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Original Article

Passive surveillance of rotavirus gastroenteritis-associated hospitalization using nationwide administrative databases in Japan☆

Tomomi Kimura [a, *], Nobuhiko Okabe [b]

[a] Medical Affairs, Astellas Pharma Inc., 2-5-1 Nihonbashi Honcho, Chuo-ku, Tokyo 103-8411, Japan
[b] Kawasaki City Institute for Public Health, 3-25-13 Tonomachi, Kawasaki-ku, Kawasaki-shi, Kanagawa 210-0821, Japan

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ABSTRACT

Simple, systematic, and sustainable passive surveillance systems for vaccine-preventable diseases (VPDs) should be useful to quantify the clinical and economic burden in a timely manner with minimum investment. This pilot study evaluated the usefulness of nationwide administrative databases (a hospital-based administrative database and an insurance claims database) for such passive surveillance of children hospitalized for VPDs using rotavirus gastroenteritis (RGE) as an example. Two rotavirus vaccines were launched in November 2011 and July 2012 in Japan. We assessed changes in the proportion of RGE hospitalizations among all-cause hospitalizations (N = 506,524) from the hospital database (April 2008–December 2016) and annual RGE hospitalization rates from the insurance claims database (January 2011–December 2016, n of beneficiaries = 460,585) in children aged <6 years. A total of 12,599 hospitalizations in 12,366 patients were associated with RGE from the hospital database. Similarly, 2038 patients had 2137 RGE-related hospitalizations from the insurance claims database. From 2009 to 2013, the proportion of RGE hospitalizations increased from 2.2% (95% confidence interval, 1.8–2.6) to 3.9% (3.7–4.0), then decreased and remained consistently low from 2014 (1.9% [1.8–2.0]) to 2016 (2.2% [2.1–2.3]). The RGE hospitalization rate decreased sharply in 2014, ranging between 2.85 and 3.52 during 2011–2013 to 0.97 (0.84–1.09) in 2014, and remained low through 2016 (1.18 [1.04–1.32]). In conclusion, we observed changes in RGE hospitalizations over time, without requiring additional data entry by clinicians. Nationwide administrative databases can be useful tools for passive surveillance of VPDs in Japan.

1. Introduction

Vaccine-preventable diseases (VPDs)[1] impose a significant burden on children and their families, as well as on the healthcare system. It is important to quantify these impacts for better understanding of unmet needs and vaccine effectiveness in the field; however, this process is long and cumbersome [1]. For example, some VPDs are reportable under the Infectious Disease Control Law in Japan, which requires data entry at the point of care [2]. Further, reporting, in principle, only begins after vaccines or treatments are available for the specific causal agent. Consequently, a simple, systematic, and sustainable passive surveillance system would be ideal that can be easily implemented worldwide, does not require additional data entry by busy clinicians, is widely applicable to various causal agents, can evaluate the pre-vaccine launch period, and have low development and maintenance cost.

Rotavirus gastroenteritis (RGE) is a VPD in young children, and two rotavirus vaccines have been launched in Japan: the monovalent vaccine RV1 (Rotarix®, GlaxoSmithKline Biologicals, Rixensart, Belgium) and the pentavalent vaccine RV5 (RotaTeq®, Merck & Co., Inc., Kenilworth, NJ, USA), launched in November 2011 and July 2012, respectively. RV1 is to be administered at 8 weeks and at 12–15 weeks of age (to be completed within 24 weeks) [3,4], while RV5 is scheduled at 8, 12, and 16 weeks of age (to be completed within 32 weeks) [4,5]. Several previous studies evaluated the effectiveness of rotavirus vaccines [6–13], but only a few included nationwide populations [6,13]. The vaccine coverage was estimated as 51% in 2013 [13], and it varied by geographic region, city, and

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* Corresponding author. Medical Affairs, Astellas Pharma Inc., 2-5-1 Nihonbashi Honcho, Chuo-ku, Tokyo 103-8411, Japan.
E-mail addresses: tomomi.kimura@astellas.com (T. Kimura), okbenobu46@gmail.com (N. Okabe).

