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Association Between Child Varicella Vaccination and Zoster in Household Adults: A Retrospective Japanese Cohort Study

So Sato[1] | Sachiko Ono[2] | Yusuke Sasabuchi[3] | Nobuaki Michihata[4] | Kohei Uemura[5] | Hideo Yasunaga[1]

[1]Department of Clinical Epidemiology and Health Economics, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan | [2]Department of Eat-Loss Medicine, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan | [3]Department of Real-World Evidence, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan | [4]Cancer Prevention Center, Chiba Cancer Center Research Institute, Chuo-ku, Chiba, Japan | [5]Department of Biostatistics & Bioinformatics, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

Correspondence: So Sato (sato-so4k9@g.ecc.u-tokyo.ac.jp)

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Keywords: exogenous boosting hypothesis | herpes zoster | vaccine | varicella

ABSTRACT

Aim: Some countries are hesitant to implement routine varicella vaccination for children because of concerns over the exogenous boosting hypothesis, which suggests that vaccinating children may increase herpes zoster cases in adults. However, substantial evidence supporting this hypothesis is lacking. This study assessed the association between a child's varicella vaccination status and herpes zoster occurrence in adults in the same household.

Methods: This retrospective cohort study analysed data from a Japanese city between April 2014 and December 2022. We included individuals aged ≥18 years living in households with a single child eligible for varicella vaccination. Children's vaccination status was categorised as unvaccinated, first-dose vaccinated or second-dose vaccinated. Cox regression analysis with time-dependent exposure assessed herpes zoster incidence in adults.

Results: Among 4023 eligible individuals, 136 (3.4%) developed herpes zoster over the median follow-up of 552 days. Neither the first nor the second dose of varicella vaccine in children was significantly associated with an increased risk of herpes zoster in adults (hazard ratio 1.24 [95% confidence interval, 0.69–2.23] for the first dose and 1.51 [0.87–2.62] for the second dose).

Conclusion: Varicella vaccination in households with a single child was not significantly associated with an increased risk of herpes zoster in adults.

1 | Introduction

Varicella zoster virus (VZV) is responsible for two distinct conditions: varicella (chickenpox) and herpes zoster (shingles) [1]. VZV is highly contagious and primarily spreads through droplet or airborne transmission, with susceptible household contacts experiencing high secondary attack rates of over 85% [2]. Varicella primarily affects children as the initial VZV infection, whereas herpes zoster occurs in adults as a result of reactivation of dormant VZV, often years after the initial infection [3].

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Revision; SCCS, self-controlled case series; v-VZV, vaccine-strain varicella zoster virus; VZV, varicella zoster virus; wt-VZV, wild-type varicella zoster virus.

Summary

- Varicella vaccination in children did not significantly increase the risk of herpes zoster among adults in the same household, based on this Japanese population-based study.
- Cox regression analyses showed no association between the first and the second vaccine dose and adult herpes zoster cases.
- The results contrast with prior studies supporting the exogenous boosting hypothesis, which suggests that varicella exposure reduces herpes zoster risk in adults.

Although varicella and herpes zoster typically present with mild symptoms, they can lead to severe illness, increased healthcare costs and reduced quality of life [4].

To mitigate the burdens associated with VZV, vaccination against varicella has become a crucial preventive measure. However, some countries, such as the United Kingdom, China and New Zealand, have hesitated to implement routine varicella vaccination programmes for children, citing concerns about the exogenous boosting hypothesis [3, 5]. The exogenous boosting hypothesis proposes that individuals who have previously been infected with VZV may reinforce their immunity by exposure to VZV-infected individuals. This immune reinforcement is believed to decrease their risk of developing herpes zoster.

Despite numerous studies exploring the exogenous boosting hypothesis in different countries, a consensus validating this hypothesis remains elusive [6–13]. Some studies have suggested a decline in herpes zoster cases during varicella epidemics [7], whereas others have reported an increase in herpes zoster following the introduction of varicella vaccine programmes [8, 10, 11]. However, these findings have not been consistently replicated [6, 9, 12, 13].

