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Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy

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ABSTRACT

A pertussis vaccination during pregnancy has recently been adopted in several countries to indirectly protect young infants. This study assessed the effect of adding a pertussis component to the tetanus vaccination, in the pregnancy immunization program in Vietnam.

A randomized controlled trial was performed. Pregnant women received either a Tdap (tetanus, diphtheria acellular pertussis) vaccine or a tetanus only vaccine between 19 and 35 weeks' gestational age. Immunoglobulin G (IgG) against tetanus (TT), diphtheria (DT), pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (Prn) were measured using commercial ELISA tests, at baseline, 1 month after maternal vaccination, at delivery, and in infants from cord blood and before and after the primary series (EPI: month 2-3-4) of a pertussis containing vaccine.

Significantly higher geometric mean concentrations (GMC) were observed for all 3 measured pertussis antigens in the offspring of the Tdap group, up to 2 months of age. One month after completion of the primary infant vaccination schedule, anti-Prn GMC, but not anti-PT and anti-FHA GMCs, was significantly ($p = 0.006$) higher in the control group.

Maternal antibodies induced by vaccination during pregnancy close the susceptibility gap for pertussis in young infants. Limited interference with the infant vaccine responses was observed. Whether this interference effect disappears with the administration of a fourth vaccine dose is further studied.

1. Introduction

Q5 In 2008, the World Health Organization (WHO) estimated that there were 16 million pertussis cases worldwide [1]. Most cases occur in low- and middle-income countries (LMICs) [2], and case-fatality rates (CFR) for infants in developing countries are as high as 4%. Global coverage of the 3 vaccine doses for DTP (Diphtheria, Tetanus, Pertussis) for infants is as high as 84% [3]. Despite universal infant vaccination, the disease has re-emerged in some industrialized countries, resulting in morbidity and mortality in young infants who are not fully vaccinated [4]. Adolescents and young adults are susceptible to pertussis due to waning antibodies after vaccination (for both aP (acellular pertussis) and wP (whole cell pertussis) vaccines) and declining naturally acquired immunity [5,6]. They represent a source of infection for newborns. It is likely that the shift in ages of those diagnosed with pertussis that has been observed in industrialized countries will eventually be observed in developing countries [7], depending on the vaccine that is used in infancy. The WHO recommends the use of wP vaccines in the Expanded Programme on Immunisation (EPI) [8] whenever a 3 + 1 infant-only schedule is used, but aP vaccines can be chosen when coverage decreases due to wP side effects [1].

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Protection against infectious diseases at birth is provided in part by maternal antibodies transferred through the placenta and lactation [9,10]. IgG pertussis antibodies have a half-life of 6 weeks [11]. The amount of antibodies transmitted depends on the placental function and on the maternal antibody concentration [12]. After pertussis vaccination/infection during childhood, antibody levels decline by childbearing age [13]. Therefore, the amount of anti-pertussis maternal antibodies transmitted is often low. Thus, increasing the load of maternal antibodies by maternal vaccination is, with the currently available vaccines, the best way to offer protection to newborns [14–17]. Some countries recommend pertussis vaccination during pregnancy (including the USA, UK, Belgium, and others). However, no studies were performed in LMICs, where the background epidemiology and vaccination statuses are different.

In Vietnam, pertussis vaccination began in 1985. Prior to that, the incidence of pertussis was up to 84.4/100,000 (1984) [18]. Overall, the reported incidence is now low (2012–2013: 0.1/100,000 to 0.06/100,000 [18]). Nevertheless, between 95 and 108 pertussis cases were recorded in 2011–2013, and over 50% of those cases occurred in infants under one year of age. In 2014, 92 out of 102 pertussis cases were reported in infants aged less than 6 months [19]. Cases are identified and confirmed based on a clinical diagnosis; laboratory confirmation is not obtained because standard laboratory diagnostic equipment is not available at the community level, and hospital diagnoses are not routinely reported. Therefore, underreporting and underdiagnosis is highly probable.

The aim of the present study was to assess the effect of vaccinating pregnant women in Vietnam with an aP vaccine, on the amount of transferred maternal antibodies and the possible interference of the vaccine with humoral immune responses in the infants.

2. Material and methods

A randomized controlled study was conducted in accordance with the Helsinki Declaration, Good Clinical Practice (ICH-GCP) and the procedures established by Vietnamese law. Ethical approval was obtained (National Institute of Hygiene and Epidemiology (NIHE), Vietnam No. 05IRB-120412; Ministry of Health: No. 978/CN-BYT-131112). Written informed consent was obtained from all participants and from both parents of the infants.