[1] AGE, acute gastroenteritis; CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; IID, intestinal infectious diseases; LoS, length of stay; PY, person-years; RGE, rotavirus gastroenteritis; VPD, vaccine-preventable diseases.

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hospital cluster: 56.5% one-dose coverage was seen in Tsu City in 2014 [9]; 14.9% in the Saga prefecture in the 2012/13 season [14]; 64.2% in Yuri-Honjo city and 91.4% in Nikaho city between 2013 and 2015 [15]; 1% in 2011, 25% in 2012, 42% in 2013, and 49% in 2014 in the Hyogo prefecture [16]; approximately 32% during the 2012 season from three pediatric clinics in Shibata City and Niigata Prefectural Shibata Hospital [17]; and 69%–92% from 2013 to 2015 in Nagoya city [7].

Administrative databases, such as those used for insurance claims, may be valuable tools for passive surveillance of the burden of VPDs [6,18–21]. This pilot study was conducted with the objective of evaluating the feasibility and usefulness of two Japanese databases, a hospital-based administrative database and an insurance claims database, for a passive surveillance system of hospitalized children for VPDs.

2. Materials and methods

2.1. Data source

This pilot study employed two distinct administrative databases as data sources: a hospital-based administrative database and an insurance claims database. The hospital database was provided by Medical Data Vision and comprised transaction-level billing data, medical and prescription claims data, and discharge summary data for more than 20 million outpatients and inpatients from over 300 Japanese Diagnosis Procedure Combination (DPC) hospitals. The "Japanese version of diagnosis-related group (DRG)" is referred to as the Diagnosis Procedure Combination (DPC) system. The DPC system is being increasingly adopted in small-, medium-, and large-sized hospitals, including university hospitals, across Japan. After this system was adopted, more hospitals gradually adopted the DPC/per-diem payment system, until 1730 hospitals, or about 490,000 hospital beds, were expected to have adopted this system by April 1, 2018. This accounts for about 83% of beds for general hospitals. As of April 1, 2018, DPC had been introduced to 1730 hospitals, which included 1493 DPC standard hospitals, 155 DPC advanced treatment hospitals, and 82 university hospitals [22].

The insurance claims database was provided by Japan Medical Data Center and comprised approximately 3 million beneficiaries. Both databases have nationwide coverage [23] and are commercially available at a cost. The data period for this analysis ranged from April 2008 to December 2016 for the hospital database and from January 2011 to December 2016 for the insurance claims database. The study was compliant with the Guidelines for Good Pharmacoepidemiology Practice (GPP). Institutional review board approval was waivered as all data were de-identified (i.e., "anonymously processed information" per Act on the Protection of Personal Information) [24]. No personal information can be restored in this database and no individual can be re-identified.

2.2. Study population

Children aged 5 years or younger upon hospitalization who were admitted on or after January 1, 2009, and discharged on or before December 31, 2016, were included from the hospital database. From the insurance claims database, children born on or after January 2005 (i.e., aged 5 years or younger as of January 2011) and enrolled in the insurance program before January 2017 were included. All beneficiaries were followed from either their date of birth, January 1, 2011, or the date of enrollment to the insurance program, whichever occurred last, until either their 6th birthday, the end of the study period (December 31, 2016), or the date of disenrollment from the insurance program, whichever came first. Date of birth was truncated for privacy; therefore, 15th of the month of birth was entered as the date of birth for all the children.

2.3. Outcomes

The diagnosis of RGE was defined using the International Classification of Diseases, 10th revision (ICD-10) code A08.0 for "rotaviral enteritis," without including a suspicion flag, appearing either in the discharge summary (hospital data only) or in monthly medical claims. Laboratory test results for rotavirus detection were not available in these databases. The validity of this diagnosis code was confirmed against laboratory test data in the same age group from eight member hospitals in the hospital database between July 2013 and June 2014 (number of patients = 650) [25]. Positive predictive value (PPV) was 97.8% (i.e., almost all patients with diagnostic code A08.8 had tested positive for rotavirus) and sensitivity was 85.0% (i.e., 85% of patients with positive test results had been assigned this diagnosis code). By including an A08.0 with a suspicion flag, sensitivity increased to 99.4%, but PPV deteriorated to 43.2%. Based on these findings, we defined RGE events as the presence of ICD-10 code A08.8, without including the suspicion flag. As a reference, intestinal infectious diseases (IID) other than RGE were defined by ICD-10 codes A01.0 to A09.9, excluding A08.0. Acute gastroenteritis (AGE) was defined as RGE plus IID.

