Application of a self-controlled case series study to a database study in children

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Running header: a self-controlled case series study in children

ABSTRACT

Introduction: Post-marketing surveillance activities are particularly important for safety issues on children, elderly and patients with severe comorbidities since these populations are usually excluded in clinical trials. In addition, using electronic databases for monitoring of safety of marketed products has been of considerable interest.

Objectives: This study aimed to clarify advantages and difficulties of the self-controlled case series method relative to cohort studies in pharmacoepidemiological studies in children using an administrative database, and to explore the impact of different handling of period eligible for analysis and recurrent events on the results.

Methods: Datasets of only individuals who had the outcome of interest were derived from an anonymized hospital administrative database in Japan from April 2003 through August 2011. We calculated incidence rate ratios (IRR) and their 95% confidence intervals (CI) for the risks of diarrhea, bronchitis, and eczema related to palivizumab treatment in young children. The analysis included "first diagnosed" events or "multiple" events during an eligible period. An eligible period was defined in two ways: the "EPA" for first-time inpatient periods of more than 3 continuous days for cases; and the "EPB", which was regarded as a continuous period in cases where the interval between visits was below the 75th percentile of the interval between visits for patients with the same diagnosis.

Results: We extracted 70,771 patients and identified 641 patients who were exposed to palivizumab. The age-adjusted IRRs for diarrhea, bronchitis, and eczema were 3.0 (95%CI: 1.7-5.4), 10.3 (CI: 8.0-13.2), and 16.9 (CI: 12-23), respectively, in multiple events and the EPB eligible period. The IRRs varied greatly between two eligible periods.

Conclusions: This method could be a useful tool in pharmacoepidemiological studies in children. Careful consideration in the handling of inpatient and outpatient periods, including sensitivity analyses, is necessary because this method is a within-individual comparison.

Key Points

self-controlled case series

administrative database

pharmacoepidemiological studies in children.

INTRODUCTION

Post-marketing surveillance activities are particularly important for safety issues in children, elderly and patients with severe comorbidities since these populations are usually excluded in clinical trials. There has been considerable interest in creating and using electronic databases for monitoring of safety of marketed products [1,2] as well as for health care planning [3] and investigating the prevalence or predictors of safety events [4,5]. In fact, large-scale databases, such as The Clinical Practice Research Datalink (CPRD) [6] and The Health Improvement Network (THIN) [7] in the UK and i3 Drug Safety [8] in the US, have been successfully used for this purpose.

In Japan, the government initiated the development of a commonly called “national database” which has been accumulating data such as claims data and physical checkup information from the entire population since April 2009 and this database is available to researchers if their application is approved after a review by the government since 2011 [9]. Other databases available in Japan include a claims database provided by Japan Medical Data Center [10] and an administrative database provided by Medical Data Vision Co. (EBM provider) and a few studies have utilized these databases [11,12]. EBM provider, which is the database used in this study, contains anonymous information from the health insurance claims of about one million patients in 16 diagnosis procedure combination (DPC) hospitals since April 2003. In DPC hospitals, medical and technical service payment is calculated per day in a prospective payment system, and since 2003 the DPC system has been implemented in 82 hospitals in Japan including advanced treatment hospitals. These hospitals met all the standard requirements including submission of data derived from electronic receipt system cooperation master in the 2 years prior to the application of DPC hospitals. The number of DPC-introduced hospitals is expected to increase continuously.

The self-controlled case series method is an appealing alternative to case-control and cohort analyses in detecting and characterizing adverse events using claims or electric health records (EHR) databases [7,13-15]. This method is an intra-patient comparison, so it allows us to control implicitly for confounders which do not vary with time over the observation period [15] as well as to achieve sufficient power with smaller sample size relative to cohort studies. Moreover, selection of a control population is not necessary.

