Introduction

Varicella-zoster virus (VZV) is responsible for two distinct clinical manifestations: varicella (chickenpox) and herpes zoster (shingles). VZV is transmitted through direct contact, inhalation of aerosols from the vesicular fluid of skin lesions, and potentially via infected respiratory secretions. [1, 2] Primary VZV infection results in varicella, characterized by a diffuse erythematous vesicular rash. In contrast, endogenous reactivation of latent VZV results in herpes zoster, manifesting as localized skin lesions.

The varicella vaccine containing the Oka strain was originally developed in Japan in 1974. [3] The implementation of this vaccine has altered the epidemiology of varicella. Indeed, routine immunization for children has substantially reduced the incidence and hospitalization of varicella cases in resource-rich countries, including the US, Canada, Germany, Australia, and others. [1, 4-8] Since 1986, the varicella vaccine has been offered as a voluntary immunization for children aged one year and older in Japan. Due to the voluntary nature of varicella vaccination, its coverage was estimated to be low at approximately 30.0-35.7%. [9] This resulted in a substantial number of varicella-associated hospitalizations, as demonstrated by the nationwide survey in 2004 (1,655 hospitalizations and seven deaths). [10] In 2012, the Japanese Pediatric Society recommended a two-dose vaccination regimen for children between the ages of 1 and 2 years as a voluntary immunization. Beginning in October 2014, the Japanese government implemented the varicella vaccine as the routine immunization program, administering two doses at 3-6 months intervals to children between the ages of 1 and 2 years. [11] Consequently, the vaccination rates increased to 94.2% (1st dose) and 70.3% (2nd dose) by 2018. [12] After a routine immunization, the number of varicella cases per sentinel site decreased substantially by 76.6% overall and by 88.2% among children aged 1-4 years in 2017. [13] However, the utilization of healthcare resources (e.g., outpatient and inpatient visits, antiviral use, and direct healthcare costs) related to varicella cases and the incidence of herpes zoster cases among children in Japan after the introduction of routine immunization remain uncertain. Previous research investigating the impact of the varicella vaccine on herpes zoster incidence has yielded inconsistent results worldwide. [14-21]

Recently, the coronavirus disease 2019 (COVID-19) pandemic has dramatically impacted the epidemiology of infectious diseases. Prior studies have focused on the epidemiological changes of infectious diseases due to respiratory viruses (e.g., influenza virus, parainfluenza virus, adenoviruses, and human metapneumovirus), which have exhibited decreasing trends during the early phase of the COVID-19 era. [22-24] In Japan, the government has implemented the policies, such as nationwide school closure and national emergency declarations, as the COVID-19 transmission and protective measure, and recommended staying at home and social distancing. [25] Additionally, the guidelines for infection control in kindergarten and schools recommend universal masking, hand hygiene, and air circulation [26], which have been widely adopted. However, the nationwide trends in varicella and herpes zoster among children during the COVID-19 pandemic remain unknown.

To address these knowledge gaps, our study investigated the impacts of routine varicella immunization and the COVID-19 pandemic on the epidemiological trends in pediatric varicella and herpes zoster cases and changes in healthcare resource utilization using a nationally representative database 2005-2022 in Japan.

Methods

Study design, data source, and study population

We conducted a retrospective cohort study to capture the nationwide epidemiology of varicella and herpes zoster cases and to ascertain the impacts of introducing the routine varicella vaccine and the COVID-19 transmission and protective measures. Our study was approved by the institutional review board at National Center for Child Health and Development in Japan with the waived requirement for informed consent because of the anonymous nature of the database (IRB number: 2022-176).

This study used the health insurance claims database developed by the Japan Medical Data Center (JMDC). [27] The data were collected from > 14 million individuals insured by the Society-Managed Health Insurance system. All administrative records were stored in the JMDC database when insured individuals visited medical facilities and received healthcare covered by the national health insurance system. Currently, the JMDC database covers up to 10% of the pediatric population in Japan. The JMDC database comprises the following variables: unique identification numbers for individuals and families, birth month, sex; dates when individuals enter and exit the health insurance; details of procedures and prescriptions; admission dates; and healthcare expenditures.

We extracted data on all children aged less than 20 years from January 2005 to May 2022 in the JMDC database. The start of follow-up was defined by the initiation of the study period or the enrollment in the health insurance. The end of follow-up was defined by the withdrawal of health insurance (e.g., parental retirement or separation, death) or rightcensoring at the end of May 2022. Consequently, we included data on 3,505,010 children with 177,605,041 person-months (mean follow-up months per person, 50.7 months) for this study.

