

Original Article

Survey of hospitalization for respiratory syncytial virus in Nagano, Japan

Short title: Survey of RSV hospitalization

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Abstract

Background: Respiratory syncytial virus (RSV) infection is one of the major causes of hospitalization of children during the winter months in Nagano, Japan. This investigation was conducted to understand the details of hospitalized patients infected with RSV in Nagano.

Methods: The study used a questionnaire to survey hospitals who treated children for RSV infection in the pediatric wards of 11 major hospitals in Nagano.

Results: Between April 2016 and March 2017, 438 patients were hospitalized with RSV infection in the 11 participating hospitals. The mean gestational age at birth was 38 weeks 2 days. Average birthweight was 2,834 g. The ratio of hospitalized patients with RSV infection to the total number of hospitalized patients was, on average, 7.0% in the second-level hospitals. Despite the use of palivizumab, six patients were hospitalized.

Conclusions: The rate of hospitalization for RSV was similar across each of the second-level hospitals in Nagano. Patients hospitalized after palivizumab treatment had received palivizumab only a few times during the season when infection rates were highest. Palivizumab is therefore advised prior to the outbreak initiation month.

Key words hospitalization, infection, palivizumab, respiratory syncytial virus, survey.

Palivizumab has been found to reduce the rate of hospitalization for respiratory syncytial virus (RSV) in premature babies with chronic lung disease (CLD) or congenital heart disease (CHD) in Japan.¹⁻³ Since 2013, palivizumab has also been approved for patients with Down syndrome or immunodeficiency disorders in Japan to decrease the number of severe RSV cases.⁴ Similar to other prefectures, RSV infection is one of the most common/frequent childhood diseases requiring hospitalization during the winter in Nagano, Japan. The most severely affected patients are transferred to Nagano Children's Hospital or Shinshu University Hospital for advanced medical treatment. In this study, we conducted a survey of hospitalized patients infected with RSV in Nagano, Japan and assessed palivizumab treatment.

Methods

We surveyed 11 major hospitals in Nagano that treated children for RSV infection in the pediatric wards between April 2016 and March 2017. Patient information was obtained from questionnaires conducted at two advanced care hospitals (Nagano Children's Hospital and Shinshu University Hospital) and nine second-level hospitals (Hokushin General Hospital, Japanese Red Cross Society

Nagano Hospital, Shinonoi General Hospital, Shinsyu Ueda Medical Center, Saku Central Hospital, Matsumoto Medical Center, Japanese Red Cross Society Suwa Hospital, Ina Central Hospital, and Iida Municipal Hospital). All patient information was collected anonymously. The study was approved by the ethics committee of Nagano Children's Hospital. The following information was collected in the survey: ratio of RSV patients who were hospitalized, age, sex, gestational age at birth, birthweight, underlying disease (CLD, CHD, respiratory tract disease, immunodeficiency, chromosomal anomalies, multiple births, other), presence of a sibling, the month the patient was admitted, age (months) at hospital admission, treatment while hospitalized, outcome, hospital transfer, palivizumab treatment, and the diagnostic method used (RSV rapid test or symptoms only).

We excluded four patients from the study who had only a diagnosis of symptoms. The rate of hospitalization of RSV-infected patients admitted to the second-level hospitals was calculated by considering the total number of patients hospitalized for RSV in each institution during the survey period (April 2016–March 2017), not including the number of hospitalized patients in the neonatal intensive care units (NICU) at each institution.