Previous studies have primarily focused on population-level analyses and lacked detailed individual-level data on the varicella vaccination status of children [6–13]. Although a previous self-controlled case series (SCCS) study within households supported the exogenous boosting hypothesis by suggesting an association between contact with varicella-infected children and reduced herpes zoster cases among adults in the same households [14], it did not specifically investigate the impact of varicella vaccination for children on adult herpes zoster cases. Therefore, the potential impact of varicella vaccination in household children on the risk of herpes zoster in adults remains unclear. Additionally, it is unknown whether the frequency of varicella vaccination among children in the same household affects the risk of developing herpes zoster in adults.

We hypothesised that VZV vaccination in children decreased exogenous boosting among household adults, potentially increasing their risk of developing herpes zoster. Therefore, the aim of our study was to assess whether adults living with VZV-vaccinated children have a higher risk of herpes zoster than those living with non-vaccinated children, using a population-based database in Japan.

2 | Methods

2.1 | Data Source

We conducted a retrospective cohort study utilising a comprehensive database that included vaccination records, health insurance claims and resident data from a city in Japan. The city, located in the Greater Tokyo area, has a population of approximately 600 000 residents. The vaccine database contains records of all vaccinations administered under routine vaccination programmes. Health insurance claims data were obtained from the National Health Insurance, which covers non-employees, individual proprietors and their dependents [15]. The database recorded diagnoses based on the International Classification of Diseases, 10th Revision (ICD-10) codes, along with the initiation dates of treatments. Resident data included unique identifiers, household identifiers, birth year and month, sex, insurance qualification and disqualification dates, and qualification and disqualification dates of the citizen. The household identifier allows for linking insured individuals with their dependents under the National Health Insurance scheme. However, the household identifier does not connect household members covered by insurance other than the National Health Insurance, such as those with employer-provided health insurance. Using unique identifiers, vaccine records, health insurance claims and resident data were integrated at the city office. All personal information was de-identified before being provided to researchers for secondary analysis.

2.2 | Varicella and Herpes Zoster Vaccination in Japan

The routine varicella vaccination programme for children aged 12–36 months began in October 2014 [16]. The second dose of the vaccine is recommended to be administered with a minimum of a 3-month interval between the first and second doses. After the introduction of this routine vaccination programme, the reported number of varicella cases decreased substantially by over 70% [17].

The administered vaccines were freeze-dried live attenuated varicella vaccine using the Oka virus strain (brand name: VARICELLA VACCINE LIVE ATTENUATED "BIKEN"—BIKEN Co. Ltd.). Each vaccine vial was dissolved in 0.7 mL of accompanying water for a solution. Subsequently, 0.5 mL of the solution was administered via subcutaneous injection, typically at the extensor side of the upper arm. Preventive measures for herpes zoster among individuals aged ≥ 50 years were initiated in March 2016 with the one-dose Zoster Vaccine Live (Zostavax) and in March 2018 with the two-dose Recombinant Zoster Vaccine (Shingrix) [18].

2.3 | Study Design and Participant Selection

This retrospective cohort study utilised data collected between April 2014 and December 2022. We included individuals who met the following criteria: (i) residing in households with only one child eligible for the routine varicella vaccination programme,

