

Epidemiology of RSV infection in Japan: A nationwide claims database analysis

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INTRODUCTION

Respiratory syncytial virus (RSV) is a major global cause of hospitalization for bronchiolitis and pneumonia in infancy. Among children younger than 5 years, an estimated three million RSV-related hospitalizations and 60,000 deaths occur annually. Very young children under six months of age account for nearly half of these hospitalizations and deaths in the world.^{1,2}

RSV is highly communicable, transmitted via respiratory droplets, with humans as the only known reservoir. It is estimated that 50% of infants become infected during their first year of life, and almost 100% by their second year. Lifetime immunity is not achieved following these initial infections.¹

In Japan, RSV infection is defined as a Category V infectious disease according to the Infectious Diseases Control law. Category V infectious diseases are monitored under the National Epidemiology Surveillance of Infectious Diseases (NESID) Programme. RSV infection is reported from the paediatric sentinel surveillance system. The publicly available data however, especially on patient age in months, clinical features, resource use and outcomes, are limited.³

OBJECTIVE

This study aimed to describe the epidemiology and clinical features of RSV infection in Japan utilising a nationwide healthcare claims database.

METHODS

Study design and data sources

- For the period 01-Jan-2017 to 31-Dec-2018, this study had a cross-sectional design for describing patient characteristics, resource use, clinical outcomes, and seasonality, and a retrospective cohort design for estimating incidence. The Japanese Medical Data Center (JMDC) database and the Statistics Bureau of Japan (SBJ) were used as data sources.^{4,5}
- The JMDC database provides inpatient, outpatient and pharmacy claims from health insurance associations in Japan through a panel of approximately seven million beneficiaries since 2005 to the present, which accounts for about 5.5% of the entire Japanese population. The database includes all insured persons consisting of employees and their insurance-covered family members aged ≤74 years.

METHODS (continued)

Study population

- The RSV population consisted of patients aged <24 months of age having at least one claim with an RSV diagnosis, during 01-Jan-2017 to 31-Dec-2018, inclusive. The index date corresponded to the first RSV diagnosis claim observed during the inclusion period.
- The incidence-eligible population consisted of all insured individuals born during the period 01-Jan-2017 to 31-Dec-2018 and who were aged <24 months.
- For each study population, outpatient and inpatient subgroups were studied, which are not mutually exclusive, as some patients could be counted in both.

Study variables

- An RSV patient was identified based on having at least one claim with an RSV diagnosis during the study period. For seasonality, an RSV case was defined as having at least one RSV diagnosis claim in a particular calendar month.
- Patients' age was defined in months at inclusion. RSV risk factor status and associated disease were defined based on having at least one claim associated with a diagnosis for any of the RSV risk factors or associated diseases of interest.
- RSV-associated clinical outcomes included hospitalizations, ICU admissions, ventilator use and death during the hospitalization while resource use included number of hospitalisations, days of hospital stay and average length of stay.

Statistical analyses

- Descriptive analyses of patient characteristics, resource use and clinical outcomes were conducted using standard descriptive statistics only for patients 0 to 23 months of age.
- Extrapolation of results from the JMDC claims data analyses to the Japanese population was performed by applying the age- and sex-specific proportions of the relevant outcome in the JMDC claims data to the corresponding age-sex subgroup of the Japanese population.
- The RSV (all infections/inpatient) incidence was calculated as the number of patients with an RSV infection during the study period divided by the total time at risk of RSV infection. Time at risk of RSV infection was defined as the time to the first RSV infection registered or the end of follow-up whichever comes first. End of follow-up occurred at the first of any of the following: death, 23 months of age, loss to follow-up, end of study period.
- To describe seasonality, numbers of RSV cases overall and by subgroup were tallied per calendar month.

