Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Evaluating the effectiveness of the universal immunization program against varicella in Japanese children

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ARTICLE INFO

Article history:
Received 16 May 2017
Received in revised form 21 July 2017
Accepted 23 July 2017
Available online xxxx

Keywords:
Varicella
Live attenuated vaccine
Vaccine effectiveness
Case control study

ABSTRACT

Objective: Matched case control study was conducted to elucidate the effectiveness of the Oka/Biken vaccine immediately after implementation of the universal immunization program in Japan.
Methods: Cases were laboratory confirmed varicella patient under 15 years of age diagnosed at 14 designated pediatric clinics between September 2015 and September 2016. Controls were selected from patients who visited the same practice for different reasons as the varicella case within 2 weeks. Swab samples were collected from varicella suspected patients and molecular diagnostic assays were used to confirm varicella cases. Matched odds ratio were used to calculate vaccine effectiveness (VE).
Results: Varicella zoster virus DNA was detected in 183 (81.3%) of 225 suspected cases. One sample was excluded because it was positive for the Oka vaccine strain (182/225, 80.9%). Three hundred twenty-three control subjects were enrolled. The effectiveness of 1 dose of the Oka/Biken vaccine compared with no vaccine was 76.7% (95% confidence interval [CI]: 58.6–86.9%; $P < 0.001$). The effectiveness of 2 doses of the Oka/Biken vaccine was 94.2% (95% CI: 85.7–97.6%; $P < 0.001$). After adjusting for potential confounding effects, the adjusted VE of 1 and 2 doses of varicella vaccine were 76.9% (95% CI: 58.1–87.3%; $P < 0.001$) and 94.7% (95% CI: 86.0–98.0%; $P < 0.001$), respectively.
Conclusions: VE of one dose of Oka/Biken varicella vaccine was insufficient to control varicella. Therefore, two doses of Oka/Biken varicella vaccine is significant for controlling varicella in Japan.

1. Introduction

The live attenuated varicella vaccine derived from the Oka/Biken strain was developed by Takahashi et al. in 1974 [1]. Initially, this vaccine was developed to prevent fatal varicella in immunocompromised children such as patients with leukemia [2–4] and nephrotic syndrome [1,5]. The varicella vaccine was approved as a voluntary vaccine in Japan in 1986. In healthy Japanese children, a single dose of the varicella vaccine induced strong immunity that persists for 20 years [6], which may be contributed by strong natural booster activity depending on varicella outbreaks. Although the varicella vaccine was developed almost four decades ago in our country, the vaccine was only administered on a voluntary basis until 2014. Therefore, in Japan, vaccine coverage rate has been insufficient to control varicella outbreaks as evidenced by a consistent seasonal epidemiological pattern of varicella [7]. Despite several post-marketing studies demonstrated that the varicella vaccine is safe and well tolerated [8–11], both pediatricians and parents remain concerned about the high frequency of breakthrough varicella (approximately 30%) in Japan [12].

Universal varicella vaccination commenced in the United States in 1996 after gaining approval from the U.S. Food and Drug Administration in 1995. Previous studies conducted in the United States demonstrated the efficacy of varicella vaccination, namely decreased varicella patients, varicella-associated admitted cases, and deaths after the adoption of the universal varicella vaccination [13–17]. The two widely used varicella vaccines in the United States and Europe, Varivax (Merck & Co., Inc.) and Varilrix (GlaxoSmithKline), are derived from the Oka/Biken virus strain.

Abbreviations: CI, confidence interval; LAMP, loop-mediated isothermal amplification; MR, measles and rubella; PCR, polymerase chain reaction; VE, vaccine effectiveness; VZV, varicella zoster virus.

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http://dx.doi.org/10.1016/j.vaccine.2017.07.090
0264-410X/

According to a recently reported meta-analysis of varicella vaccine effectiveness (VE) [18], a single dose of varicella vaccine was moderately effective in preventing varicella and highly effective in preventing moderate/severe varicella, and the second dose of the vaccine added protection efficacy against varicella. However, it is considered that VE is dependent on vaccine formulation, seroepidemiology of varicella zoster virus (VZV), and the characteristics of varicella outbreak.

The data analyzed in the meta-analysis was mainly from the United States and Europe that either Varivax or Varilrix were used as universal immunization [18]. Unlike those countries, Japan uses solely the original Oka/Biken vaccine. As the varicella VE may be influenced by the circumstances of each country, we conducted a matched case-control study to determine the VE of Oka/Biken varicella vaccine in Japan immediately after the implementation of the universal immunization program.

2. Methods

Children less than 15 years of age who visited 14 pediatric practices and hospitals located in Aichi prefecture (Nagoya VZV study group) between September 2015 and September 2016 were eligible for the study. The written informed consent was obtained from a parent if the child was eligible for the study and parents agreed to participate in the study. Children for whom the varicella vaccine is contraindicated, such as those who were immunocompromised because of an underlying illness (e.g., leukemia) or medications (e.g., prednisone) were excluded from the study. Children were also excluded if they had been previously diagnosed with varicella.

