Effectiveness of Varicella Vaccination Program in Preventing Laboratory-Confirmed Cases in Children in Seoul, Korea

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INTRODUCTION

Varicella is an acute contagious disease caused by the varicella-zoster virus (VZV). A live attenuated varicella vaccine was first developed in 1974 and is now used widely in many countries including the United States, Germany, China, Taiwan, and Republic of Korea (1-5). In a recent meta-analysis of global varicella vaccine effectiveness, varicella vaccine was reported to be effective in preventing varicella (6). In specific, the United States where a universal two-dose varicella vaccination program was adopted since 2006 experienced declines in the incidence of the disease, the hospitalization of infected patients, and disease outbreaks (7).

In Korea, the varicella vaccination has been recommended for children in high-risk groups since 1988. Following the introduction of universal varicella vaccination by the National Immunization Program (NIP) in 2005, one-dose varicella vaccine has been recommended for all children aged 12-15 months. Four live attenuated varicella vaccines are available; three are based on the Oka strain, and one is based on the MAV strain.

However, the incidence of varicella has yet to decline and, in fact, has been continuously rising, from 22.5 per 100,000 persons in 2006 to 73.2 in 2013 (8). The objective of this study was to evaluate the effectiveness of one-dose varicella vaccination program in Korea by performing a matched case-control on children in Seoul.

MATERIALS AND METHODS

We performed a matched case-control study on children who were younger than 12 years of age in Seoul, Korea. Relevant data were collected from the National Notifiable Disease Surveillance System (NNDSS). The NNDSS, which was established in 2001, consists of case-based national infectious disease data collected via a surveillance system; nationally notifiable diseases such as varicella must be reported by all local public health centers in the country. The varicella case data in the NNDSS include demographic and clinical details such as patient name, date of birth, gender, address, date of disease onset, laboratory confirmation, and vaccination status.
All cases were children with varicella identified in Seoul between January 2013 and December 2013. Cases were composed of confirmed and possible cases and we only use the former to avoid misclassification bias. We excluded cases born prior to universal varicella vaccination adopted in 2004 or after 2012, because varicella vaccination is recommended for children aged 12-15 months. In order to estimate the exact effectiveness of varicella vaccine, we also excluded subjects who developed varicella within 42 days after vaccination (the so-called “wild-type” varicella) and who were vaccinated twice.

We aimed at selecting controls to represent the source population from which varicella cases arose. From the same NNDSS data, mumps and scarlet fever were considered appropriate as controls for the following reasons; 1) mumps and scarlet fever are infectious diseases independent of varicella, 2) age distribution in incidence of mumps or scarlet fever is similar to that of varicella.

In recruiting age-matched controls who had suffered from mumps or scarlet fever but had no history of varicella were identified in Seoul between January 2013 and December 2013 in the same NNDSS population where cases were reported. We matched each control by date of birth to a 1-month interval centered on the birth date of each case; a single control was randomly chosen if more than one candidate seemed appropriate. Ultimately, we created a list of 1:1 individually matched controls.

The effectiveness of a vaccine was estimated as follows; we calculated vaccine effectiveness by substituting the matched overall risk (OR) for the relative risk (RR) (1-RR); this approximates the RR in a case-control study (9).

Statistical analysis

The χ² test was used to compare the groups in terms of categorical variables, and the paired t-test was used to compare them with regard to continuous variables. To estimate the effectiveness of one-dose vaccination, we performed conditional logistic regression analysis on the 1:1 matched pairs after adjusting for the effects of possible confounders such as sex and age at vaccination; we then calculated matched odds ratios with 95% confidence intervals (CIs). When calculating the effect of time since vaccination, we used conditional logistic models with dummy-coded variables (10). A two-sided P value < 0.05 was considered statistically significant. All data were analyzed with the aid of SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Subjects

In 2013, a total of 3,622 cases were reported. Of the 3,622, we excluded 2,807 possible varicella cases. Of the remaining 815 cases, we also excluded 278 cases; 230 had been born before June 2004, 27 had been infected within 12 months of birth, 5 had wild-type varicella, 16 had received two doses of vaccine (Fig. 1). Finally, we included 537 varicella cases in the study.

