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Effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among Japanese pregnant women: A prospective observational study assessing antibody efficacy

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ABSTRACT

In order to estimate the effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among pregnant women, we prospectively observed 135 Japanese pregnant women who received an influenza A (H1N1) 2009 monovalent vaccine during November 2009. We calculated an index of "antibody efficacy", in which the medical visits for respiratory illnesses were compared between those with and without post-vaccination hemagglutination inhibition (HI) titer ≥1:40. The product of antibody efficacy and achievement rate is theoretically equivalent to the vaccine effectiveness. Among all subjects, an inverse but non-significant relationship during the epidemic period was observed between post-vaccination HI titer ≥1:40 and medical visits for respiratory illnesses. After stratification by trimester at recruitment, a significant inverse association during the epidemic period was found among subjects in the first or second trimester (antibody efficacy: 91%, vaccine effectiveness: 79%). The influenza A (H1N1) 2009 monovalent vaccine administered in the first or second trimester reduced medical visits for respiratory illnesses among Japanese pregnant women.

1. Introduction

It is widely known that pregnant women are at increased risk of complications from influenza. Severe influenza illness and fatality among pregnant women were observed during the most recent 2009 pandemic of influenza A (H1N1) [1–10], as well as during previous pandemics [11–14]. Even in the inter-pandemic periods, rates of medical visits for acute respiratory diseases attributable to influenza were greater among pregnant women than non-pregnant women [15]. The rate of hospitalization during influenza season due to respiratory illness or acute cardiopulmonary disease increased at the later stages of pregnancy [16,17]. Elevated risk for influenza among pregnant women is likely due to alterations in cardiovascular and respiratory systems, including increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity [18]. Immunologic changes during pregnancy may also contribute to increased susceptibility to influenza viruses, because of suppression of cell-mediated immunity while retaining normal humoral immunity [19].

Several guidelines or statements recommend receiving inactivated influenza vaccination during any trimester of pregnancy [20,21]. Previous studies showed adequate immune response and safety of maternal influenza vaccination [22–26]. A recent publication also confirmed that immunogenicity of an influenza A (H1N1) 2009 monovalent vaccine was excellent in Japanese pregnant women [27,28]. Regarding the vaccine effectiveness, there has been a growing number of reports that influenza vaccination during pregnancy was associated with a reduced risk of influenza virus infection or hospitalization in infants [29–32]. On the other hand, few studies have assessed the effectiveness of maternal influenza vaccination in protecting pregnant women from influenza-related outcomes, and the findings were inconsistent [29,33]. Because the current recommendation with regard to influenza vaccination during pregnancy seems to be dependent on health impact, immunogenicity and safety data, additional findings of vaccine effectiveness in pregnant women are needed to support the recommendation.

During the 2009 influenza pandemic, the Ministry of Health, Labor and Welfare in Japan stated that pregnant women were one of the initial target groups for receiving a 2009 influenza A (H1N1) monovalent vaccine. This statement placed ethical

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constraints on the use of a randomized controlled trial to evaluate efficacy of maternal immunization. It was also not easy to obtain a sufficient number of unvaccinated pregnant women to evaluate vaccine effectiveness, in which the outcome occurrence is compared between vaccinee and non-vaccinee, because of the vaccination efforts of both pregnant women and obstetricians. An index of "antibody efficacy", in which the outcome occurrence is compared between those with and without a protective level of post-vaccination hemagglutination inhibition (HI) titer, has been shown to be a valid alternative to evaluate vaccine effectiveness [34–36].

An influenza pandemic is likely to provide an ideal opportunity for evaluating influenza vaccine effectiveness. However, if a large-scale pandemic occurs, the anticipated vaccine supply is substantially delayed. On the other hand, the pandemic may subside when the vaccine is sufficiently distributed. Such trade-off might partly explain the fact that, to the best of our knowledge, there has been no prospective study of vaccine effectiveness among pregnant women during the 2009 influenza pandemic. In this prospective observational study assessing antibody efficacy, our objective was to estimate the effectiveness of an influenza A (H1N1) 2009 monovalent vaccine in Japanese pregnant women.

2. Methods

2.1. Study subjects and vaccination

Eligible subjects were pregnant women who were willing to receive an influenza A (H1N1) 2009 monovalent vaccine at two medical institutions in Osaka, Japan, during November 2009. A total of 150 pregnant women were recruited. Subjects were excluded if they had an episode of prior 2009 influenza A (H1N1) infection, an acute febrile illness or signs of severe acute illness at the time of vaccination, a history of anaphylaxis due to vaccine components, or other conditions which precluded them from receiving vaccination. None of the subjects met the exclusion criteria. All subjects gave written consent prior to their participation in this study. The study protocol was approved by the ethics committee of Osaka City University Faculty of Medicine.