Results

A total of 438 children were hospitalized with RSV infection. During the analysis, we ensured that any patient who was transferred from a second-level hospital to a third-level hospital ($n = 8$) during the survey period was not included in the survey twice. There were 420 hospitalizations in second-level hospitals due to RSV during the survey period (Table 1). The ratio of RSV-infected patients to the total number of hospitalized patients at each institution, not including NICU inpatients, was

7.0%, averaged across the participating institutions. There was little variation in the ratio between hospitals. Twenty-three patients were hospitalized at Nagano Prefectural Children's Hospital, including hospital transfers from the research institute (n = 7), hospital transfers from institutions outside of the investigation (n = 6), and direct hospitalization to Nagano Prefectural Children's Hospital (n = 10). One patient was transferred to Shinshu University Hospital from the investigation hospital. The average birthweight of RSV-infected hospitalized patients was 2,834 g (range, 388–3,926 g; unknown, 25.3%; Fig. 1a), and the mean gestational age at birth was 38 weeks and 2 days (range, 22 weeks and 1 day–42 weeks and 3 days; unknown, 25.8%; Fig. 1b). Of the patients included in the analysis, 34 were born prematurely (7.8%). The majority of the premature patients were infected at ages beyond the adaptive age of palivizumab. Average patient age at admission was 1 year and 4 months (range, 12 days–9 years and 6 months; Fig. 2). Children aged <24 months accounted for 80.1% of the present patients. Similarly, children aged <12 months comprised 50.9% of the subjects, while those who were 1 month of age comprised 5.3% of the subjects.

Table 2 lists the sex, presence of a sibling, the existence of any underlying conditions, whether the patient received palivizumab, the treatment, and the outcomes for all of the RSV-infected patients surveyed. The sex of the patient did not appear to be a factor that increased or decreased the likelihood of the individual contracting RSV, and 67.1% of the inpatients had siblings. An underlying disease was identified in 74 of cases.

The majority of the patients with an underlying disease had respiratory tract disease (Table 3), predominantly asthma. In descending order of occurrence,

respiratory tract disease was followed by chromosomal anomalies, CHD, and CLD. We used two definitions of CLD: CLD28 or CLD36, regardless of the use of home oxygen therapy.

Palivizumab was used in six of the patients. A total of 69.2% of the patients received oxygenation, and 1.8% required respiratory management.

The number of patients admitted for treatment of RSV varied throughout the year. The number of RSV-infected patients admitted to the hospitals increased from October to December of 2016 (Fig. 3), consistent with a survey conducted by Nagano Prefecture in 2016.⁵

The majority of the patients surveyed were treated successfully and were discharged, including 10 patients who were transferred to a local hospital from Nagano Children's Hospital. There were no cases that resulted in death or sequelae. Most of the patients did not qualify to receive palivizumab. Seven patients who had met the criteria for receiving palivizumab were infected with RSV before receiving palivizumab. There were six RSV-infected patients who had already received palivizumab, but they had been administered only a few times in the season during which palivizumab is recommended.

Discussion

Patient age during the month of admission and gestational age were similar to those in a national survey by Kusuda *et al.*⁶ Many of the patients who were hospitalized after palivizumab treatment have been described.⁷⁻⁹ In the present cohort, six patients were hospitalized after palivizumab treatment (premature, n = 3; congenital heart disease, n = 3; Table 4). These patients were given palivizumab only a few times. The purpose of palivizumab was to prevent worsening of the

condition. No patient required intubation, and all were discharged. Palivizumab-resistant RSV infections have been reported abroad,¹⁰ but no reports exist in Japan. More than two palivizumab injections during the RSV season have been shown to raise the trough blood level upon pharmacokinetic inspection.¹¹

Based on the present survey results and the aforementioned report, multiple i.m. injections of palivizumab appear to be needed to reach a level that can protect the individual. A previous study also reported that patients were frequently treated intensively when they were infected with RSV and had low palivizumab blood levels.¹²

In conclusion, the rate of hospitalization for RSV was approximately the same across each of the second-level hospitals in Nagano. The patients hospitalized with RSV infection had been given palivizumab only a few times during the season, during which infection rates were highest. Palivizumab is recommended 1 or 2 months prior to the outbreak initiation month.

Acknowledgments

We would like to express our sincere gratitude to the individuals enrolled in the survey. Representative physicians include Yozo Nakazawa, Takehiko Hiroma, Masanori Sato, Takenori Natsume, Takefumi Ishida, Fumio Morohashi, Ei Shimazaki, Yuta Maruyama, Tatsuya Yoda, Yasushi Iwasaki, Kenji Kurata, Atsushi Baba, Tatsuya Kinoshita, Eri Okura, Yousuke Shima, and Yūka Miyajima.