RGE and IID hospitalizations were defined as hospitalizations with RGE or IID occurring during the month of admission. If the diagnosis codes were identified in consecutive months during a single hospitalization event, only the first month was counted.

The outcomes of this study were designed based on the characteristics of the database. From the insurance claims data, the annual RGE hospitalization rate per 1000 person-years (PY) and annual RGE outpatient visit rate per 1000 PY were evaluated. Total beneficiaries in the database can be used as the denominator, like in population-based studies. An incidence rate cannot be estimated from hospital data because the catchment area is unknown. Also, because the number of member hospitals—and accordingly, the number of patients—has increased over time, the absolute number of RGE hospitalizations cannot provide a meaningful measure of the effect of vaccines. Therefore, we calculated the proportion of RGE hospitalizations among all-cause hospitalizations as a measure, from the hospital-based administrative database. We also examined the proportion of RGE hospitalizations among AGE hospitalizations and the proportion of IID hospitalizations among all-cause hospitalizations as a reference.

Vaccination records are not available in either database because it is not reimbursed (but subsidized by local government). Length of stay (LoS; days) and RGE hospitalization cost were also examined in both databases. All outcomes were categorized and evaluated by calendar month, calendar year, sex, and age group (0–5, 6–11, 12–17, and 18–23 months and 2, 3, 4, and 5 years).

2.4. Statistical analyses

All analyses were performed separately for each database with hospitalization (not patient) as the unit of analysis (i.e., a single patient could have multiple hospitalizations). The proportions of RGE and IID hospitalizations among all-cause hospitalizations were calculated for the entire cohort, as well as by age group, calendar month, sex, and calendar year. RGE hospitalization rate and RGE outpatient visit rate per 1000 PY were calculated by dividing the number of hospitalizations and outpatient visits by PY of follow-up for the entire cohort of beneficiaries, and by age group, sex, and calendar year. LoS for RGE hospitalization was calculated by subtracting the admission date from the discharge date and adding 1 day. Hospitalization cost was calculated as the sum of all medical fees acquired during an RGE hospitalization. Data are presented as

mean (95% confidence interval [CI]) unless otherwise specified. All analyses were descriptive and performed using Statistical Analysis Software Studio 3.5.

3. Results

3.1. Study population

During the 8 years and 9 months of the study period, a total of 506,524 hospitalizations in 381,970 patients aged 0–5 years were identified in the hospital database (56% boys, 44% girls). Among them, 12,599 hospitalizations in 12,366 patients were associated with RGE, and 38,387 hospitalizations in 34,621 patients were associated with IID (Table 1). From the insurance claims database, a total of 460,585 beneficiaries were included (51% boys, 49% girls) during 5 years of the study period. Of these, 2038 patients (56% boys, 44% girls) had 2137 RGE-related hospitalizations and 8230 patients (55% boys, 45% girls) had 10,866 RGE-related outpatient visits. In the hospital-based dataset, the proportion of RGE hospitalizations (12,599 events) among any acute gastroenteritis hospitalization (in our study, RGE + IID; 50,986 events) was 32.8% (Table 1).