Measurements

The measurement variables included the birth month, sex (male vs. female), the time of enrollment, disenrollment, and diagnosing as year and month, diagnoses of varicella and herpes zoster, healthcare resource utilization (e.g., outpatient visits, admissions, antiviral use, and direct healthcare costs) due to varicella or herpes zoster from 2005 to 2022. Diagnoses of varicella and herpes zoster were defined by the International Classification of Diseases, 10th revision (ICD-10) codes (varicella, B01.x; herpes zoster, B02.x). We defined cases with varicella only as those that had been clinically confirmed (suspected cases were not included). Antiviral agents consisted of acyclovir, valacyclovir, and famciclovir in accordance with the Anatomical Therapeutic Chemical classification system.

Statistical analyses

The data analysis was executed in five steps using Stata/MP software version 16.1 (StataCorp LP, TX, USA). First, we summarized baseline characteristics (numbers of individuals, person-months, age, sex) and incidence of varicella and herpes zoster by calculating means with standard deviations (SDs) for continuous variables and frequencies with proportions for categorical variables from 2005 to 2022.

Second, we assessed the impact of the routine varicella vaccination program, which was introduced in 2014, and the COVID-19 transmission and protective measures, which were implemented in 2020, on incidence rates of varicella and herpes zoster, as well as healthcare resource utilization. The Japanese government has implemented the following policies as the COVID-19 transmission and protective measure: once nationwide school closure (February 27 to May 6, 2020) and four times of national emergency declarations: 1) April 7 to May 25, 2020; 2) January 8 to March 21, 2021; 3) April 25 to June 20, 2021; 4) July 12 to September 30, 2021). [25] These implements have a possibility to affect the varicella transmission or healthcare visit behavior. To estimate these impacts, interrupted time series analyses were conducted with two intervention periods: 1st intervention period, November 2014 to March 2020; 2nd intervention period, April 2020 to May 2022. [28] We constructed multivariate Poisson regression models that included outcomes of interest as dependent variables, person-months as offset variables, time (months in years) and intervention indicators and a set of covariates (e.g., age, sex) as independent variables. Level changes and slope changes during 1st and 2nd intervention periods were reported as the impacts of routine immunization and COVID-19 transmission prevention measures. Level changes and slope changes generally represent immediate and contentious effects, respectively. Generalized linear models with cluster robust variance estimates were used to estimate the level and slope changes as incidence rate ratios (IRRs) with 95% confidence intervals (CIs) after standardizing age and sex distributions to the total cohort and adjusting for seasonality with months. Third, we stratified data by age (0-4, 5-9, 10-14, 15-19 years) and sex (male vs. female) categories and repeated the interrupted time series analyses.

Fourth, we estimated age-specific incidence rates of varicella cases, total healthcare costs, and antiviral agent use as DOTs per 1000 person-years across different years (2008, 5 years before routine vaccination introduction; 2013, 1 year before routine vaccination introduction; 2018, 1 year before COVID-19 pandemic; 2021, 1 year after COVID-19 pandemic). Because age and sex distributions were different across years, estimated incidence rates were standardized to the total pediatric population in 2021 in Japan. [29]

Fifth, we created a birth cohort of 701,643 children with a total of 34,795,182 person-months by focusing the data on children whose study enrollement was initiated at their birth and following up then at the end of study period or disenrollement. Then, we estimated the cumulative incidence of varicella and herpes zoster and compared them between children born in different calender years (2005-2009, 2010-2013, 2014-2022).

Results

Distributions of the study cohort

Descriptive statistics are summarized in Table 1. The number of study participants consistently increased from 2005 to 2022. Mean age increased from 8.2 years (SD, 5.6) in 2005 to 9.7 years (SD, 5.6) in 2022, with very slight male predominance (51 to 52%).

Interrupted time-series analyses

The starting level of varicella incidence rate in January 2005 was estimated at 2.83 cases per 1000 person-months (Figure 1; Supplemental Table 1). The incidence rates showed a very slight decreasing trend of 0.66% relative reduction per month (adjusted IRR, 0.993; 95%CI, 0.992 to 0.995) until October 2014. After introducing the routine vaccination program, we observed a level change of 45.6% relative reduction in the varicella rates (adjusted IRR, 0.544; 95%CI, 0.440 to 0.671) without slope change (adjusted IRR, 1.003; 95%CI, 0.997 to 1.008). After introducing the infection prevention measures against COVID-19 in March 2020, we observed a further level change of 57.2% relative reduction (adjusted IRR, 0.428; 95%CI, 0.329 to 0.555) with a slight slope change (adjusted IRR, 0.986; 95%CI, 0.980 to 0.991). Correspondingly, healthcare costs (starting level, 22,006 JPY per 1000 person-months [95%CI, 15,302 to 31,649]; Figure 1B) showed a substantial reduction by 48.7% after routine vaccination program (adjusted IRR, 0.513; 95%CI, 0.427 to 0.618) and by 49.1% after the COVID-19 pandemic (adjusted IRR, 0.509; 95%CI, 0.384 to 0.673). Similarly, we observed substantial reductions in antiviral agent use (Figure 1C) and the number of office visits (Figure 1D) after the routine immunization program and the COVID-19 pandemic (Supplemental Table 1).

