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Short communication

Immune thrombocytopenic purpura and Guillain-Barré syndrome after 23-valent pneumococcal polysaccharide vaccination in Japan: The vaccine effectiveness, networking, and universal safety (VENUS) study

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ABSTRACT

Background: To address the lack of an active vaccine safety surveillance system in Japan, the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) study was initiated in 2021 as a pilot system using existing health insurance claims data and vaccination records.
Methods: This study evaluated the value of the VENUS study by assessing the incidence of immune thrombocytopenic purpura (ITP) and Guillain-Barré syndrome (GBS) following vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) using a self-controlled case series (SCCS) design.
Results: Incidence rate ratios for ITP during 28-day and 42-day risk periods were 0.89 (95% confidence interval [CI], 0.12–6.4), and 0.58 (95% CI, 0.081–4.2), respectively. Neither was statistically significant. Incidence rate ratios could not be estimated for GBS due to the limited sample size.
Conclusion: The VENUS study can provide valuable insights to facilitate the establishment of an advanced vaccine monitoring system in Japan.

1. Introduction

All vaccines undergo a rigorous safety assessment before receiving licensure. Nevertheless, it is crucial to continue monitoring vaccine safety after approval due to the potential for rare adverse events following immunization (AEFIs) that might be difficult to detect during clinical trials. There are two types of vaccine safety monitoring systems: passive and active. A passive monitoring system relies on spontaneous reporting by physicians or patients and serves as an early AEFIs alert system. In contrast, an active monitoring system enables more detailed analyses that assess causal associations between vaccines and adverse events. In Japan, a passive monitoring system was established in 1996. However, there is still no active monitoring system in place. This lack of an active monitoring system has hindered the scientific evaluation of associations between vaccines and AEFIs. Compounding the issue, Japan is recognized for having one of the world's lowest levels of public trust in vaccines [1]. This combination of lack of a rigorous monitoring system and widespread public concerns has culminated in what is termed the "vaccine gap" in Japan [2]. Although vaccine safety data are available from other countries, it is imperative to assess the safety specific to the Japanese population as this demographic is often underrepresented in other studies, resulting in data that may not resonate or be deemed convincing for Japanese communities.

In 2021, the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) study was initiated in Japan as a pilot system for active vaccine safety monitoring using existing health insurance claims data that include vaccination records [3]. The goal of the VENUS study is to create a database that enables scientific assessment of causal associations

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between vaccines and AEFIs. A pilot study utilizing the VENUS database had already been undertaken to assess the safety of the influenza vaccine during the 2018–2019 influenza season, heightening the database's capability to support comparative evaluations of vaccine safety (vaccinated vs. unvaccinated) [3]. Yet, this investigation was limited, focusing solely on a one-year period, a single study design (case-control), and one vaccine. There is a pressing need to expand the exploration of the VENUS database by considering multi-year periods, diverse vaccines, and various study designs typically employed in vaccine safety research. In light of this, our study examined the value of the VENUS system by evaluating the incidence of immune thrombocytopenic purpura (ITP) or Guillain-Barré syndrome (GBS) following receipt of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in multi-year periods, using a self-controlled case series (SCCS) design. ITP and GBS were selected as AEFIs of interest because they are rare diseases likely to be detected only in large databases, have relatively high specificity as diseases in this system, and provide some validity to the information about onset date.

2. Methods

Using data from the VENUS study, we evaluated the risk of ITP or GBS following PPSV23 vaccination. The observation period of this study was April 1, 2015 to March 31, 2020. The eligibility age was set at 64 years or older because PPSV23 vaccination is recommended in the fiscal year when individuals turn 65 in Japan. The study was approved by the Kyushu University Institutional Review Board for Clinical Research (approval number, 22114–01).

2.1. Data source

In the VENUS study, we used information from the Longevity Improvement & Fair Evidence (LIFE) study, which is a long-term multi-regional database managed by Kyushu University in Fukuoka, Japan [4]. The LIFE study was established in 2019 as a project to measure, evaluate, and propose solutions for health-related problems among community residents in Japan using a life-course perspective. In the LIFE Study, we routinely collect claims data and vaccination records from participating municipalities to support research aimed at improving healthy life expectancy and reducing health disparities in Japan. As of April 2023, 27 municipalities have provided data to the LIFE Study on 2.51 million individuals [5].

In Japan, comprehensive universal health care insurance has been implemented. There are three types of health insurance systems: Employees' Health Insurance (EHI), National Health Insurance (NHI), and latter-stage elderly healthcare insurance system. EHI is provided by employers. NHI is cooperatively operated by prefectural and municipal governments. All individuals aged 75 years or older join the latter-stage elderly healthcare system in Japan.