3.2. Trend in RGE hospitalizations

The insurance claims database allows evaluation of rates (e.g., annual RGE hospitalization rate per 1000 PY) because total beneficiaries in the database can be used as the denominator, like in population-based studies. Although the hospitalization rate is not available from the hospital data, the proportion of RGE hospitalization could be determined to assess the relative burden among the hospitalized children in the same age group. Overall, the proportion of RGE hospitalizations among all-cause hospitalizations from the hospital database was 2.5% (95% CI, 2.4–2.5%). The proportion of RGE hospitalizations among all AGE hospitalizations (RGE + IID) was 20.4% during the entire study period. The proportion of RGE hospitalization was higher among girls than boys (2.6% [2.5–2.6%] vs. 2.4% [2.4–2.5%]); this trend was present in all age groups. The proportion of RGE hospitalizations among all-cause hospitalizations increased from 2.2% (1.8–2.6%) in 2009 to 3.9% (3.7–4.0%) in 2013. Thereafter, it decreased and remained consistently low from 2014 (1.9% [1.8–2.0%]) to 2016 (2.2% [2.1–2.3%]) (Fig. 1A).

Data gathered from insurance claims revealed a mean RGE hospitalization rate of 1.89/1000 PY (95% CI, 1.81–1.97) during the entire study period. RGE hospitalization rate was higher among boys than girls (2.07 [1.95–2.18] vs. 1.70 [1.59–1.81]) and tended to be higher in boys for all age categories. This rate decreased sharply in 2014, ranging between 2.85 and 3.52 during 2011–2013 to 0.97 (0.84–1.09) in 2014, and remained low through 2016 (1.18 [1.04–1.32]) (Fig. 1B).

3.3. Impact by age groups

Hospital-based administrative database: After both vaccines became available, the proportion of RGE hospitalizations decreased to 1.9–2.2% in 2014 across all age groups. Among children aged 6–11 months, hospitalization peaked in 2011 and then decreased gradually from 2012 to 2016. In children aged 12–17 months, 18–23 months, and 2 years, hospitalization peaked in 2013, then sharply decreased in 2014 and remained low through 2016. Hospitalization was consistently low in children aged 0–5 months. Among children 3 years old or older, RGE hospitalization was also generally low, peaking in 2013, before decreasing and remaining low from 2014 to 2016 (Fig. 2A).

Insurance claims database: The hospitalization rate in children aged 6–11 months peaked in 2012 and then decreased gradually. In children aged 12–17 months, hospitalization rate was highest in 2011, also decreasing gradually. In those aged 18–23 months, hospitalization peaked in 2013, then decreased and remained low from 2014 to 2016. The hospitalization rate decreased more slowly in children aged 12–17 months from 2011 to 2014 (Fig. 2B). The pattern of RGE outpatient visits was similar to that of RGE hospitalizations: children aged 12–17 months had the highest outpatient visit rate from 2011 to 2013, followed by those aged 18–23 months and 6–11 months (Fig. 2C).

3.4. Seasonality and monthly trend in RGE

Monthly trend in proportion of RGE hospitalizations among any hospitalizations is illustrated in Fig. 3. It peaked in early spring (March and April) every year (Fig. 3). Before the second RGE vaccine became available, this seasonal trend in RGE hospitalizations magnified, increasing from 11% in spring of 2009 to 17.1% in spring of 2012. Thereafter, these annual peaks decreased slightly in 2013 (12.5%) and further decreased to consistently low levels between 2014 (6.2%) and 2016 (5.8%). The proportion of IID hospitalizations among any hospitalizations generally peaked in autumn and spring until 2013. Thereafter, a decrease in the size of monthly IID hospitalization peaks was observed.

3.5. Other RGE-related outcomes

In addition to hospitalizations, outpatient visits for RGE were also explored in the insurance claims data. We identified a total of 10,866 RGE outpatient visits from 8230 patients, with an overall rate of 9.6 visits/1000 PY (95% CI, 9.4–9.8). The rate of outpatient visits was similar between 2011 and 2013 (16.1 [15.3–16.8] and 14.1 [13.5–14.6] visits per 1000 PY, respectively), then decreased by 50–70% and remained low between 2014 and 2016 (5.6 [5.3–5.9] and 6.9 [6.6–7.3], respectively).

Resource utilization can also be measured in these databases. The median (range) LoS for RGE hospitalizations was similar

Table 1
Study populations.