These features are particularly appealing in pharmacoepidemiological studies for drug safety in children, such as studies of palivizumab, an anti-RSV humanized monoclonal antibody used for prophylaxis of severe lower respiratory tract infection in children. The specific indication of palivizumab is for children at risk of severe respiratory syncytial virus (RSV) infection, which has been demonstrated in randomized clinical trials, the IMpact-RSV study [16] and the palivizumab cardiac study [17]. The percentages of patients with any adverse event were similar between the palivizumab and control groups (96.4% [482/500] and 95.9% [961/1002] in the IMpact-RSV study [16] and 96.5% [625/648] and 95.6% [611/639] in the palivizumab cardiac study [17], respectively) and there were no significant differences in specific adverse events such as fever, nervousness, injection site reaction and diarrhea. Although palivizumab is expensive, the universal public pension insurance system extending to all citizens in Japan and a subsidy for patients with an indication for palivizumab permits almost all patients who need the drug to receive administration. In addition, most periods of palivizumab exposure could be extracted from the database since physicians administered this drug by injection in weight adjusted dose at a hospital. Only very few children have indications for palivizumab exposure, and they are not likely to visit more than one hospital.

The aims of this study are therefore two-fold: to clarify advantages and difficulties of the self-controlled case series method relative to cohort studies in pharmacoepidemiological studies in children using an administrative database, and to explore the impact of different handling of period eligible for analysis and recurrent events on the results.

1. METHODS

2.1 Study Design

We evaluated the self-controlled case-series method [15] through analysis of data from EBM provider on the associations between palivizumab and adverse events reported in previous information such as the drug package insert. This method estimates the incidence rate ratio of palivizumab using data on only individuals who had the outcome of interest. As this is an intra-person comparison, time-fixed confounders are implicitly controlled. Furthermore, temporal variation in the incidence rate can by modeled by splitting individuals' observation period into intervals according to age groups (e.g. 6-month bands).

In analysis of databases incapable of tracking patients across hospitals, it is necessary to specify the timing of "lost to follow-up", that is, the end of periods in which adverse events can be included in the analysis. There were two potential definitions of the eligible period in this study. The eligible period defined as "EPA" covered first-time inpatient periods of more than 3 continuous days. The "EPB" eligible period included "lost to follow-up" cases and was regarded as a continuous period in cases where the interval between visits was below the 75th percentile of the interval between visits for patients with the same diagnosis. Another statistical consideration was handling of recurrent events, because analysis using only the first event can yield results substantially different from that using multiple events. The self-controlled case-series method assumes that events arise in a non-homogeneous Poisson process [15]. This is a probability model that inherently assumes recurrent events, but the self-controlled case series method is applicable for non-recurrent events when the incidence rate is small over the observation period. On the other hand, the assumption is violated when events are recurrent, but occurrence of one event increases the probability of subsequent events [15]. Therefore the secondary objective of this study was to explore the impact of different handling of period eligible for analysis and recurrent events on the results.

This study was approved by the Ethics Committee of the Kyoto University Graduate

School and Faculty of Medicine.

2.2 Data Sources

EBM provider database is an anonymized hospital administrative database that has been provided by Medical Data Vision Co. (Tokyo, Japan) since April 2003. The database we used contains information from over one million patients registered in 16 hospitals with more than 300 beds in Japan. In these hospitals, medical and technical service payment is calculated in the DPC system. The database includes patient demographic data (sex, age, birth year and month), information about prescriptions (date, drug name, volume, dose), and diagnostic and procedure information (date, disease name) performed at the hospitals included in the database. The coding of diagnoses and disease names is standardized using the International Classification of Diseases (ICD-10) and the disease codes by Medical Information System Development Center (MEDIS-DC), respectively. Drug prescriptions are coded using the Anatomical Therapeutic Chemical (ATC) classification system. The quality of data held in the database is maintained through rigorous checks and regular audits.

The advantages of this database are inclusion of newborns and the elderly and its relatively large-scale among databases available in Japan: 127 of about 1500 DPC hospitals are covered in 2013. Mortality information and laboratory data are also available. On the other hand, the information on dispensing of medication by a pharmacist is not included in the database. The database is incapable of tracking patients across hospitals. The usability of this database was assessed in a study of cardio-cerebrovascular events in hypertensive patients and the authors concluded that this database was as valid and reliable as data from other epidemiological studies in terms of the incidence of the investigated events [12].

2.3 Study Population

Patients were selected from the population of individuals registered in the database from April 2003 to August 2011. Eligibility criteria were patients between 0 and 5 years and, for statistical analyses, we extracted those with at least one record of diagnosis of an adverse event of interest for each of the two eligibility definitions, EPA and EPB. We did not set a pre-period to identify new users of palivizumab and their first event occurrences because eligible patients were children.