Disclosure

The expendables were a gift from the manufacturer. The authors declare no conflicts of interest.

Author contributions

T.Y. and T.N. conceptualized and designed the study, carried out the data analysis, and drafted the initial manuscript. TN critically reviewed and revised the manuscript. Both authors read and approved the final manuscript.

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Fig. 1 (a) Birthweight and (b) gestational age vs no. hospitalizations for respiratory syncytial virus infection.

Fig. 2 Age at time of hospital admission for respiratory syncytial virus infection.

Fig. 3 Time of hospitalization for respiratory syncytial virus infection vs (–) a Nagano infection surveillance report in 2016.⁵

Table 1 Pediatric hospitalizations for RSV infection

Second-level hospitals	No. hospitalizations for RSV	RSV/total hospitalizations (%) [†]	No. transfers to advanced hospitals
Overall	420	7.01	8
1	41	6.60	2
2	39	6.80	1
3	36	8.10	-
4	83	5.82	-
5	48	6.00	1
6	40	7.40	1
7	39	8.20	-
8	53	8.30	1
9	41	8.70	2

[†]Neonatal intensive care unit patients excluded. RSV, respiratory syncytial virus.

Table 2 RSV inpatient background

	No. patients	%
Sex		
Male	236	53.9
Female	202	46.1
Siblings		
Yes	294	67.1
No	119	27.2

Unknown	25	5.7
Underlying disease [†]		
Yes	74	16.9
No	364	83.1
Palivizumab		
Yes	6	1.4
No	432	98.6
Treatment [‡]		
Oxygen	303	69.2
β 2 adrenergic receptor agonists	263	60.1
DPAP	5	1.1
Nasal high flow	17	3.9
Respirator	8	1.8
Outcome		
Discharged	426	97.3
Transfer to advanced hospital	8	1.8
Transfer between general hospitals	3	0.7
Hospitalized with other disease	1	0.2
Sequelae	—	—
Death	—	—

[†]Conditions that were not associated with the worsening of RSV infection (e.g. iron-deficiency anemia) were excluded. [‡]Treatment includes a double item. DPAP, directional positive airway pressure; RSV, respiratory syncytial virus.

Table 3 Underlying disease

	No. patients	% total patients
Respiratory tract disease	31	7.08
Chromosomal anomalies	12	2.74
CHD	12	2.74
CLD	9	2.05
Multiple births	7	1.60
Immunodeficiency	–	–
Other [†]	18	4.11
Total [‡]	75	16.89

[†]West syndrome, porencephaly, lissencephaly, cerebral hemorrhage, neuroblastoma, brain tumor, hypoxic encephalopathy, and nephrosis. [‡]Duplication excluded. CHD, congenital heart disease; CLD, chronic lung disease.

Table 4 Hospitalizations for RSV infection despite palivizumab treatment

Sex	Birthweight (g)	Gestational age at birth (weeks)	Age at hospital admission (months)	Month of hospital admission	Underlying disease	Sibling	Oxygen	Mechanical ventilation
F	1495	31	2	12	–	Yes	No	No
M	1587	31	2	10	–	No	No	No

M	2452	34	2	2	–	Yes	Yes	No
F	3118	36	14	11	CHD	Yes	Yes	No
F	2722	38	14	9	CHD	Unkno wn	Yes	No
F	3280	39	21	11	CHD	Yes	No	No

CHD, congenital heart disease; RSV, respiratory syncytial virus.