	Hospital-based dataset (April 2008–December 2016)			Insurance claims dataset (January 2011–December 2016)		
	Total hospitalizations	RGE hospitalizations	IID hospitalizations	Total beneficiaries	RGE hospitalizations	RGE outpatient visits
Events, N	506,524	12,599	38,387	N/A	2137	10,866
Patients/beneficiaries, N[a]	381,970	12,366	34,621	460,585	2038	8230
Boys, n (%)	212,598 (56%)	6775 (55%)	19,445 (56%)	237,024 (51%)	1136 (56%)	4528 (55%)
Girls, n (%)	169,372 (44%)	5591 (45%)	15,176 (44%)	223,561 (49%)	902 (44%)	3702 (45%)

IID, intestinal infectious diseases other than RGE; RGE, rotavirus gastroenteritis; N/A, not applicable.
[a] Number of patients included from hospital database and number of beneficiaries from insurance claims database.

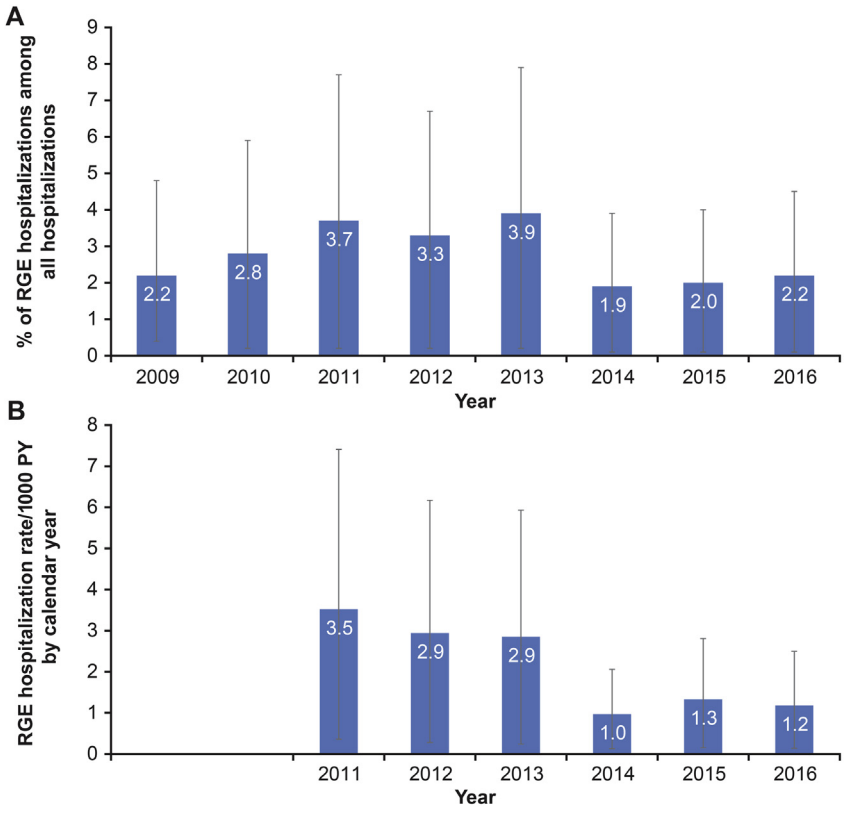

Fig. 1. RGE hospitalizations in children aged 5 years or younger presented as (A) proportion of RGE hospitalizations among all-cause hospitalizations with 95% CI from the hospital database (2009–2016) and (B) RGE hospitalization rate/1000 PY with 95% CI from the insurance claims database (2011–2016). CI, confidence interval; RGE, rotavirus gastroenteritis; PY, person-years.

between the hospital data and insurance claims data (4–5 [1–174] days and 4 to 5 [1–56] days, respectively). No changes were observed in LoS before and after the vaccine launch. The median (range) RGE hospitalization cost was also comparable between the hospital data (approximately ¥200,000–250,000 [21,450–15,674,610]) and insurance claims data (approximately ¥200,000–250,000 [40,830–4,077,740]). LoS and hospitalization cost did not vary by age group in either database.