Table 1. Characteristics of children with varicella and matched controls

| Characteristics                      | Cases (n = 537) | Controls (n = 537) | P value |
|--------------------------------------|----------------|-------------------|---------|
| Age, mon                             |                |                   | 0.967   |
| Mean ± SD (Median range)             | 68.6 ± 22.7    | 68.5 ± 22.7       |         |
| Gender, No. (%)                      |                |                   | 0.297   |
| Male                                 | 289 (53.8)     | 306 (57.0)        |         |
| Female                               | 248 (46.2)     | 231 (43.0)        |         |
| MMR vaccine status, No. (%)          |                |                   | < 0.001 |
| Unvaccinated                         | 440 (81.9)     | 524 (97.6)        |         |
| Received MMR vaccine                 | 97 (18.1)      | 13 (2.4)          |         |
| No. of varicella vaccination within 28 days of MMR vaccine | 1 (0.19) | 3 (0.56) | |
| Vaccination status, No. (%)          |                |                   | 0.385   |
| Unvaccinated                         | 130 (24.2)     | 118 (22.0)        |         |
| Vaccinated                           | 407 (75.8)     | 419 (78.0)        |         |
| Age at vaccination, mon              |                |                   | 0.002   |
| ≤ 15                                 | 379 (93.1)     | 366 (87.4)        |         |
| > 15                                 | 28 (6.9)       | 53 (12.6)         |         |
| Type of vaccination                  |                |                   | 0.001   |
| A                                    | 241 (59.2)     | 227 (54.2)        |         |
| B                                    | 53 (13.0)      | 42 (10.0)         |         |
| C                                    | 24 (5.9)       | 49 (11.7)         |         |
| D                                    | 6 (1.5)        | 21 (5.0)          |         |
| Unknown                              | 83 (20.4)      | 80 (19.1)         |         |

Number of who received varicella vaccine at age younger than 12 months was 5 in controls.

MMR = measles-mumps-rubella.

Fig. 1. Subject recruitment procedures for 1:1 matched case-control study.

Laboratory and epidemiologic confirmed case n = 845

Excluded cases, n = 2,807
  - Possible cases, n = 2,807

Excluded cases, n = 278
  - Born before June 2004, n = 230
  - Infected within 12 months after birth, n = 27
  - Wild-type varicella, n = 5
  - 2-dose vaccinated, n = 16

Children eligible for the study n = 537

Reported cases with varicella in Seoul, Korea, 2013 n = 3,622
**Characteristics of cases and controls**
The 537 cases and their individually matched controls were similar in terms of both age and gender. The proportions of vaccinated cases and controls were similar, at 407 (75.8%) and 419 (78.0%), respectively (Table 1).

Of those who were vaccinated, 379/407 (93.1%) cases and 366/419 (87.4%) controls were vaccinated before 15 months of age, as recommended by the national vaccination policy. The proportion of cases vaccinated was significantly higher than the proportion of controls vaccinated ($P < 0.002$).

More than half of all vaccinated cases (241/407; 59.2%) and 227/419 (54.2%) of the controls received vaccine A; the proportions of the other vaccines used were as follows: Unknown (20.4% of cases and 19.1% of controls) > vaccine B (13.0% and 10.0%, respectively) > vaccine C (5.9% and 11.7%, respectively) > vaccine D (1.5% and 5%, respectively). However, the proportions of the vaccines used were significantly different between the groups ($P = 0.001$). Thus, both age at vaccination and type of vaccination were entered into the conditional logistic model.

**Effectiveness of varicella vaccination**
According to the conditional logistic regression analysis of the data for matched pairs, the overall effectiveness of one-dose varicella vaccination was 13% (95% CI, -17.3-35.6). The unadjusted estimate of vaccine effectiveness was 11.8% (95% CI, -17.1-33.6, $P = 0.385$) (Table 2).

Conditional logistic regression analysis of vaccine effectiveness by each of the four vaccine manufacturers showed that the effectiveness of different vaccines varied (Table 3). Only vaccine C exhibited statistically significant effectiveness (88.9%; 95% CI, 52.1-97.4). The vaccine effectiveness were -5% (95% CI, -61.9-31.9) for vaccine A, -100% (95% CI, -700-50.1) for vaccine B, 71.4% (95% CI, -37.5-94.1) for vaccine D, and -16.7% (95% CI, -101-32.4) for the vaccine of an unknown manufacturer.

Overall, the effectiveness of a one-dose varicella vaccination was 75.8% (95% CI, 22.8-92.4) in the first year after vaccination. Thereafter, effectiveness decreased, falling to zero (or below) in the fourth and the sixth years. When adjusted for sex, age at vaccination and measles-mumps-rubella (MMR) vaccination within 28 days of birth, the effectiveness of varicella vaccine was not significant even in the first year after vaccination (Table 4).