2.4 Outcome

We selected outcomes of interest based on adverse events reported in the drug package insert. We used ICD-10 code and the disease codes by MEDIS-DC to identify adverse events and extracted a confirmed diagnosis to identify the event. Medical diagnoses in EBM provider are recorded through a disease-code master for standardizing disease names in Japan. This system was developed and is maintained by MEDIS-DC, which is commissioned by the Ministry of Health, Labor and Welfare (MHLW). This master system includes approximately 20,000 disease names, which are compliant with ICD-10. For analyzing adverse events, we developed categories based on Major Diagnostic Category (MDC) codes, which are used for DPC system coding; Febrile convulsion (R560), Twitch (P90, R252, R568), Tachyarrhythmia (R000), Bradycardia (R001), Tachycardia (R000), Diarrhea (A09), Vomiting (R11), Stridor (R061), Dyspnea (P220, R060), Rhinitis (J00, J310), Rhinorrhea (J348), Upper respiratory infection (J069), Pneumonia (J101, J110, J111, J121, J129, J13, J152, J157, J159, J180, J189), Bronchitis (J205, J208, J209, J40), Bronchiolitis (J210, J219), Reduced blood platelet count (D696), Exanthema (B082, B084, B09, R21, R238), Eczema (L208, L210, L211, L219, L259, L301, L309), Fever (R509), Pain (R529), Viral infection (B009, B340, B348, B349), Otitis media (H659, H669, H660). Clinical validity of these categories was confirmed by 2 medical doctors independently.

Recurrent events were handled by using only the first diagnosed events or as multiple events which were defined as one episode that occurred repeatedly within the 75th percentile of the interval between visits for patients with the same diagnosis.

2.5 Exposure

We identified prescriptions for palivizumab within each eligible period using information on the drug code and prescription dates. The ATC code was used as the drug code in the database. Although palivizumab is administered intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season, the half-life of palivizumab is about 30 days and patients in the database were injected every couple of months. Thus palivizumab treatment was assumed to be continuous when any apparent treatment break was less than 100 days, to allow for partial noncompliance. A 30-day period was added to the last prescription date within the continuous period; hence, the exposure period included all duration with drug exposure within the eligible period. All other observation times within the study window were taken as the baseline (unexposed) period (Figure 1).

2.6 Covariates

We extracted data on characteristics of patients including sex, status of hospitalization including inpatient or outpatient, and diagnosis according to the ICD-10 code from the database. The data on covariates is used to describe characteristics of patients but not used as explicit adjustment factors in the self-controlled case series analysis.

2.7 Analysis Method

The data processing process in our analysis is as follows: (1) We extracted patients with at least one prescription record for palivizumab from patients who met the eligibility criteria in the EBM provider database, (2) we identified patients with at least one record of diagnosis of an adverse event of interest with or without prescription records of the drug within each of the two eligibility periods, EPA and EPB, which started from the first day of first-time inpatient periods of more than 3 continuous days and could cover the period before the first prescription of palivizumab, (3) we identified exposure periods as defined in "2.5 Exposure" section, which could include multiple exposure periods, and occurrence of the adverse event within the eligible period, and (4) we analyzed the data using self-controlled case series method.

The self-controlled case-series method assumes that events arise in a non-homogeneous Poisson process [15]. The incidence rate is supposed to depend on each individual, temporal effects and exposure. Temporal effects are modeled through segmentation of the eligible period of each individual into user-specified intervals. Given that palivizumab is administered mainly between September and April, we used age groups in 6-month age bands and season groups based on calendar months. Specifically we consider a log-linear model $\lambda_{ijk}=\exp(\varphi_i+\alpha_j+\beta_k)$, where φ_i represents a log-transformed rate for the i th individual, α_j represents a log-transformed rate for the j th group for temporal effects, and β_k represents a log-transformed rate for the k th exposure group. The log-transformed rate ratios and their 95% confidence intervals are calculated by maximizing conditional likelihood for the log-linear Poisson model.