(ii) aged ≥18 years, and (iii) subscribed to National Health Insurance for at least 6 months before the index date, which is the first day of the month when their child became 9 months old, to ensure a lookback period as defined below. To simplify the analysis and avoid potential confounding effects from multiple children within a household, we specifically focused on households with only one child. We excluded individuals who (i) were immunosuppressed [14, 19], (ii) had a history of varicella infection (ICD-10: B01x), (iii) had a history of herpes zoster infection (B02x) and (iv) were aged ≥50 years (to mitigate the potential influence of the zoster vaccine approved for those aged ≥50 years). Our analysis targeted individuals under 50 years old, particularly the generation responsible for child-rearing, which reported increased susceptibility to herpes zoster because of varicella vaccination among children [8, 10, 11]. The index date for each individual was defined as the first day of the month when their child became 9 months old, taking into account that maternal varicella antibodies last for less than 6 months [20]. Comorbidities and medications were identified if recorded within 6 months before the index date (a lookback period of 6 months). Eligible individuals were tracked from the index date until the occurrence of herpes zoster infection, varicella infection with a household member, birth of a second child, the first day of the month when they became 50 years old, disenrollment from the database because of relocation or change in insurance, death or conclusion of the study, whichever occurred first.

2.4 | Exposure of Interest

In our analysis, we examined two exposures: (i) a household child receiving the first dose of varicella vaccine and (ii) a household child receiving the second dose of varicella vaccine. These exposures were compared with the reference group of a household child receiving no varicella vaccine.

2.5 | Outcomes and Other Variables

In the study, the occurrence of herpes zoster (shingles) was the primary outcome of interest. It was determined based on diagnosis using the ICD-10 code B02x or the use of anti-varicella drugs such as acyclovir, valacyclovir, famciclovir, vidarabine and amenamevir.

Other variables were age (18–29, 30–39, 40–49 years), sex, Charlson Comorbidity Index (0–2, ≥3) [21], the child's varicella vaccination status (first or second dose), the fiscal year of the child's varicella vaccination (2014–2022) and the season of the child's varicella vaccination (spring, summer, autumn, winter). Comorbidities related to the Charlson Comorbidity Index were identified using diagnoses within 6 months prior to the index date. Regarding the seasons, they were categorised into spring (March–May), summer (June–August), autumn (September–November) and winter (December–February).

2.6 | Statistical Analysis

The baseline characteristics of the study participants were summarised using proportions for binary variables and mean with standard deviations for continuous variables. To estimate the incidence of varicella virus infection during the study period, the incidence rate of varicella cases among children eligible for the universal varicella vaccination programme was estimated. Additionally, we recorded the timing of the first and second varicella vaccination doses administered to these children.

To assess the effect of household child varicella vaccination dose on herpes zoster infection, the Cox regression model with time-dependent exposures was used [22]. This analysis considered the vaccination status of children in the household as a variable that could change over time. It tracked whether a child had not received any varicella vaccine, received the first dose or received the second dose during the study period. This approach allowed for an accurate reflection of changes in vaccination status over time and the evaluation of its effects.

The preventive effect of each vaccine dose against varicella infection was defined to begin 28 days after administration [23]. Incidence rates of herpes zoster were estimated for each exposure status. Both univariable and multivariable Cox regression analyses were conducted. The multivariable analysis included age and sex as covariates. Hazard ratios (HRs) were calculated to determine the association between varicella vaccine exposure and herpes zoster infection. The reference group for the HR calculations was children who had not received any varicella vaccine. We performed two sensitivity analyses to validate our findings. First, we conducted an SCCS analysis to evaluate the risk of herpes zoster infection during different time periods within the same individual [24]. The SCCS method inherently adjusts for time-independent confounders, such as sex, socio-economic status and genetic factors [25]. Using a Poisson regression model, we estimated the incidence rate ratios for exposure periods compared with non-exposure periods. Figure S1 illustrates the SCCS method applied in this study. We included only individuals who developed herpes zoster and whose children had received the varicella vaccine. The observation period began when the child became 9 months old, aligning with the Cox regression analysis. Exposure periods started 28 days after each varicella vaccination dose and continued until the end of the study period [26]. All other times were considered control periods. The analysis treated the first and second vaccine doses as separate exposures. Second, we included individuals aged ≥50 years who were eligible for herpes zoster vaccination in the main cohort.

The significance threshold for determining statistical significance was set at a p-value of 0.05.