**DISCUSSION**
The results of this study show that the overall effectiveness of one-dose varicella vaccination in preventing confirmed cases of varicella was low and insignificant (13%; 95% CI, -17.3-35.6). Specifically, the vaccine effectiveness of vaccine A, which was used in more than half of all vaccinations, was -5% (95% CI, -61.9-31.9), whereas vaccine C was highly effective (88.9%; 95% CI, 52.1-97.4). Vaccination was effective for only 1 year (the estimate of 75.8% fell to 67.1% after adjustment for confounders).

These results are consistent with those of a recent clinical case-control study assessing the effectiveness of an MAV strain-based varicella vaccine in Korea (11). The estimated effectiveness was statistically insignificant (54%; 95% CI, -0.10-2.05) and the vac-

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**Table 2. Overall effectiveness of varicella vaccine**

| Cases | Matched control | VE (95% CI) | $P$ value |
|-------|-----------------|------------|----------|
|        | Vaccinated | Unvaccinated |            |          |
| Vaccinated | 327     | 80         | 13.0 (-17.3-35.6) | 0.361    |
| Unvaccinated | 92      | 38         |            |          |

When unadjusted for matched pairs, vaccine’s effectiveness (1-OR) was 11.8% (-17.1%-33.6%, $P = 0.385$).

VE = vaccine effectiveness, CI = confidence interval, OR = overall risk.

**Table 3. Effectiveness of varicella vaccine by manufacturers**

| Vaccines | Vaccinated cases with unvaccinated controls | Unvaccinated cases with vaccinated controls | VE (95% CI) | $P$ value |
|----------|---------------------------------------------|-------------------------------------------|------------|----------|
| A        | 42                                          | 40                                        | -5 (-61.9-31.9) | 0.825    |
| B        | 6                                           | 3                                         | -100 (-700-50.0) | 0.327    |
| C        | 2                                           | 18                                        | 88.9 (52.1-97.4) | 0.003    |
| D        | 2                                           | 7                                         | 71.4 (37.5-94.1) | 0.118    |
| Unknown  | 28                                          | 24                                        | -16.7 (-101-32.4) | 0.580    |

VE = vaccine effectiveness, CI = confidence interval.

**Table 4. Overall effectiveness of varicella vaccination by time since vaccination**

| Time since vaccination, yr | No. of vaccination | Unadjusted VE (95% CI) | $P$ value | Adjusted VE* (95% CI) | $P$ value |
|---------------------------|--------------------|------------------------|----------|-----------------------|----------|
|                           | Case               | Control                |          |                       |          |
| 1                         | 19                 | 31                     | 75.8 (22.8-92.4) | 0.017 | 67.1 (12.0-90.3) | 0.075    |
| 2                         | 39                 | 41                     | 60.4 (-49.2-89.5) | 0.171 | 49.5 (96.0-87.0) | 0.323    |
| 3                         | 37                 | 42                     | 57.9 (-24.5-85.7) | 0.118 | 52.1 (45.7-15.8) | 0.195    |
| 4                         | 84                 | 80                     | -7.2 (-130.9-50.2) | 0.859 | -15.7 (-153.6-47.2) | 0.716    |
| 5                         | 83                 | 88                     | 8.6 (-59.5-47.6) | 0.752 | -10.0 (-75.2-44.1) | 0.973    |
| 6                         | 86                 | 68                     | -58.3 (-184.1-11.8) | 0.124 | -59.8 (-188.9-11.6) | 0.120    |
| 7                         | 37                 | 41                     | 13.2 (-60.5-51.7) | 0.636 | -10.9 (-60.5-50.6) | 0.700    |
| 8                         | 22                 | 28                     | 26.8 (-37.2-60.9) | 0.091 | 25.3 (-40.4-60.2) | 0.366    |

VE = vaccine effectiveness, CI = confidence interval, MMR = measles-mumps-rubella.

*Results are adjusted for sex, MMR vaccination within 28 days, age at vaccination.
The one-dose varicella vaccination program did not clearly protect against varicella. Therefore, it is necessary to further investigate why we had reduced effectiveness of varicella vaccine in Korea.

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DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Study conception and design: Lee YH, Cho SI, Oh MD. Supervision of whole aspects of this study: Oh MD. Data collection and analysis: Lee YH, Kang CR. Writing the manuscript: Lee YH. Critical revision of the manuscript: Choe YJ, Cho SI, Bang JH, Lee JK. Review and approval of the final version of the manuscript: all authors.

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