During recruitment, from November 7–27, 2009, all subjects received the first dose of subcutaneous injections of an influenza A (H1N1) 2009 monovalent inactivated vaccine into their arms. A 0.5 mL prefilled syringe type vaccine was used (Lot. NM001A, Kitasato Institute, Japan). Each dose contained 15 μg of hemagglutinin antigen. The seed virus was prepared from reassortant vaccine virus A/California/7/2009 NYMC X-179A (New York Medical College, Valhalla, NY) distributed by the Centers for Disease Control and Prevention in the United States (US). The vaccine contained neither preservative (thimerosal) nor adjuvant. During December 3–18, 2009, the subjects received a second dose of vaccine after a 3-week interval from the first vaccination.

As of November 11, 2009, Ministry of Health, Labor and Welfare in Japan stated that one dose of an influenza A (H1N1) 2009 monovalent vaccine was thought to be enough to induce a sufficient immune response for pregnant women. However, this issue was still controversial when we started recruitment. Thus, we asked the subjects in this study to receive vaccination twice.

2.2. Information collection at recruitment and follow-up

A self-administered questionnaire was used to collect a subject's baseline characteristics at recruitment such as age, height and body weight before pregnancy, underlying medical conditions, food/drug allergies, smoking history, number of family members, reproductive history and years of schooling. Underlying medical conditions were defined as chronic pulmonary disease (including asthma), cardiovascular disease (excluding hypertension), renal disease, hepatic disease, hematological disease, diabetes, neuromuscular disease, immunocompromised conditions, malignant tumors, connective tissue disease, or atopy. The subjects were also asked to provide a history of their 2009–2010 seasonal influenza vaccination, their 2008–2009 seasonal influenza vaccination, and a physician diagnosis of influenza during the 2008–2009 season. The obstetrician in charge provided information regarding the subject's gestational age and maternal disorders predominantly related to pregnancy.

We prospectively conducted weekly follow-up surveys using a self-administered postal questionnaire. The subjects were requested to report medical visits for respiratory illnesses and hospitalization until the end of this study (March 28, 2010). In addition, the date of delivery was provided by the obstetrician in charge.

2.3. Serum specimen and HI titer measurement

The subjects provided serum samples at three time points: before vaccination; 3 weeks after the first dose; and 4 weeks after the second dose. Serum was frozen at −80 °C until assayed simultaneously at the Kitasato Institute in February 2010. Serum HI titers were measured using a standard method with the same antigens that were in the vaccine.

In this study population, we confirmed that a single dose of influenza A (H1N1) 2009 monovalent vaccine induced an adequately protective level of immunity in accordance with the international licensing criteria, and that a second dose conferred little additional induction of antibodies [27,37,38]. We therefore compared the outcome occurrence between those subjects with and without an HI titer ≥1:40 at 3 weeks after the first vaccination (hereafter referred to as "post-vaccination titer").

2.4. Regional epidemic and observation period

Influenza is designated as one of the target diseases of the sentinel surveillance program in Japan. During 2009, Osaka prefecture had 305 sentinel medical institutions for influenza that should report the number of influenza patients aggregated by sex and age groups. Fig. 1 shows the number of reported influenza patients per sentinel in Osaka prefecture during the study period. Based on the epidemic curve, antibody efficacy was examined for the following three periods: (1) the entire period (from 3 weeks following the first vaccination until March 28, 2010); (2) period A, when the number of reported patients per sentinel was at least one (until February 21, 2010); and (3) period B, when the number of reported patients per sentinel was at least five (until January 31, 2010). All influenza viruses isolated in Osaka prefecture during the period were 2009 pandemic influenza A (H1N1) virus strain.

2.5. Statistical analysis

The outcome measures for this study were medical visits for respiratory illnesses and hospitalization for reasons other than delivery. We considered outcome occurrence from 3 weeks following the first vaccination to March 28, 2010, regardless of the subject's delivery. If a subject experienced the outcome once or more during the pre-specified observation period, we considered the subject as having the outcome occurrence. Logistic regression analyses were employed to estimate odds ratios (ORs) of those with post-vaccination HI titer ≥1:40 and the 95% confidence intervals (CIs). An antibody efficacy was calculated as $[1 - \mathrm{OR}] \times 100\%$ [34–36]. The product of antibody efficacy and achievement rate (i.e., the proportion of those who achieved post-vaccination HI titer