4. Discussion

We evaluated the feasibility and usefulness of Japanese administrative databases for a simple, systematic, and sustainable passive surveillance system for children hospitalized for VPD. Using data from nearly a million patients, we evaluated RGE hospitalization rate, outpatient visit rate, proportion of RGE hospitalizations, and changes in these variables over time. All data were obtained directly from two administrative databases, without requiring additional data entry by clinicians. To our knowledge, this is the largest study analyzing nationwide VPD trends among children in Japan.

We observed a decline in RGE hospitalizations (rate and proportion) after the launch of the two rotavirus vaccines; however, the causality is not conclusive. Although this trend has been reported in previous studies [6–9], the present study confirmed it in a nationwide sample, in a timely manner (the lag time for data is 2 months for hospital data and 5 months for insurance claims data) and with minimum effort. Another significant benefit was the availability of data before the vaccine launch, as national VPD surveillance typically only begins after a vaccine is released. Although both RGE vaccines were available by mid-2012, both the proportion and rate of RGE hospitalization increased slightly but steadily from 2009 until 2013.

The seasonal trend in RGE hospitalizations, seen as annual peaks, decreased slightly in 2013 and remained consistently low between 2014 and 2016. The corresponding decrease in the size of monthly IID hospitalization peaks could be attributed to a decrease in RGE events that may have been misclassified to the IID group or improvement in overall treatment of infectious diseases, including widespread use of oral rehydration therapy.

National statistics are usually summarized by year of age, but in these databases, patient age in months was also available. This is important for pediatric research. When analyzed by age group, a steady decrease in RGE hospitalization rate was observed in children aged 6–11 months, the age group most likely to have been vaccinated. Slightly older children (aged 12–17 and 18–23 months) experienced a more gradual decrease in hospitalization rate, which may indicate an indirect benefit by herd immunity. These findings are also consistent with the recommended vaccination schedules.

A number of observational studies have reported the proportion or rate of RGE hospitalization [6–9]. Although the results from some previous studies are similar to ours [9], our findings tended to show lower point estimates compared to prior reports. One of the potential reasons can be difference in age; we included 5-year-old children of pre-school age, but some studies targeted <5-year-old children. RGE was indeed rare in 5-year-old children, but the proportion of RGE hospitalization among any hospitalizations for <5-year-old children was the same as that for <6-year-old children. Another potential reason may be secondary data use, which is less sensitive compared to evaluation of collected primary data. Indeed, our previous validation study showed that 15% of rotavirus test-positive patients did not have the diagnosis code [25], probably