All analyses were conducted using STATA software version 11 (LightStone Co, Tokyo, Japan) using STATA codes provided by [15] and the outputs were also verified using SAS software version 9.2 (SAS institute, Cary, NC). The authors had full access to the data and take responsibility for its integrity. All reported P values for statistical tests are 2-tailed, and $P<0.05$ was taken to indicate statistical significance.

2. RESULTS

Of all patients in the EBM provider database, 70,771 met the eligibility criteria and were extracted from the database. As shown in Table 1, 37,571 (53%) were male and the median of the period in which administrative records continue between the ages of 0 and 5 years was 13 months (min-max: 0-60 months). The most frequent comorbidities among the patients were acute gastroenteritis, dehydration, and asthma frequently (Table 1). Among the eligible patients, 57,042 had inpatient records. We identified 641 patients in the database with at least one prescription record for palivizumab between April 2003 and August 2011. Of these, 358 (55.8%) were male and the median age at the time of their first exposure to palivizumab was 2 months old (min-max: 0-27 months old). The first injection of palivizumab occurred within the first 6 months of life in 90% of the patients. An overview of the number and proportion of adverse events recorded between April 2003 and August 2011 in the 641 patients who received palivizumab is shown in Table 2. Among patients with palivizumab, the number of patients with diagnosis records related to the digestive system, respiratory system, and skin occurred in 128, 445, and 248 patients, respectively, while the patients with records related to circulatory organs was relatively few.

Of all the adverse event categories, diarrhea, bronchitis, and eczema were most frequently reported. Upper respiratory infection was also frequent but the majority of RSV infections present as mild upper respiratory illnesses, thus the high incidence rate may be attributable to confounding by indication and diagnoses for prescription or examination. To estimate IRRs for 3 frequently reported adverse events, diarrhea, bronchitis, and eczema, patients who had a record of each adverse event were selected from the 70,771 patients. The number of adverse events during EPA, EPB and the corresponding exposure periods are described in Table 3. The numbers of events in the EPB were approximately 4 times higher for diarrhea and nearly 6 times higher for bronchitis and eczema compared to those in the EPA. The occurrence of diarrhea during the exposure periods was the same in the EPA and EPB, while events of bronchitis and eczema increased approximately 6 to 7 times in the EPB compared with the EPA. The median eligible period was about one week in the EPA and about one month in the EPB. The duration of eligible period and exposure period was expanded in the EPB.

The numbers of events per 6-month band are shown in Figure 2 and 3. Most primary events occurred within the first year and a half of life. Event occurrence from 6 to 12 months increased in patients with diarrhea and bronchitis when in the EPB, while the distribution of occurrence of eczema was similar for the two eligible periods. An increased number of multiple events occurred from 24 to 60 months for diarrhea and bronchitis.

The age-adjusted incidence rate ratios (IRR) for diarrhea, bronchitis, and eczema adverse events are shown in Table 4, stratified by adverse event categories and eligible periods. The IRRs of the 3 adverse events of diarrhea, bronchitis, and eczema were significant and varied greatly between two eligible periods. IRRs adjusted for age and seasonal effect were similar to IRR estimates simply adjusted for age, suggesting that the seasonal effect was small (data not shown).

3. DISCUSSION

In this study, we applied the self-controlled case-series method to investigate associations between palivizumab for children and adverse events based on the previous information such as package insert using an administrative database. Overall, this method was feasible with the national database [9], claims databases [10] and administrative databases such as the EBM provider and the assumptions required for this method [15] appeared to be satisfied in this study based on the observed data. On the other hand, the incidence rates of adverse events in children included in this study declined over time, indicating that the influence of handling of the eligible period on results can be substantial, and in fact the IRRs differed between the EPA and EPB in fact. Our findings suggest the importance of rigorously precise handling of ages and timings when this method is used.