Fig.1 Birth weight

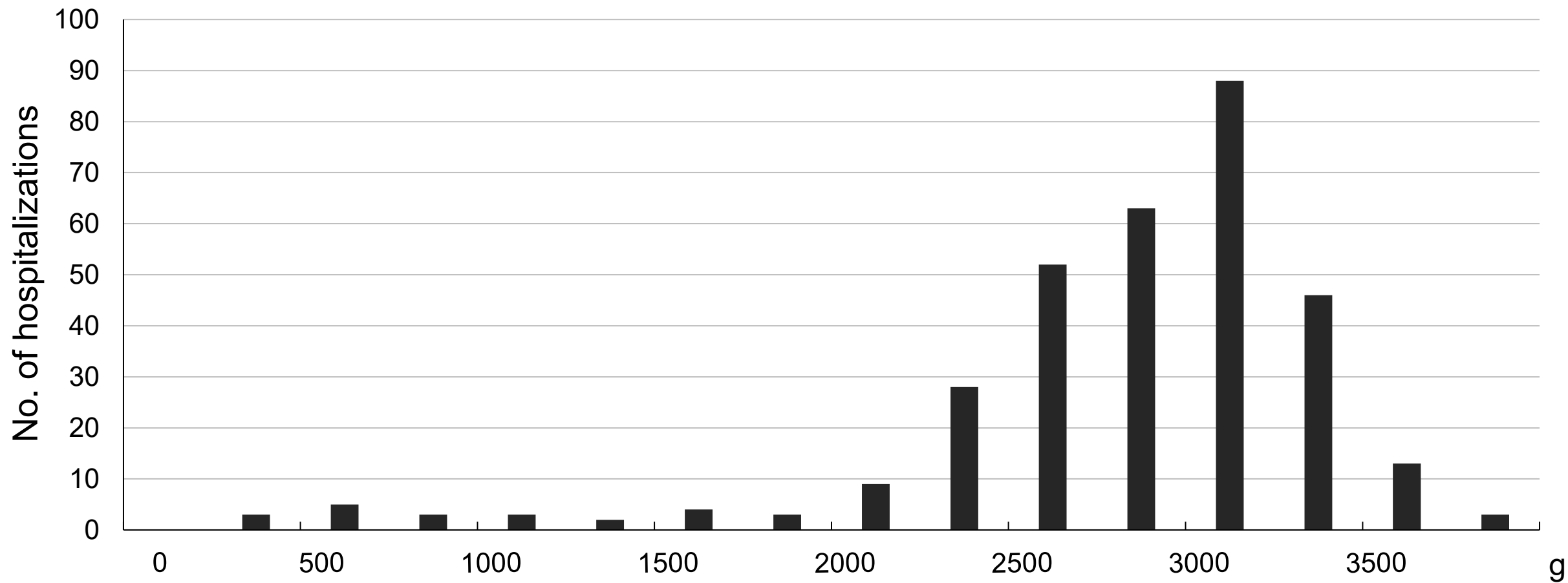


Fig.2 Gestational age

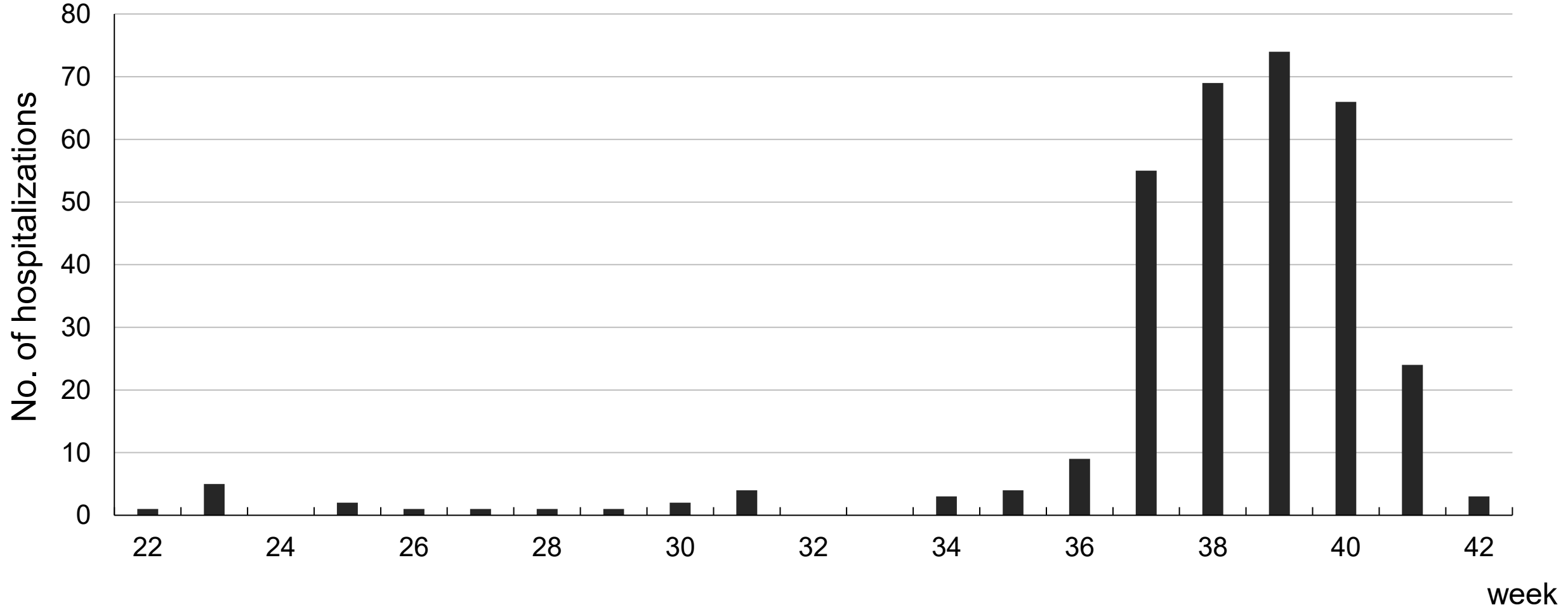