Swab samples were collected from skin eruptions using a cotton-tipped swab, and then the swab was immersed in 1 ml of physiologic saline. Direct loop-mediated isothermal amplification (LAMP) assays without DNA extraction were performed on all specimens to detect VZV DNA by investigators who were blinded to participant information. Positive and negative specimens were classified based on the detection of VZV DNA. If the specimen was negative for direct LAMP assay, we extracted DNA from the swab samples and conducted the LAMP assay again. If both the LAMP assay with and without DNA extraction were negative, a more sensitive real-time polymerase chain reaction (PCR) for detection of viral DNA was performed. LAMP products were digested with the *Sma*I restriction enzyme for differentiation between wild type and Oka/Biken vaccine strains [19].

For each VZV DNA positive case, two controls were randomly selected from patients who visited the same clinic with no varicella within 2 weeks from the case. Controls were also matched by age (±1 year) and sex.

If the parents of the case or the control agreed their child being enrolled to the study, practitioner explained the objective and methods of the study. Then, we collected demographics, background information (numbers of sibling, attendance at day care or school, living with grandparents), clinical symptoms including incidence of febrile episodes, duration of febrile period, numbers of skin eruption at the first visit to the clinic, complications, and recent VZV exposures by using self-reporting questionnaire. The medical records and maternity health record books of the participants were reviewed to obtain all relevant information such as previous immunization records and significant medical illnesses by physician. Participants were considered being vaccinated if there was a written documentation of varicella vaccine at least 4 weeks before the onset for the case and before the visit to the clinic for the control.

The participants less than 1 year old were excluded from the calculation of VE because the first dose of VZV vaccine is typically administered after the child's first birthday. Student's *t*-test was used as appropriate to assess statistical significance of differences between groups in continuous variables, and a χ^2 test was used to assess statistical differences between categorical values. All *P* values are 2-sided. Results were considered statistically significant if the 2-tailed *P* value was <0.05. The designed matched case control study was analyzed by logistic regression analysis. The potential confounding factors were adjusted by presence of siblings and whereabouts during daytime. The conditional regression analysis was performed by SAS software, version 9.4, for Windows (SAS Institute, Inc. Cary, NC). The VE was calculated as 1 – the matched odds ratios × 100% [20].

This study was approved by the Institutional Review Board of our university (No.15–247).

3. Results

3.1. Characteristics of subjects

Two hundred twenty-five varicella suspected cases were enrolled from September 1, 2015 to September 30, 2016. Results of molecular analysis for the diagnosis of varicella are shown in Fig. 1. Direct LAMP assay (without DNA extraction) detected VZV DNA from swab samples in 164 (72.9%) of the 225 specimens. After DNA extraction, the LAMP assay was repeated and 12 (5.3%) of the 61 direct LAMP negative samples were found to be positive. Furthermore, VZV DNA was detected in 7 (3.1%) of the 49 LAMP negative samples by real-time PCR assay. Total of 183 samples were confirmed as varicella by virological testing. However, strain from one sample was identified as a vaccine strain that 182 (80.9%) of the 225 suspected cases were determined as varicella cases in this study conclusively. Concurrently, total of 323 matched controls were also enrolled in this study.

Characteristics of the participants are shown in Table 1. Between cases and controls, no statistical difference was observed in most of the variables except the number of siblings was significantly higher among cases (1.5 ± 1.2) than controls (1.2 ± 0.9) ($P = 0.001$), and day care attendance was also significantly higher among cases (156/182, 85.2%) than controls (246/323, 76.2%) ($P = 0.011$).

3.2. Immunization with varicella vaccine

Vaccination status was only examined in the subjects over 1 year old ($n = 168$; 3 unknown cases were excluded from the 171 cases) (Table 1), because 1st doses of MR and varicella vaccines are recommended in 1 year old. Of the 168 subjects with varicella, 67 (39.9%) were unimmunized by the varicella vaccine, 86 (51.2%) had received 1 dose, and 15 (8.9%) had received 2 doses. Among the 301 controls, 41 (13.6%) were unimmunized by the varicella vaccine, 176 (58.5%) had received 1 dose, and 84 (27.9%) had received 2 doses ($P < 0.001$). As nearly all cases and controls had received 1 dose of the MR vaccine, no statistical difference in status of MR vaccination was demonstrated between cases and controls ($P = 0.789$).

3.3. Effectiveness of the Oka/Biken varicella vaccine

Among unvaccinated and 1 dose cases, the effectiveness of 1 dose of the varicella vaccine was 76.7% (95% confidence interval [CI]: 58.6–86.9%; $P < 0.001$) against varicella (Table 2). The effectiveness of 2 doses of the vaccine was 94.2% (95% CI: 85.7–97.6%; $P < 0.001$). The odds ratio for 2 doses versus 1 dose of the vaccine was 0.250 (95% CI: 0.113–0.550; $P < 0.001$), indicating that the odds of developing varicella for children who had received 2 doses of the varicella vaccine were 25% lower than for those who had

Please cite this article in press as: Hattori F et al. Evaluating the effectiveness of the universal immunization program against varicella in Japanese children. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.07.090