The data in the VENUS study were collected from health insurance claims data from NHI or the latter-stage elderly healthcare insurance system through the LIFE study. In contrast, vaccination records were stored directly by the local governments, regardless of insurance status.

2.2. Study design

We used a SCCS design (Fig. 1) [6,7]. In the SCCS design, the analysis population comprises individuals who have experienced the outcome of interest. The individual's study observation period is divided into risk and control periods. We defined risk periods as 1–28 days and 1–42 days after vaccination (with the date of vaccination defined as day 0) based on prior studies [8,9]. The control period was defined as the study observation period except for the risk periods and 6 weeks before vaccination to account for the healthy vaccinee effect. We compared the incidence of the outcomes (ITP and GBS) between risk and control periods for vaccinees. The advantage of the SCCS design is that it inherently controls for known confounders and time-fixed unmeasured confounders such as sex, race/ethnicity, genetic factors, and socioeconomic status since each case acts as its own control [10].

2.3. Outcomes

Cases of ITP and GBS in the inpatient setting were identified based on International Classification of Diseases, Tenth Revision (ICD-10) codes D69.3 and D61.0, respectively. Only the first occurrence within the observation period was used for analysis. Cases with the following ICD-10 codes were excluded based on prior reports with a lookback of 1 year to rule out past occurrences of the same disease and other etiologies for thrombocytopenia: G65.0 for GBS and B20, C00–C96, D18.0*, D59.0–D59.2, D59.3, D61.*, D65, D69.0, D80–D89, K70–K77, and M32. * for ITP [11]. In the VENUS study database, we used the date of hospitalization for ITP or GBS for each individual because the ICD-10 data in the VENUS study only contains information on the month of the outcome.

2.4. Statistical analysis

We described background information (age at vaccination, sex, city, number of medical visits, and comorbidities) of the analysis population for the SCCS design. In addition, background information on the cohort population, the source population for the SCCS analysis, was also summarized (Table S1). We calculated incidence rates for each group and then estimated incidence rate ratios with 95 % confidence intervals (CIs) using conditional Poisson regression models. The statistical significance was set at 5 %. P values below this level were considered statistically significant. All analyses were performed in R (version 4.2.1, R Project for Statistical Computing, Vienna, Austria).

3. Results

Between April 1, 2015 and March 31, 2020, 1,118,879 individuals entered the cohort. Of these, 165,492 individuals aged 64 years or older

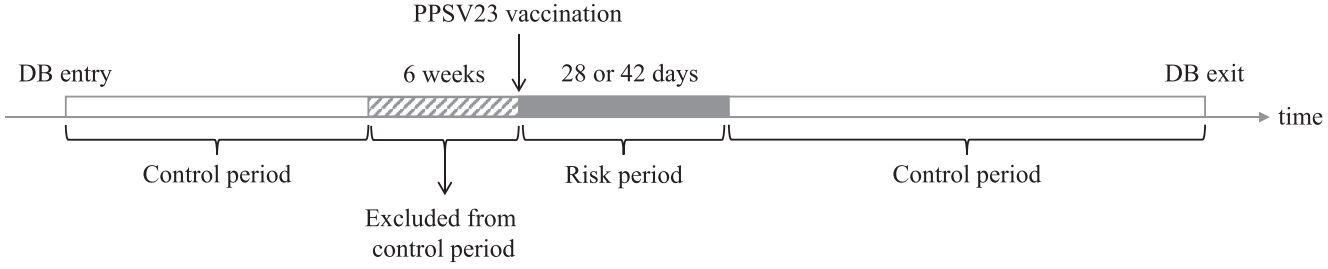

Fig. 1. Overview of the self-controlled case series design. Individuals who developed the outcome of interest were included in the analysis population. For each individual, the study observation period was divided into a risk period and a control period. Abbreviations: DB, database; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

were administered PPSV23. A total of 53 cases of ITP and 24 cases of GBS were identified (Fig. 2). Demographic characteristics of the cases in the SCCS analysis are shown in Table 1. The median age of patients with ITP was 75 years and 60 % were female. The median age of patients with GBS was 74 years and 42 % were female. For both outcomes, many patients were between the ages of 70 and 74. Table S1 (Supplementary materials) showed summarized characteristics in the cohort. In the SCCS analyses, the incidence of ITP during the 28-day risk period was 0.67 per 1,000 person-days. The rate during the 42-day risk period was 0.45 per 1,000 person-days (Table 2). The incidence rate ratios for ITP were 0.89 (95 % CI, 0.12–6.4) during the 28-day risk period and 0.58 (95 % CI, 0.081–4.2) during the 42-day risk period. Neither was statistically significant. Incidence rate ratios could not be estimated for GBS due to the limited sample size.