Fig.3 Age at the RSV infection

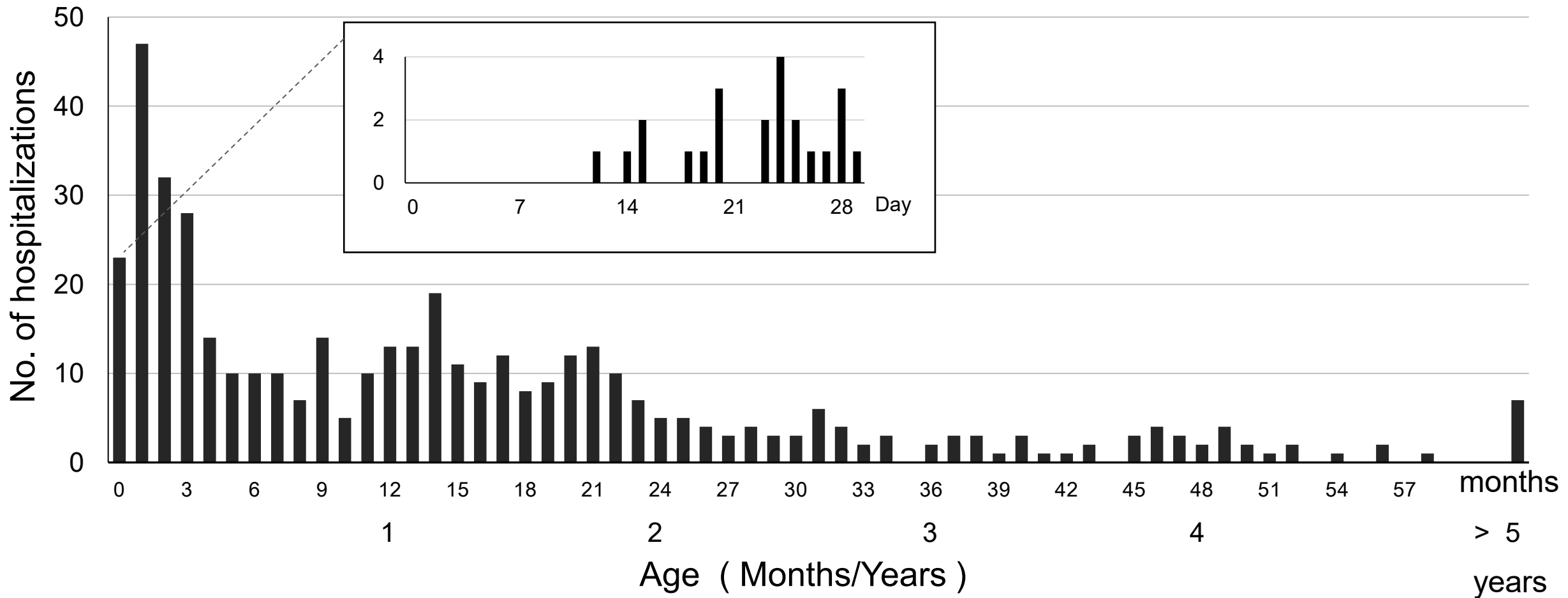