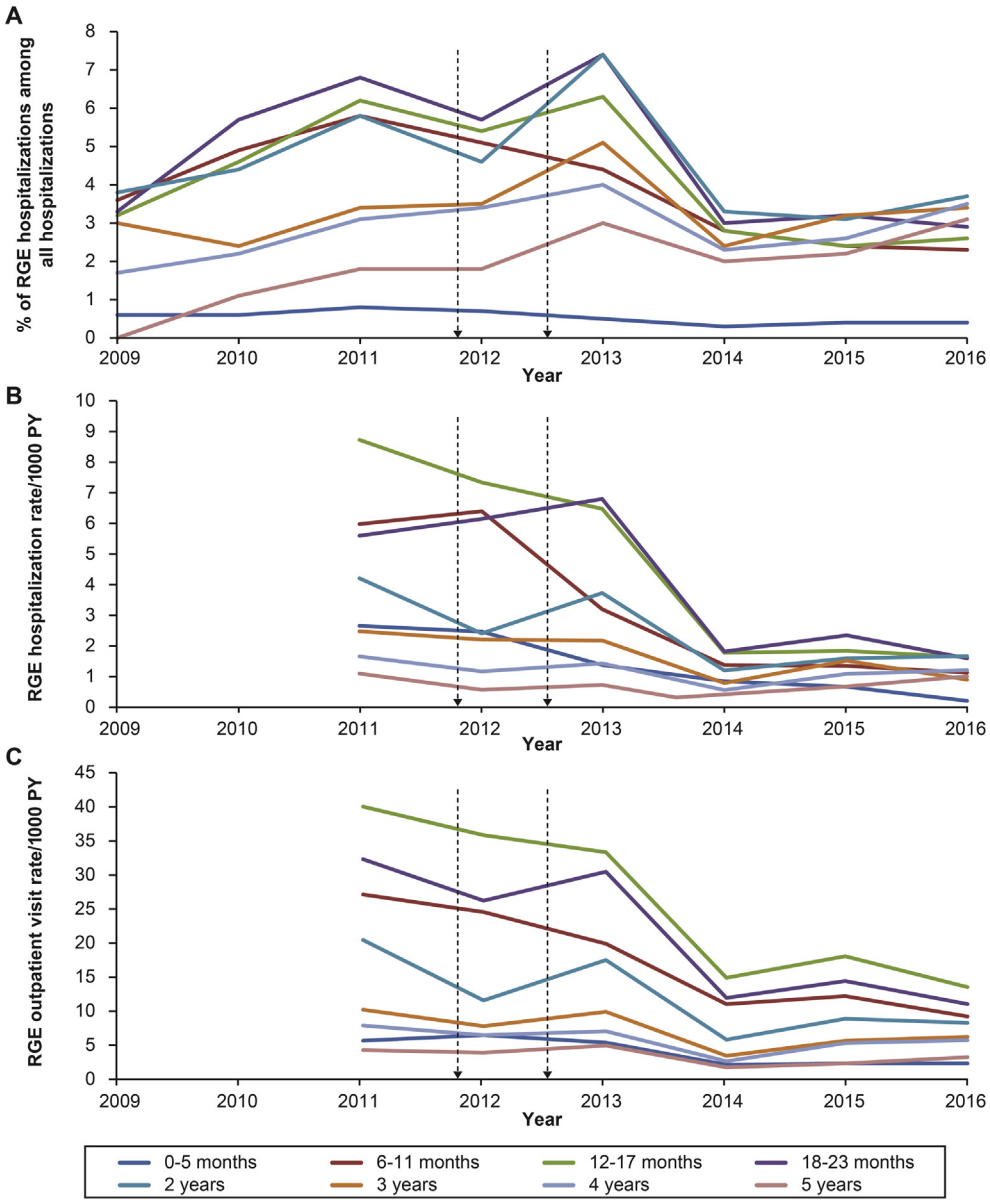

Fig. 2. Trend by age group and presented as (A) proportion of RGE hospitalizations among all-cause hospitalizations from the hospital database (2009–2016), (B) annual RGE hospitalization rate from the insurance claims database (2011–2016), and (C) annual RGE outpatient visit rate by age group from the insurance claims database (2011–2016). RGE, rotavirus gastroenteritis; PY, person-years. Dotted lines represent vaccine launch month (November 2011 and July 2012).

because no specific treatment is available for RGE and the specific diagnosis might not be essential for reimbursement purpose. For example, when hospital medical charts were used [11], the proportion of RGE hospitalizations was higher than that reported here (4.8% [665/13,767] in 2008–2009 vs. 2.2% [115/5184] in 2009, respectively). Similarly, RGE hospitalization rates from 2007 to 2009 (2.8–4.7/1000 PY) [10] and 2010–2011 (5.2/1000 PY) [12] were marginally higher than that reported in this study (3.52/1000 PY in 2011). Also, by using laboratory results in addition to ICD-10 diagnosis, the RGE hospitalization rates were reported to be higher both in the pre-vaccine (5.59/1000 PY in 2007–2011) and post-vaccine (3.65 in 2012–2016) periods [7].