All statistical analyses were performed using R Statistical Software, specifically version 3.6.1, developed by the R Foundation for Statistical Computing in Vienna, Austria.

2.7 | Ethical Approval

This study was approved by the Institutional Review Board of the Graduate School of Medicine, The University of Tokyo (2021187NI-[3]). The requirement for written consent was waived because of the anonymous nature of the data.

3 | Results

The study included 4023 individuals who had a single eligible child in the routine varicella vaccine programme between April 2014 and December 2022 (Figure 1).

Table 1 summarises the baseline characteristics of the participants. The median age at the index day was 31.2 years, with a standard deviation of 6.4 years. Among the participants, 3221 individuals (80.1%) had their household child's first dose of varicella vaccination, and 2516 individuals (62.5%) had their household child's second dose of varicella vaccination at the end of the observation period. The median follow-up duration for the total cohort was 552 days, with an interquartile range of 266–1009 days. The median (interquartile range) follow-up duration was 126 (100, 220) days for household adults with no vaccinated children, 192 (64, 240) days for those with children who received one dose and 484 (202, 990) days for those with children who received two doses. The incidence rate of varicella among children was 14.1 cases per 1000 person-years (95% confidence interval [CI], 11.4–17.5). Figure S2 illustrates the timing of the first and second vaccine doses among children eligible for the universal varicella vaccination programme. Most eligible children received their first dose near the start of the observation period and their second dose approximately 3 months later. During the follow-up period, a total of 136 individuals (3.4%) developed herpes zoster, with 3 cases (0.1%) requiring hospitalisation. Of these cases, 52 were identified solely through ICD-10 codes, whereas 84 were diagnosed based on both ICD-10 codes and drug treatment records. The total person-years of follow-up were 8508. The incidence rate of herpes zoster was calculated as 9.8 cases per 1000 person-years, with a 95% CI ranging from 7.9 to 12.1.

The incidence rates of herpes zoster per 1000 person-years were calculated for different exposure statuses. For households where the child received no vaccination, the incidence rate was 8.2 (95% CI, 5.5–12.1). For households with exposure to the first dose, the incidence rate was 7.2 (95% CI, 4.4–11.8), and for households with exposure to the second dose, the incidence rate was 11.2 (95% CI, 8.3–15.2).

Table 2 presents the results of both univariable and multivariable Cox regression analyses. The HRs were calculated to assess the association between varicella vaccine exposure and the incidence of herpes zoster. The HR remained consistent before and after adjusting for age and sex variables. Neither the first dose (adjusted HR 1.24, 95% CI 0.69–2.23, $p = 0.476$) nor the second dose (adjusted HR 1.51, 95% CI 0.87–2.62, $p = 0.143$) of the varicella vaccine to a household child was found to be significantly associated with the incidence of herpes zoster. The results of the sensitivity analyses were consistent with those of the primary analysis (Tables S1–S3).

4 | Discussion

This study aimed to investigate the association between the varicella vaccination status of children in a household and the risk of herpes zoster in adults within the same household, using a population-based database from a Japanese city. The incidence rate of varicella among children eligible for the universal varicella vaccination programme (aged 1–3 years) was 14.1 cases per 1000 person-years, comparable to the rate observed in children aged 1–4 years in the US pre-introduction of the varicella vaccination programme [27]. The results revealed that neither the first nor the second dose of varicella vaccination for a household child had a significant association with an increased risk of herpes zoster in adults living in the same household.

Previous studies on the association between varicella and herpes zoster utilised community-level aggregated data in nationwide settings [6–13]. One study conducted in the United Kingdom, which employed individual-level data with household information, reported that contact with varicella-infected children reduced the incidence of herpes zoster among adults in the household, suggesting the existence of exogenous boosting [14]. However, these studies did not specifically address the impact of varicella vaccine immunisation on the incidence of herpes zoster.