This study demonstrated that the self-controlled case series method is particularly useful in pharmacoepidemiological studies of children using a database. First, the self-controlled case series method allowed us to adjust for the temporal effects of age on adverse events. Generally speaking, children are unlikely to have comorbidities, so age would be a major risk factor of most diseases. Furthermore, children tend to have fewer administrations of drugs, and bias due to time-dependent confounding related to medication is expected to be small. There was an inverse correlation between occurrence of events and age (Figure 2 and 3). Second, censoring due to death, a major source of bias in the self-controlled case series method, does not occur frequently in children. The assumption of the self-controlled case series method fails when the occurrence of an event does not alter the probability of subsequent exposure and events. The number of patients with independent and recurrent events was relatively high in Table 1 and Table 2, suggesting that this assumption could hold. Third, it is necessary to specify the first administration to extract new users of a targeted drug and this is particularly easy in a study of young children in which the number of new user is high. In this study, we extracted patients between 0 and 5 years of age, and we did not set a pre-period to identify new users of palivizumab and first event occurrences. The median age of their first exposure to palivizumab was 2 months (min-max: 0 to 27 months). Fourth, the method could retain good power in a relatively small population. The database used in this study contained information on about 70,000 patients from medium-sized hospitals, so the proportion of institutes with a neonatal intensive care unit may have been small and fewer patients were treated with palivizumab than in a real-life clinical setting. The IRRs in this analysis were significant, suggesting that an adequate sample was obtained from this population because of the intra-patient comparison. Finally, we were able to avoid selecting a control group, which is difficult in cohort studies and spontaneous reporting system.

Furthermore, we clarified that it is important to be rigorously precise about the handling of ages and timings. Specifically, we defined two types of eligible period, namely EPA and EPB. The EPB includes outpatient periods in addition to the EPA which only accounts for inpatient periods. The EPB was used as an eligible period because young children are likely to go to the same hospital in most situations. The median length of the EPA and EPB was about one week and one month, respectively, and the number of each adverse event increased when the period was expanded. On the other hand, the incidence rates declined over time (Figure 2 and 3). These results imply that the influence of the handling of eligible period on results can be substantial. As shown in Table 4, the IRRs in the EPA were much higher than those in the EPB. Theoretically, the EPB leads to greater accuracy and higher power than the EPA because of an increase in the number of event, so the EPB seems to be better from a statistical viewpoint. However, the choice between the EPA and EPB should be mainly based on clinical considerations about the difference in health conditions and medical environment of inpatients and outpatients. For example, if there is a potential for an effect modification between inpatients and outpatients, the true effects based on the EPA and EPB would be different. During the EPA, the patients stayed in hospital, and therefore treatment information was assumed to have been collected almost completely. Patients in hospital are also generally prone to have more diagnostic records or they could be more severe cases. The EPA analysis estimates the rate ratio for inpatients but the EPB analysis provides a weighted average of the two rate ratios in both the inpatient and outpatient situations. Such sensitivity to handling of inpatient and outpatient periods is a weak point of this method relative to cohort studies and we recommend that sensitivity analysis using different handling of age and timing is routinely performed.

Our analysis indicates elevated risks of adverse events of palivizumab; the estimated IRRs ranged from 3.00 to 102 for diarrhea, from 10.3 to 34.0 for bronchitis, from 16.9 to 53.9 for eczema. Only 2 studies have reported adverse events of palivizumab in comparison with a placebo group [16, 17]. In the IMpact-RSV study, diarrhea developed in 2 (0.4%) and 10 (1.0%) patients in the palivizumab and placebo groups, respectively (p=0.357), while the palivizumab cardiac study observed 3 (0.5%) patients with diarrhea in both of the palivizumab and placebo groups. Bronchitis and eczema developed in less than 3 patients in these studies. These frequencies of adverse events are, however, not comparable with the observations in this study given the differences in patient population (e.g. in- or outpatient and ethnicity), medical environment and methods for assessing adverse events. Therefore, it is difficult to discuss the usefulness of the self-controlled case series method based on comparisons with previous studies. Rather, these results should be interpreted in the context of potential sources of bias in a self-controlled case series study. Our analysis is “bidirectional”, that is, periods both before and after the first exposure were used. The bidirectional method is expected to be less susceptible to exposure-trend bias than the unidirectional method [18]. We selected the bidirectional method in this study because palivizumab was released in 2002 in Japan and its use probably increased between April 2003 and August 2011, the period covered by the database we used. However, if an adverse event of interest is fatal, occurrence of the event eliminates a child's future opportunity for exposure, yielding potential of overestimation of exposure effects on the event. Such bias, called immortal-time bias, can be eliminated if periods before the first exposure were not used [18]. It is not plausible, however, that the elevated risks of diarrhea, bronchitis and eczema are fully attributable to immortal-time bias since these adverse events are not fatal. Furthermore, the self-controlled case series method tends to have less exposure misclassification bias and time-varying confounding if exposures are brief [18].