However, even by using the same insurance claims database that evaluated all children aged <5 years between January 2009–December 2015, the RGE hospitalization rates in the pre-vaccine (2009–2011: 6.3–9.3/1000 PY) and post-vaccine (2.3 in 2014 and 3.0 in 2015) years were higher [6] compared with our study. We could not identify the specific reason underlying the differences. However, we indeed observed a clear pattern of RGE hospitalizations over time, which was congruent with anticipated differences related to age group and with vaccination schedules, as well as with the potential effects of herd immunity in older children who were not eligible for direct vaccination at the time of launch of the vaccines. Furthermore, these databases offered a view over several years—including pre-vaccine years—into the burden of RGE in terms of hospitalization and resource utilization, which are not captured with current VPD reporting. This system can be applied to evaluate VPDs other than RGE in other age groups (e.g., elderly) and outpatient visits for VPDs or resource utilization associated with VPDs for future studies.

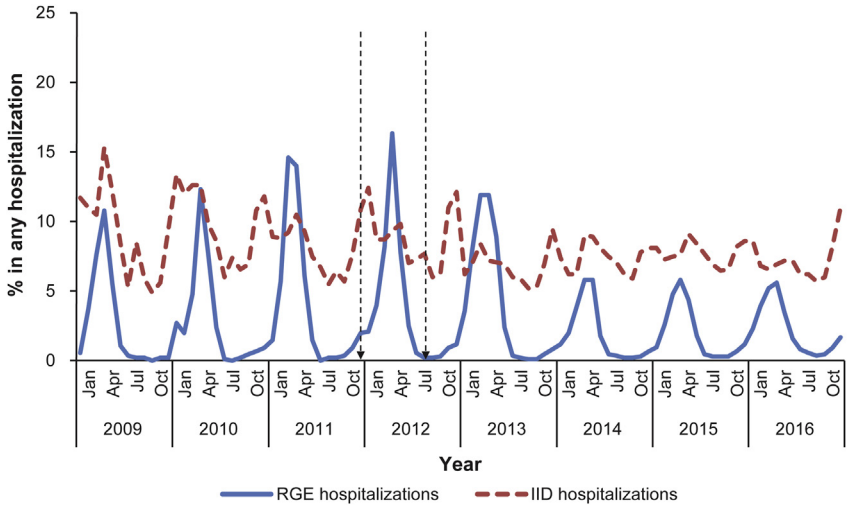

Fig. 3. Monthly trend in proportion of RGE and IID hospitalizations among any hospitalizations during the study period from the hospital database. IID, intestinal infectious diseases other than RGE; RGE, rotavirus gastroenteritis. Dotted lines represent vaccine launch month (November 2011 and July 2012).

Indeed, changes in RGE outpatient visit over time, length of hospital stay, and cost for RGE hospitalization could be estimated with minimum effort. In the future, we may be able to use the system for multiple diseases with minimum effort, for example, by developing a macro program and running it as a routine practice.

A limitation of this study is the unavailability of vaccination history, as a result of which, study results do not reflect causation. Additionally, RGE encounters were determined using diagnostic codes rather than positive laboratory values. The previous validation study suggested that this method is sound and viable for the same age group as was investigated in this analysis; however, PPV and sensitivity data for individual age group categories are not available [25]. These databases do not have immunization records and are not currently linkable to any other immunization registry. We did not evaluate the RGE testing density in these databases; hence, the results are inconclusive. Further, the possibility of excluding true RGE cases with a suspicion flag could not be ruled out. Future users of this system can include cases with the suspicion flag if it would be more suitable for the study objective. Additionally, this system may not be suitable for evaluation of rare events, e.g., Japanese encephalitis, invasive meningococcal disease, and polio, and will never replace the current surveillance system.

5. Conclusions

We demonstrated that nationwide administrative databases in Japan can be used for simple, systematic, and sustainable passive surveillance purposes that are nonintrusive to practicing clinicians, using RGE as an illustration. The proportion of RGE hospitalizations among all-cause hospitalizations as well as the annual RGE hospitalization rate declined within 2 years after RGE vaccines became available. Further research is needed to investigate whether this passive surveillance method can be systematically applied for monitoring other VPDs.

Conflict of interest

Tomomi Kimura is a full-time employee of Astellas Pharma. Nobuhiko Okabe has no conflicts of interest to declare.

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