In the present study, Cox regression analyses were performed, and the results showed no significant association between the first and the second dose of varicella vaccination in household children and the risk of herpes zoster among adults in the same household. These findings are inconsistent with previous studies that supported the exogenous boosting hypothesis [7, 10, 11, 14]. Although direct evidence supporting the exogenous boosting hypothesis is lacking, many countries with different settings have observed an increased incidence of herpes zoster following the introduction of varicella vaccination programmes [7, 10, 11, 14]. Therefore, it is possible that certain unique characteristics specific to Japan may have influenced the incidence of herpes zoster.

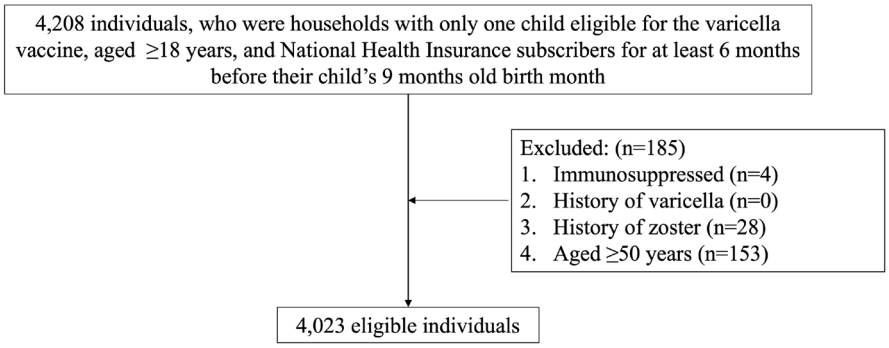

FIGURE 1 | Flow chart showcasing the inclusion criteria of study participants.

TABLE 1 | Characteristics of participants.

	Total $N = 4023$ (n)	(%)
Age (mean [standard deviation]), years	31.2	(6.4)
18–29	1697	(42.2)
30–39	1876	(46.6)
40–49	450	(11.2)
Female	2002	(49.8)
Charlson Comorbidity Index (mean (standard deviation))	0.1	(0.3)
0–2	4015	(99.8)
≥3	8	(0.2)
Child with the first injection	3221	(80.1)
The fiscal year of the child's first injection		
2014	470	(14.6)
2015	433	(13.4)
2016	421	(13.1)
2017	407	(12.6)
2018	349	(10.8)
2019	327	(10.2)
2020	335	(10.4)
2021	248	(7.7)
2022	231	(7.2)
Season of the child's first injection		
Spring	728	(22.6)
Summer	807	(25.1)
Autumn	934	(29.0)
Winter	750	(23.3)
Child with the second injection	2516	(62.5)
Fiscal year of the child's second injection		
2014	48	(1.9)
2015	409	(16.3)
2016	341	(13.6)
2017	367	(14.6)
2018	347	(13.8)
2019	289	(11.5)
2020	299	(11.9)
2021	251	(10.0)
2022	165	(6.6)
Season of the child's second injection		
Spring	724	(28.8)
Summer	598	(23.8)
Autumn	597	(23.7)
Winter	594	(23.6)

A key distinction between this study and previous studies lies in the varicella vaccination coverage. The differences in types of past VZV exposure, such as live-attenuated vaccine-strain VZV (v-VZV), wild-type VZV (wt-VZV) [28, 29] or a combination of wt-VZV and v-VZV [30–33], may have influenced the results [13, 28]. A previous review suggested that individuals primarily exposed to wt-VZV in the past were at a higher risk of herpes zoster than those primarily exposed to v-VZV [13, 28]. In the United States, the younger generation, primarily exposed to v-VZV through varicella vaccination, did not exhibit an increased incidence of herpes zoster. Conversely, the older generation, who had not received varicella vaccination and were primarily exposed to wt-VZV, showed a higher incidence of herpes zoster [13]. Therefore, varicella vaccination coverage, which indicates the proportion of individuals primarily exposed to v-VZV, may impact the occurrence of exogenous boosting. In this study, the voluntary varicella vaccination coverage among Japanese individuals aged 18–28 years was approximately 20% [34]. However, in other countries where access to varicella vaccination was limited, the proportion of adults primarily exposed to v-VZV may have been even lower [11]. Another possible explanation is that participants in this study might have been exposed to VZV outside household settings. For instance, nursery teachers and healthcare workers are likely to encounter VZV in their workplaces. Therefore, potential exposure to VZV outside the household may have influenced the results towards null. Further investigation is required to examine the effect of community exposure on the risk of herpes zoster.