Several study limitations warrant mention. First, the definitions of outcomes were based on disease names constructed for medical service fee and were not validated because the EBM provider is anonymized. In this study, occurrence of adverse events could better to be considered as occurrence of action related to adverse events. Second, patients are linked anonymously within each institute, so information on the outpatient status of each patient is restricted to a single institute. In this study, we extracted the period which covered all information or the period which patients were assume to go one hospital, resulting that inpatient period was short. Third, the strong temporal effects on adverse events in this study would be attributable to the growth of children, so our observation may not be generalized to studies in adult patients. Fourth, true IRRs for exposure to palivizumab are unknown. Finally, timeliness is a crucial aspect of drug safety but it is difficult to draw conclusion about the performance of the self-controlled case series method from this view point. However, standardization of the data structure would substantially effect for timeliness given that the most time-consuming process in this study was data handling.

4. CONCLUSION

The self-controlled case series method could be a useful tool in pharmacoepidemiological studies in children that use administrative databases but they should be interpreted as hypothesis-generating rather than confirmatory. Once detected, the safety signal should be analyzed in detail using pharmacological and biological information on drugs, molecular targets, and pathways. Careful consideration in the handling of inpatient and outpatient periods, including sensitivity analyses, is necessary because this method is within-individual comparison.

CONFLICT OF INTEREST

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Table 1. Background characteristics of patients extracted from the database and patients treated with palivizumab

	Extracted patients	Patients treated with palivizumab
No. of patients	70771	641
No. of male (%)	37571 (53.0)	358 (55.8)
Months from registration to the last record or the 5th birthday (Median, Min-Max)	13, 0-60	18, 0-58
No. of patients with inpatient records (%)	57042 (80.6)	546 (85.2)
Comorbidities		
Acute gastroenteritis (%)	15371 (21.7)	146 (22.8)
Dehydration (%)	14035 (19.8)	160 (25.0)
Asthma (%)	13402 (18.9)	234 (36.5)
Allergic rhinitis (%)	11714 (16.6)	165 (25.7)
Pharyngitis (%)	11275 (15.9)	51 (8.0)
Asthmatic bronchitis (%)	10642 (15.0)	160 (25.0)
Acute pharyngitis (%)	6888 (9.7)	29 (4.5)
Diaper dermatitis (%)	6309 (8.9)	157 (24.5)
Cerumen impaction (%)	5360 (7.6)	76 (11.9)
Costiveness (%)	4695 (6.6)	329 (51.3)

Table 2. Occurrence of adverse events among 641patients treated with palivizumab

AE category	No. of patients	(%)
Nervous system		
Febrile convulsion	34	5.3
Twitch	16	2.5
Subtotal	44	6.9
Circulatory		
Cardiac dysrhythmia	2	0.3
Bradycardia	4	0.6
Tachysystole	5	0.8
Subtotal	7	1.1
Digestive system		
Diarrhea	79	12.3
Vomiting	70	10.9
Subtotal	128	20.0
Respiratory system		
Stridor	2	0.3
Dyspnea	77	12.0
Rhinitis	40	6.2
Rhinorrhea	1	0.2
Upper respiratory infection	358	55.9
Pneumonia	97	15.1
Viral pneumonia	41	6.4
Bacterial pneumonia	67	10.5
Bronchiolitis	18	2.8
Bronchitis	314	49.0
Subtotal	445	69.4
Vasculature		
Thrombopenia	11	1.7
Dermal system		
Anthema	31	4.8
Eczema	238	37.1
Subtotal	248	38.7
Other		
Fever	46	7.2
Pain	1	0.2
Viral infection	15	2.3
Viral infection (including RSV infection)	493	76.9
Tympanitis	78	12.2

Table 3. Occurrence of adverse events and duration within eligible and exposure periods

