalies.

As of March 2014, congenital anomaly data from more than 4000 pregnant women who received different types of adjuvanted and non-adjuvanted influenza vaccination during the first trimester, and over 19,000 during any trimester, were published [9–20] and comprehensively reviewed [21]. Of individual studies, the largest that included first trimester exposures reported pregnancy outcomes for 323 woman immunized with adjuvanted or non-adjuvanted A(H1N1)v2009 influenza vaccines and 1329 control subjects. The rate of major malformations did not vary between the two cohorts (all trimesters: OR 0.87; 95% confidence interval [CI] 0.38, 1.77; preconception and first trimester exposure: OR 0.79; 95% CI 0.13, 2.64) [16]. The review authors concluded that maternal influenza vaccination is not associated with an increased risk of congenital malformations. However, statistical imprecision, and clinical and methodological heterogeneity of included studies made it impossible to totally exclude harm [21]. A 2014 Cochrane systematic review combining five studies in a meta-analysis also found influenza immunization during pregnancy was not associated with a higher risk of congenital anomalies, pooled estimate OR 1.06 (95% CI, 0.90, 1.25) [11–13,16,17,22].

Since March 2014 there have been at least three retrospective studies published investigating congenital anomaly outcomes following monovalent influenza A (H1N1) vaccines [23–25]. The largest of the three studies was conducted in Lombardy, Italy, during the pandemic period (October 1, 2009–September 30, 2010) and included 6246 pregnant women immunized with a MF59 adjuvanted pandemic A (H1N1) vaccine [24]. Pregnancies were excluded if either chromosomal aberrations or congenital viral infections were reported in the birth registry. Cases were identified with ICD-9 coding and retained according to EUROCAT guidelines. Unmatched analysis identified 284/6246 (4.5%) cases of congenital malformations in the immunized cohort and 3246/79,925 (4.1%) in the unimmunized cohort, OR 1.13 (95% CI, 0.99, 1.28), and propensity matched OR 1.14 (95% CI, 0.99, 1.31) [24]. Rates and estimates were also available for specific anomalies.

1.1.1.2. Tetanus diphtheria, acellular pertussis vaccines (Tdap). Many countries recommend administration of the acellular pertussis vaccine during the third trimester of pregnancy [26,27]. One placebo randomized controlled trial, conducted from 2008 to 2012, examined infant congenital anomaly outcomes following maternal Tdap administration during pregnancy. Between 30 and 32 weeks gestation, 33 women received the Tdap vaccine and 15 received a placebo vaccine, with crossover immunization postpartum. In the vaccinated cohort one infant had a congenital anomaly, as compared to two infants with congenital anomalies in the control group [28]. To date, two retrospective observational studies of Tdap administration during pregnancy have been published in the United States; both suggest there is not a significantly increased risk of major congenital anomalies in infants born to mothers who were vaccinated during pregnancy [29,30]. The remaining evidence regarding the safety of pertussis containing vaccines is derived from passive surveillance [31].

Maternal and neonatal tetanus remain problematic in geographic areas where childbirth occurs under conditions that do not meet minimum standards of hygiene and immunization coverage of the population is low. In these regions, women with inadequate immunization history are recommended to receive two doses of tetanus toxoid (TT) containing vaccine as early as possible during pregnancy [32]. Between 1959 and 1965 a large prospective study in the United States was conducted that included 337 mother and child pairs evaluated for TT vaccine exposure before 20 weeks