Previous studies have reported an increasing trend in herpes zoster cases, both before and after the implementation of varicella vaccination programmes [8, 35]. This suggests that mechanisms beyond exogenous boosting may contribute to this trend, although these mechanisms remain unclear. Factors such as the proportion of immunosuppressed individuals have been evaluated in prior research [36], but no definitive conclusions have been drawn. In our study, we excluded immunosuppressed individuals to minimise the potential influence of immunosuppression on our findings. However, other factors, such as health-seeking behaviour, could not be assessed because of data limitations. Future research on exogenous boosting should account for both the exogenous boosting effect and the various additional potential factors to better understand the observed trends.

Based on our results, there was no significant impact of varicella vaccination in household children on the incidence of herpes zoster in adults within the same household. This information can be valuable for future decision-making processes in

TABLE 2 | Results of Cox regression analyses of herpes zoster incidence.

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Child with first injection	1.23	0.69–2.22	0.483	1.24	0.69–2.23	0.476
Child with second injection	1.47	0.85–2.54	0.164	1.51	0.87–2.62	0.143
Sex						
Male				reference		
Female				1.22	0.87–1.73	0.254
Age (years)				0.99	0.96–1.02	0.523

Abbreviations: CI, confidence interval; HR, hazard ratio.

countries that have not yet implemented routine varicella vaccination programmes.

We acknowledge several limitations of this study. First, as a retrospective study using a population-based claims database, there may be limitations in data accuracy and missing information. Claims data cannot account for individuals who do not seek medical care, potentially underestimating the incidence of herpes zoster. Although we applied a consistent method to detect herpes zoster during both non-exposure and exposure periods, potential misclassification could have biased the results towards the null. Furthermore, the data did not include information on voluntary varicella vaccinations in children (1987–2014) or herpes zoster vaccinations in adults aged ≥ 50 years, which may have overestimated the exogenous boosting effect. Other unmeasured confounders, such as socio-economic status or vaccine hesitancy, could also have introduced bias. Second, our findings may have limited generalisability. The study relied on data from the National Health Insurance programme, excluding household members covered by other insurance types. Additionally, restricting the analysis to single-child households may limit its applicability to multi-child households. Finally, the study may have had limited statistical power to detect an exogenous boosting effect, as this effect may be modest. Future studies with larger sample sizes would be valuable for a more robust assessment of the exogenous boosting effect.

In conclusion, varicella vaccination in household children did not demonstrate a significant association with an increased risk of herpes zoster in adults within the same household. These findings can provide valuable insights for policymakers when making decisions regarding the implementation of routine varicella vaccination programmes in countries that have not yet adopted them.

Author Contributions

So Sato: conceptualization, investigation, writing – original draft, methodology, formal analysis. **Sachiko Ono:** conceptualization, investigation, writing – review and editing, visualization. **Yusuke Sasabuchi:** conceptualization, investigation, writing – review and editing, formal analysis, supervision. **Nobuaki Michihata:** writing – review and editing, data curation. **Kohei Uemura:** writing – review and editing, data curation. **Hideo Yasunaga:** conceptualization, investigation, funding acquisition, writing – review and editing, project administration, resources.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The database used in this study was maintained by a city in Japan. Restrictions applied to the availability of data that were used with permission for this study. Therefore, the data are not publicly available.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.