AE category	No. of patients*	No. of Male (%)	Eligible period**			Exposure period**		
			No. of first event	No. of multiple events	Median (min-max)	No. of first event	No. of multiple events	Median (min-max)
EPA								
Diarrhea	664	365 (55.0)	664	670	6 (2-907)	15	16	83 (4-345)
Bronchitis	2294	1249 (54.4)	2294	2298	5 (2-1213)	15	15	35 (1-279)
Eczema	732	443 (60.5)	732	744	6 (2-1213)	15	18	58 (1-345)
EPB								
Diarrhea	2356	1297 (55.1)	2356	2686	25 (2-1411)	20	23	217 (30-527)
Bronchitis	12009	6418 (53.4)	12009	14417	31 (2-1723)	104	108	175 (7-609)
Eczema	4332	2319 (53.5)	4332	4596	34 (2-1568)	87	94	156 (1-553)

*Patients who had a record of the adverse event (diarrhea, bronchitis, or eczema) during the eligible period.

**The EPA eligible period covered first-time inpatient periods of more than 3 continuous days. The “EPB” eligible period included “lost to follow-up” cases and was regarded as a continuous period in cases where the interval between visits was below the 75th percentile of the interval between visits for patients with the same diagnosis. The exposure period is defined as a period from the first prescription for palivizumab within each eligible period to 30 days after the last prescription date within the continuous period.

Table 4. Age-adjusted incidence rate ratios for the associations between palivizumab and adverse events

	First event only		Multiple events	
	EPA	EPB	EPA	EPB
AE category	IRR(95%CI)	IRR(95%CI)	IRR(95%CI)	IRR(95%CI)
Diarrhea	102 (31- 334)	15.7 (7.02-35.2)	66.8 (23.9-187)	3.00 (1.66-5.44)
Bronchitis	34.0 (14.6-79.7)	14.2 (10.3-19.6)	26.6 (11.7-60.8)	10.3 (8.04-13.2)
Eczema	53.9 (21.7-134)	27.0 (18.0-40.4)	47.3 (21.0-107)	16.9 (12.2-23.4)

*IRR: Incidence Rate Ratio, CI: Confidence Interval

FIGURE LEGENDS

Fig. 1. Pictorial representation of the self-controlled case series approach. Figure illustrates single individual prescribed palivizumab during the eligible period. All patients included in analysis had at least one record of diagnosis of interest with or without prescription records of the drug. Incident outcomes can occur during the baseline or exposed period.

Fig. 2. Pattern of primary events in the eligible periods. The numbers of “first diagnosed” events that occurred in the two types of eligible periods were compared in 6-month bands.

Fig. 3. Pattern of multiple events in the eligible periods. The numbers of “multiple” events that occurred in the two types of eligible periods were compared in 6-month bands.