4. Discussion

In this study of a pilot vaccine safety surveillance system in Japan (VENUS study), we found no associations between PPSV23 vaccination and ITP. We were unable to assess GBS due to the limited sample size. We evaluated the incidence of ITP in different risk periods (28 days and 42 days), but the results remained the same. Although some previous studies reported that measles-mumps-rubella and inactivated influenza vaccination increases the risk for ITP and GBS, respectively [12,13], there are few studies that specifically evaluated ITP and GBS after PPSV23 vaccination [8,14]. Although the package insert for PPSV23 in Japan lists thrombocytopenia and GBS as potential adverse events, the frequencies are unknown. A previous study using case-centered analyses reported no statistically significant associations between PPSV23 vaccination and GBS [14]. Tseng et al. reported incidences for thrombocytopenia and GBS after PPSV23 vaccination in the United States using Vaccine Safety Datalink (VSD) data, with rates of 21–100 per 6,428,155 person-days (0.0032–0.0156 per 1,000 person-days) and 8 per 9,572,008 person-days (0.000836 per 1,000 person-days), respectively [8].

This study has several strengths. First, the VENUS study is composed of insurance claims data and accurate vaccination information, both of which were provided systematically by local governments [3,15,16]. Second, we used the SCCS design to inherently control for individual-level potential confounding factors that do not vary over time [17]. Glanz et al. conducted a simulation study using VSD data to empirically compare four study designs (cohort, case-control, risk-interval, and SCCS) used to assess vaccine safety. They concluded that the SCCS design is an efficient and valid alternative to the cohort design [10]. We tried to evaluate the association between PPSV23 vaccination with ITP or GBS using a cohort study design. However, with the available sample size, neither AEFIs allowed us to estimate association measures such as risk ratios. Given these factors, we view the VENUS cohort as a potential valuable active vaccine safety monitoring system that could be used to evaluate other vaccines, including those administered to children. Moreover, the establishment of a domestic active vaccine safety monitoring system in Japan can be facilitated while minimizing new

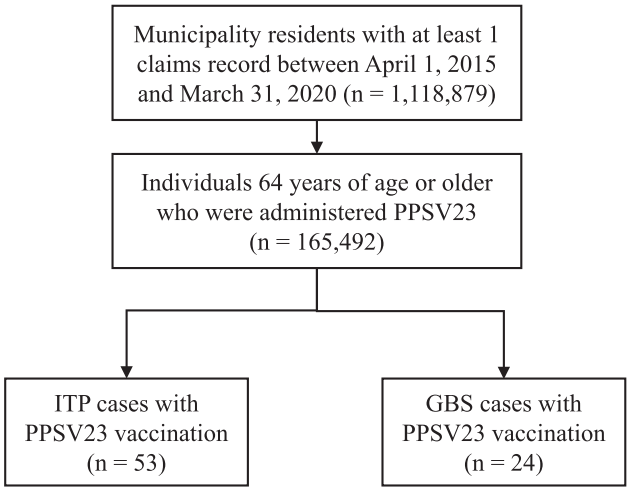

Fig. 2. Identifying the population to be analyzed for idiopathic thrombocytopenic purpura (ITP) and Guillain-Barré syndrome (GBS). Abbreviations: PPSV23, 23-valent pneumococcal polysaccharide vaccine; ITP, idiopathic thrombocytopenic purpura; GBS, Guillain-Barré syndrome.

Table 1
Characteristics of participants with PPSV23 vaccination who had an outcome in the SCCS design.

Characteristic	ITP cases (n = 53)	GBS cases (n = 24)
Age, median (min, max), years [a]	75 (64–90)	74 (64–94)
64–70 (%)	8 (15.1)	6 (25.0)
70–74 (%)	14 (26.4)	6 (25.0)
75–79 (%)	15 (28.3)	2 (8.3)
80–84 (%)	7 (13.2)	8 (33.3)
85–90 (%)	6 (11.3)	1 (4.2)
>90 (%)	3 (5.7)	1 (4.2)
Sex, female, n (%)	32 (60.4)	10 (41.7)
Number of clinical/hospital visits, median (min, max) [b]	6.0 (1.0–6.0)	6.0 (1.0–6.0)
Number of comorbidities, median (min, max) [c]	1.0 (0.0–5.0)	0.0 (0.0–2.0)
Comorbidity, n (%) [d]		
Congestive heart failure	8 (15.4)	0 (0.0)
Peripheral vascular disease	4 (7.7)	2 (8.7)
Cerebrovascular disease	5 (9.6)	4 (17.4)
Dementia	1 (1.9)	3 (13.0)
Chronic pulmonary disease	8 (15.4)	1 (4.3)
Rheumatologic disease	3 (5.8)	0 (0.0)
Peptic ulcer disease	8 (15.4)	0 (0.0)
Mild, moderate, or severe liver disease	11 (21.2)	3 (13.0)
Diabetes	1 (1.9)	1 (4.3)
Renal disease	3 (5.8)	0 (0.0)
Any malignancy	4 (7.7)	0 (0.0)
Missing	1 (1.9)	1 (4.2)