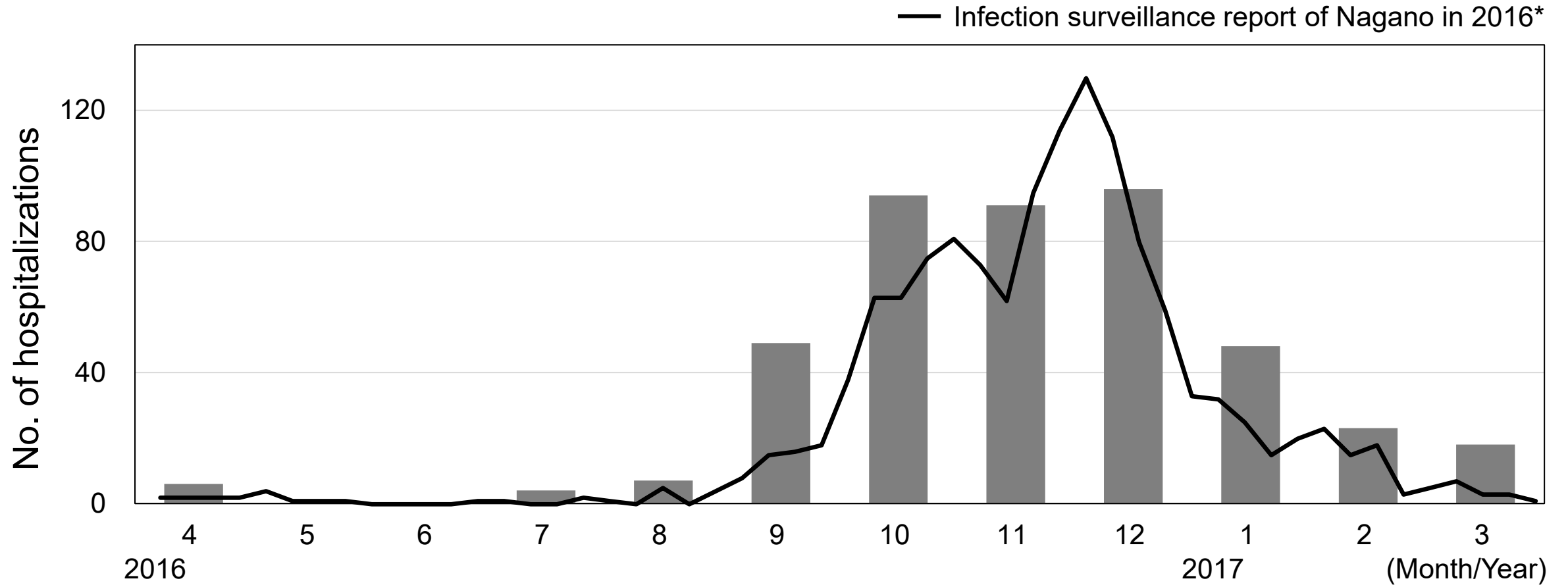


Fig.4 Months at hospital admission



*Obtained from the website of Nagano Prefecture.