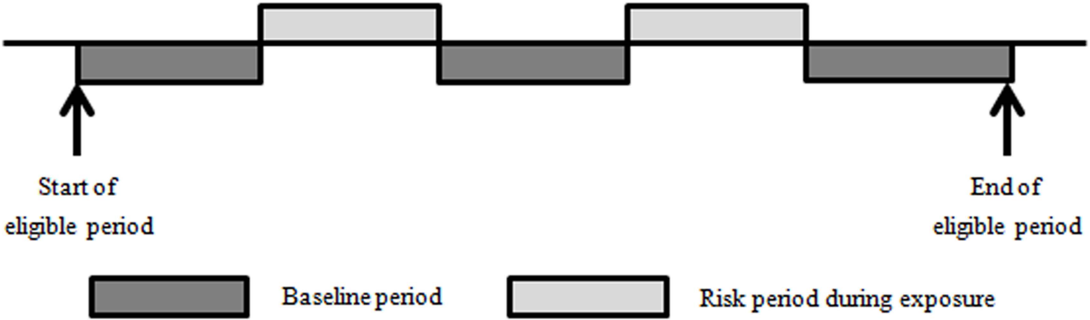

Fig 1. Ueyama, H. *et al.*

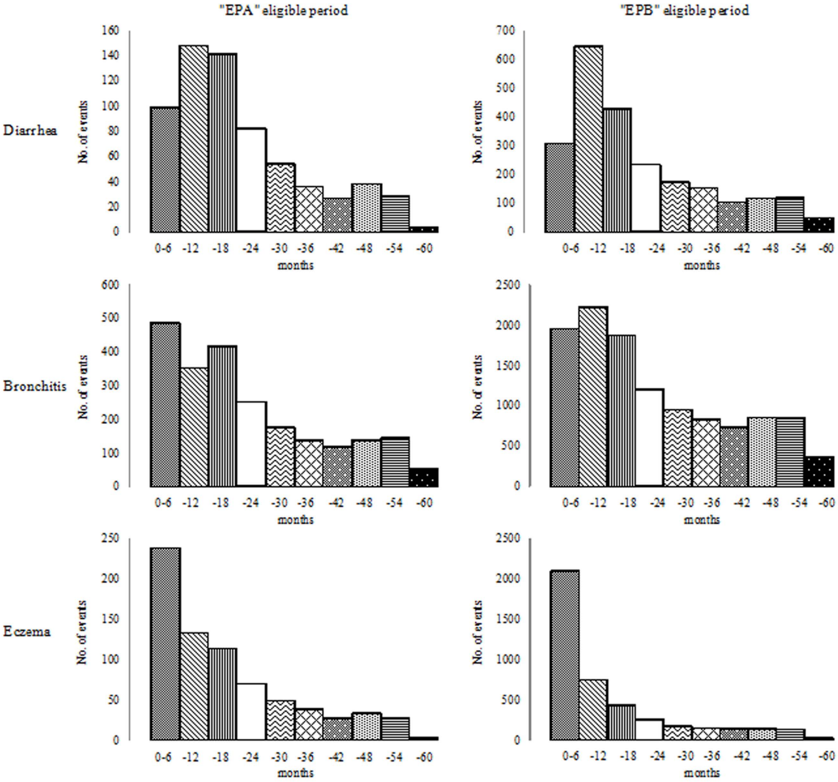

Fig 2. Ueyama, H. *et al*.

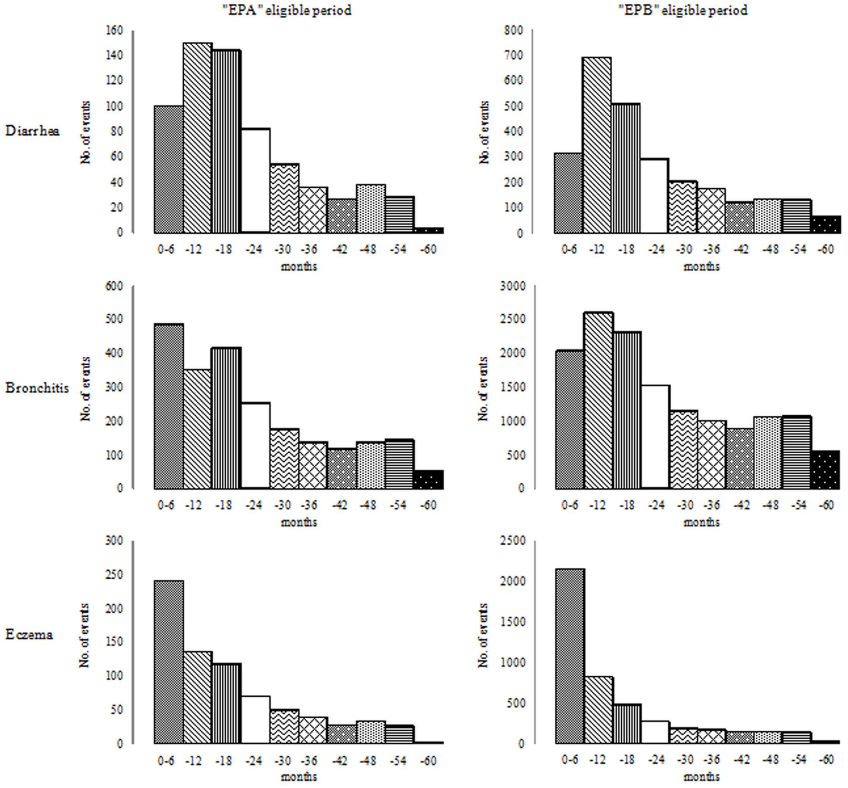

Fig 3. Ueyama, H. *et al*.