Abbreviations: PPSV23, 23-valent pneumococcal polysaccharide vaccine; SCCS, self-controlled case series; ITP, idiopathic thrombocytopenic purpura; GBS, Guillain-Barré syndrome.
[a] Age at vaccination was used.
[b] The number of months of medical visits from index date to six months prior to index date.
[c] The Charlson comorbidity index at vaccination was used.
[d] Items in the Charlson comorbidity index that were 0 are not shown.

Table 2
Incidence and adjusted rate ratio for each outcome after PPSV23 vaccination using the SCCS design.

Outcome (risk period from index date)	Number of events/person-days (incidence, per 1,000 person-days)		Incidence rate ratio (95 % CI) [a]
	Risk period	Control period	
Idiopathic thrombocytopenic purpura (28 days)	1/1,484 (0.67)	52/72,886 (0.71)	0.89 (0.12, 6.4)
Idiopathic thrombocytopenic purpura (42 days)	1/2,226 (0.45)	52/72,144 (0.72)	0.58 (0.081, 4.2)
Guillain-Barré syndrome (28 days)	0/672 (0)	24/34,830 (0.69)	NC
Guillain-Barré syndrome (42 days)	0/1,008 (0)	24/34,494 (0.70)	NC

Abbreviations: NC, not calculated; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SCCS, self-controlled case series; CI, confidence interval.
[a] Incidence rate ratios were estimated using conditional Poisson regression models.

investments by leveraging existing vaccination and claims data maintained by local governments. The development and implementation of a robust domestic monitoring system such as the VENUS system would enhance the evaluation of vaccine safety. Ultimately, we hope this will bolster vaccine confidence in Japanese communities, which currently harbor significant skepticism about vaccine safety.

This study is subject to limitations. First, the health insurance claims data in the VENUS study were derived solely from NHI or the latter-stage elderly healthcare insurance system. In 2021, they cover only 23.2 % and 14.5 % of the entire Japanese population. Therefore, it is difficult to generalize the results of the VENUS study to the entire Japanese population. For example, NHI members have lower income than EHI members. Second, the current VENUS study lacks the ability to conduct chart review to confirm the diagnosis of outcomes identified by ICD-10 codes and obtain a more accurate onset of outcomes. To mitigate potential misclassification, we implemented strict exclusion criteria based on previous studies [11,18]. Third, since both PPSV23 and inactivated influenza virus vaccines (IIV) are recommended for the elderly in Japan, simultaneous administration of both vaccines could potentially impact our findings. Nonetheless, of the PPSV23-vaccinated participants, only 0.87 % (238/27,365) were administered IIV on the same day (albeit only one municipality was able to provide influenza vaccination data). Given the low co-administration rates within this cohort, the influence on our findings seems minimal. Finally, as the VENUS cohort is still in the development phase, it might be underpowered to detect extremely rare adverse events such as GBS. If the usefulness of the VENUS study is confirmed through pilot studies, this limitation will be addressed promptly by encouraging more local governments to participate, potentially through government mandates or orders.

5. Conclusion

We evaluated the risk of ITP and GBS following PPSV23 vaccination using a pilot VENUS cohort. We found no associations between PPSV23 vaccination and ITP but were unable to assess associations with GBS. The identification of several key limitations of the VENUS study through this study can provide valuable insights to facilitate the establishment of an advanced vaccine monitoring system in Japan.

6. Financial support

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7. Declaration of interest statement

Y. Kawazoe, M. Takahashi, and H. Fukuda have no reported conflicts. S. Sato received payment for lectures from Nippon Boehringer Ingelheim Co., Ltd. T. Katsuta received payment for lectures from Merck Sharp & Dohme Corp. S. Kamidani's institution has received funding from NIH to conduct clinical trials of Moderna and Janssen COVID-19 vaccines and funding from Pfizer to conduct clinical trials of Pfizer-BioNTech COVID-19 vaccines.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.11.053.

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