A sample size calculation was performed based on previous results [15]. The goal was to vaccinate 50 pregnant women with a combined Tdap (tetanus, diphtheria, acellular pertussis) booster vaccine (Tdap group) at between 18 and 36 weeks of pregnancy and 50 pregnant control women with a tetanus only vaccine, as recommended within the EPI (TT group). The study was conducted in three villages of 1 region, Ha Nam province, in Northern Vietnam. Both study groups were present in each village and the same MD and nurse performed the study visits for both groups. Pregnant women were randomly recruited for either the Tdap group or the TT group during routine preventive visits. Infants were offered pertussis immunization at 2, 3 and 4 months of age using a hexavalent vaccine on fixed days by the same study personnel.

A questionnaire was completed on each woman's general medical history, obstetrical factors, demographics, and general and pertussis-specific vaccination histories. Growth parameters, breastfeeding statuses, day care attendance, immunization data, and medical histories were recorded at each visit. Inclusion and exclusion criteria can be viewed in Annex 1.

2.1. Study vaccines

Women in the Tdap group received Adacel® (Sanofi Pasteur, Canada) containing 5Lf tetanus toxoid (TT), 2Lf Diphtheria toxoid (DT), 2.5 μg pertussis toxin (PT), 5 mcg filamentous haemagglutinin (FHA), 3 mcg pertactin (Prn) and 5 mcg fimbriae types 2 and 3 (FIM 2 and FIM3). The TT group received monovalent tetanus vaccine TT-VAC (IVAC®, Vietnam) including at least 10 Lf of TT.

Infants received the hexavalent vaccine Infanrix hexa® (GSK Biologicals, Belgium), containing 10 Lf TT, 25 Lf DT, 25 mcg PT, 25 mcg FHA and 8 mcg Prn plus inactivated poliovirus, hepatitis B surface antigens and *Haemophilus influenzae* type B polysaccharide.

2.2. Study procedures

Venous blood was taken from the women immediately preceding vaccination (5 cm^3) and at 1 month after vaccination (in the Tdap group) (5 cm^3). At delivery, a maternal blood sample (5 cm^3) and a cord blood sample (5 cm^3) were taken. Blood samples from infants were taken at week 8 before the first vaccine dose was administered (2.5 cm^3) and at 1 month after the third vaccine dose (2.5 cm^3). All samples were collected at the Commune Health Center and transported to the Ha Nam Preventive Medicine Center on the same day. Samples were centrifuged and stored at −80 °C. All samples were monthly sent to the Department of Bacteriology at NIHE.

2.3. Safety assessments

Systemic reactions were monitored in both groups by a medical doctor for 30 min post-vaccination. Other adverse events were monitored for 30 days post-vaccination through a diary and visits to the local health center. Solicited adverse events included pain at the injection site, swelling, erythema and general symptoms, e.g., myalgia and fever. Serious adverse events (SAE) were recorded throughout each pregnancy. The causality of an adverse event was judged by the investigators based on its temporality, biologic plausibility and the identification of alternative etiologies. Possible congenital abnormalities were monitored in the offspring.

2.4. Laboratory

Anti-PT IgG antibodies were detected using the Virion/Serion® kit (ANL Copenhagen). Anti-FHA and anti-Prn IgG antibodies were detected with the EuroImmune® ELISA kit. Anti-TT and anti-DT IgG antibodies were detected using the Virotech/Sekisui® ELISA. Serum samples were tested in duplicate at a dilution of 1:100 (PT, TT and DT), 1:400 (FHA) and 1:800 (Prn). All titers are expressed in International Units IU/ml, using respective WHO standards (NIBSC 06/140 for pertussis, NIBSC code TE-3 for tetanus and NIBSC 00/496 for diphtheria). The limit of detection was 0.01 IU/mL and 0.03 IU/mL for tetanus and diphtheria, respectively. All analyses were performed at laboratory of the Scientific Public Health Institute in Brussels (Belgium), except for TT ELISA in the infant samples. An international independent validation of the pertussis toxin results was performed to guarantee the reliability of the results at the Canadian Center for Vaccinology, Halifax. The correlate of protection is 0.1 IU/mL for tetanus and 0.01–0.1 IU/mL for diphtheria. No correlate of protection is known for pertussis [20].

2.5. Statistics

All statistical analyses were performed with R statistical software. IgG antibodies were expressed as geometric mean concentration (GMC) with their 95% confidence intervals. p-Values <0.05 were considered significant.

Statistical tests included parametric tests: (paired) t-tests and chi-square tests and their nonparametric alternatives: (paired) Wilcoxon tests and Fisher Exact tests whenever the underlying assumptions of the parametric tests were violated, i.e. normality and sparseness, respectively [21].

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