The starting level of incidence rate for herpes zoster (Figure 1E) was estimated at 0.094 cases per 1000 person-month (95%CI, 0.082 to 0.109; Supplemental Table 2) with a very slight increasing trend (adjusted IRR, 1.001; 95%CI, 1.000 to 1.002). After the routine immunization program, we observed elevated levels of the rates by 9.4% (adjusted IRR, 1.094; 95%CI, 1.038 to 1.154) with a decreasing trend (adjusted IRR, 0.996; 95%CI, 0.994 to 0.998). Also, the changes in level (adjusted IRR, 0.913; 95%CI, 0.859 to 0.959) and slope (adjusted IRR, 0.993; 95%CI, 0.988 to 0.999) were observed after the COVID-19 pandemic. Similarly, we observed a temporal increase in antiviral agent use after the routine immunization program, but a decreasing trend after the COVID-19 pandemic (Figure 1F; Supplemental Table 2).

Interrupted time-series analyses by age and sex categories

When we stratified the data by sex and age categories, we observed similar outcome trends between male and female (Supplemental Figure 1). Substantial reductions in incidence rates of varicella and corresponding healthcare resource use (Supplemental Figure 2-4) after the routine immunization program and the COVID-19 pandemic were observed among children aged 0-9 years, whereas these changes appeared small due to very small incidence rates at baseline among children aged 10-19 years (Supplemental Table 3). There were almost no changes in incidence rates of herpes zoster cases among children aged 0-4 years and those aged 15-19 years over the study period (Supplemental Figure 5). Decreasing trends in the rates were observed after the COVID-19 pandemic among children aged 5-14 years. Antiviral use for herpes zoster was almost stable over the study period (Supplemental Figure 6).

Age-specific estimates for varicella cases standardized to the total population in Japan

Supplemental Figure 7 shows the age-specific incidence rates, healthcare cost, and antiviral agent use, standardized to the total pediatric population in Japan. Incidence rates and antiviral agent use consistently reduced from 2008 to 2021, and the reductions were substantial among children aged 0-9 years. Similar patterns were observed for healthcare costs, but the costs between 2008 and 2013 were almost identical for all age groups.

Cumulative incidence of varicella and herpes zoster

The cumulative incidence of varicella and herpes zoster was examined among the birth cohort of 701,643 children born during 2005-2022. The highest cumulative incidence of varicella occurred among children born during 2005-2009, followed by those born during 2010-2013 and those born during 2014-2022 (Figure 2A). Similarly, the pattern for the cumulative incidence of herpes zoster followed the same trend (Figure 2B), while the cumulative incidence of herpes zoster was almost similar across different birth cohorts among children who developed varicella (Supplemental Figure 8).

Additionally, we analyzed data on children diagnosed with varicella and estimated the cumulative incidence of herpes zoster after varicella (Supplemental Figure 9 and 10). The cumulative incidence of herpes zoster was higher among children who had varicella during the age of 1-2 years, and their birth years did not appear to impact on the incidence.

Furthermore, the cumulative incidence of herpes zoster after different timing of varicella infection across different birth cohort showed the decreasing tendency along with age.

Discussion

A nationwide database allowed us to quantify the epidemiology and health resource utilization of varicella and herpes zoster among Japanese children during the recent 18 years, including the COVID-19 era. We observed the decreasing trends in varicella incidence, healthcare costs, antiviral agent use, and the number of office visits after introducing the routine immunization program in 2014, and the COVID-19 pandemic accelerated the reduction in varicella incidence and health resource utilization. The cumulative incidence of herpes zoster in children born after 2014 was lower than that before 2014.

We observed the level change of 45.6% relative reduction in the varicella rates after the implementation of the routine vaccination program. This change was consistent with the actual sentinel surveillance data of varicella. [13] The level change generally represents immediate effects, thus our data and the previous surveillance data seemed to reflect the rapid uptake of the immunization rate according to the vaccine nature change from voluntary to routine immunization. This is also supported by the vaccination rate survey results in 2018, which was 94.2% (1st dose) and 70.3% (2nd dose) for the targeted population. [12] Of interest, the increase in the vaccination rates appeared to reduce not only varicella incidence, but also relevant healthcare costs, antiviral agent use, and the number of office visits. Although the healthcare seeking behavior may have influenced by COVID-19 pandemic [30-32], the findings of healthcare utilization are consistent with the cost-effectiveness and cost-saving of universal varicella vaccination programs observed in other resource-rich countries. [33-35]

Furthermore, the level change of 57.2% relative reduction in varicella incidence rates was observed after the COVID-19 pandemic. This would attribute to the immediate permeating the infection control measures in educational institutes and restriction of population flow. The guidelines for infection control in the kindergarten and schools advocate for universal masking, hand hygiene, documentation of health status (e.g., body temperature and cold symptoms), and improved air circulation [20], and it appears that most children and teachers adhered to these protocols. The risk of transmission can be partially mitigated by using mask or hand hygiene, our data supports that these infection control measures likely contributed to reducing the infection risk.

The association between the varicella vaccine and herpes zoster incidence has been the subject of considerable debate. [14-21] In 1965, Edgar Hope-Simpson postulated the "exogenous boosting hypothesis," which suggests that repeated exposure to circulating varicella prevents the reactivation. [36] This hypothesis predicts that varicella immunization would increase herpes zoster incidence by reducing the likelihood of exogenous boosting. While a study conducted in the United Kingdom in 2002 partially supported this hypothesis based on different odds of elderly’s contact with children with varicella between herpes-zoster cases and controls [37], another study from the United States in 2010 failed to show such a difference. [38] Notably, the rise in herpes zoster incidence has been observed even in countries without routine varicella immunization. [39] In our study among children, the cumulative incidence of herpes zoster did not increase even after introducing routine varicella vaccine, which may not support the Hope-Simpson hypothesis. Rather, we found the incidence of herpes zoster was lower in the cohort of children after the introduction of routine immunization. This difference was not observed in children who developed varicella, suggesting that the prevention of varicella by the vaccine itself is an effective measure to decrease herpes zoster because the risk of herpes zoster due to vaccine-strain is much lower than that due to wild-type stain. [18] Additionally, the fact decreasing the incidence of herpes zoster along with age is thought to be associated with the immaturity of the immune response to varicella. The previous publication describing that varicella in the first year of life increases the risk for development of childhood herpes zoster supports our data. [40] Furthermore, the cumulative incidence of herpes zoster in those born during 2005-2009 with 10 to 15-year follow-up was around 70%, which is also consistent with the previously reported seroprevalence surveillance data in Japan (around 60-70%). [41] However, because detailed clinical information (e.g., vaccination status, exposure to varicella cases) was not available in our database, further well-designed long-term cohort studies are necessary to confirm the validity of the relationship between varicella and herpes zoster.

Our study has several limitations. First, the ICD-10 codes were used for detecting varicella and herpes zoster because many patient characteristics (e.g., medical chart description) were not available in the JMDC database. The possibility of misclassification existed in this study, as indicated by the presence of the herpes zoster patients who had no history of varicella and the possible use of antiviral agents for other viral infections. However, our data was consistent with the actual sentinel surveillance data of varicella [13], thus the similar trends in surveillance data are reassuring the findings of this study. Second, the lack of vaccination status information in the JMDC database precluded our ability to investigate the real-world vaccine effectiveness. Future studies using other data sources would be beneficial in supplementing our findings. Third, it was difficult to accurately distinguish the impact of COVID-19 prevention measures, healthcare seeking behaviors, and varicella vaccine effectiveness during the post-COVID-19 era because this study contained the apparent interventions as routine vaccination and the COVID-19 pandemic. Forth, the generalizability of the database is still controversial. However, the distributions of hospitals and clinics were similar between the JMDC database and general population. Also, most local governments provide free medical subsidies for children, which ensures equal access to healthcare for children and may enhance the generalizability of our study findings. Finally, the transportability of our findings to other countries would be unclear: the impact of varicella vaccine on varicella cases and relevant health resource utilization could be dependent on different contexts for healthcare delivered to children.

Our study confirmed the impact of the routine varicella vaccination program in 2014 and infection prevention measures against COVID-19 on incidence rates of varicella and related healthcare utilization among children in Japan. Varicella incidence and healthcare resource use were largely affected by the vaccine program and the COVID-19 pandemic, while the impacts of those for herpes zoster were relatively small, particularly for children who had experienced varicella. Future monitoring of varicella and herpes zoster trends will provide useful information when infection control practice for COVID-19 restrictions is lifted.

Figure Legends

Figure 1. Trends in incidence rate of varicella (A), healthcare costs for varicella cases (B), antiviral agent use for varicella as days of therapy per 1000 person-months (C), incidence rates of varicella related office visits (D), incidence rates of herpes zoster (E), antiviral agent use for herpes zoster as days of therapy per 1000 person-months (F).

Figure 2. Cumulative incidence of varicella (A) and herpes zoster (B) across different birth cohorts.

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