RESULTS

Demographic and clinical characteristics (JMDC database)

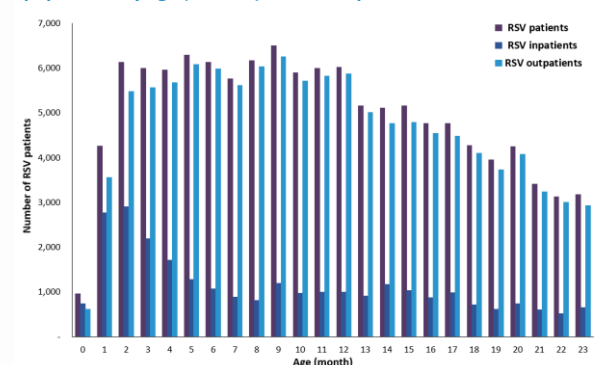
- In the JMDC database, 9,711 and 8,509 children <24 months of age had RSV-related diagnoses in 2017 and 2018, respectively. Of these, 2,473 (25%) and 2,083 (24%) were hospitalized (Table 1).
- Fifty percent of all RSV patients were aged 11 months or younger, with more than half being boys. Hospitalized RSV patients were younger on average than patients treated in an outpatient setting. Only 10% of all children <24 months of age who were hospitalized due to RSV infection had specific risk factors (prematurity, bronchopulmonary dysplasia, Down's syndrome, chronic heart disease, immunodeficiency) (Table 1).

	2017			2018		
	All (n=9,711)	Outpatients (n=9,183)	Inpatients (n=2,473)	All (n=8,509)	Outpatients (n=8,055)	Inpatients (n=2,083)
Male (n, %)	5,347 (55.1)	5,073 (55.2)	1,380 (55.8)	4,654 (54.7)	4,409 (54.7)	1,167 (56.0)
Age mean (SD)	11.1 (6.3)	11.2 (6.3)	9.4 (6.8)	10.9 (6.3)	10.9 (6.2)	8.9 (6.8)
Age median	11	11	8	10	10	8
Any RSV risk factor (n, %)	651 (6.7)	588 (6.4)	229 (9.3)	621 (7.3)	566 (7.0)	214 (10.3)
Prematurity	356 (3.7)	318 (3.5)	123 (5.0)	327 (3.8)	297 (3.7)	112 (5.4)
BPD	12 (0.1)	10 (0.1)	6 (0.2)	10 (0.1)	10 (0.1)	4 (0.2)
Down's syndrome	25 (0.3)	23 (0.3)	12 (0.5)	31 (0.4)	26 (0.3)	14 (0.7)
CHD	275 (2.8)	249 (2.7)	98 (4.0)	269 (3.2)	244 (3.0)	93 (4.5)
Immune deficiency	47 (0.5)	40 (0.4)	20 (0.8)	59 (0.7)	53 (0.7)	29 (1.4)

Extrapolated to all Japan: number and age distribution

- When extrapolated to the entire Japanese population, 138,059 and 119,205 RSV-related diagnoses and 33,355 and 27,339 RSV-associated hospitalizations were estimated in Japan in 2017 and 2018, respectively.
- Infants less than six months of age accounted for between 39% (2017) and 42% (2018) of total hospitalizations for RSV. A peak in RSV hospitalizations was observed at age 2 months (Figure 1).

Figure 1. Estimated number of RSV patients in the Japanese population by age (months) and in/outpatient status for 2018



RSV-associated clinical outcomes

- In hospitalized children (<24 months), about 7% (5.8% in 2017; 7.1% in 2018) required mechanical ventilation and about 0.1% were admitted into the ICU. Of those who used a ventilator, about 50% were younger than 6 months (Table 2).
- About twenty percent of hospitalized patients less than one year of age experienced dehydration, and more than 10% of those younger than 6 months had acute respiratory failure. Bronchial asthma, acute bronchitis, asthmatic bronchitis were also consistently observed in the ten most frequently occurring RSV-associated diseases.

Age (months)	All*	0 to 2	3 to 5	6 to 11	12 to 23
RSV hospitalisations	27,339	6,405	5,184	5,945	9,804
ICU admissions	15	15	0	0	0
Ventilator use	1,950	453	522	696	279
RSV mortality	0	0	0	0	0

* 0 to 23 months

RSV hospitalization rate and RSV incidence (JMDC database)

- Among children <2 years in the JMDC population from 2017 to 2018, the incidence of RSV in the inpatient or outpatient setting was 85 per 1,000 patient-years. The incidence of hospitalized RSV was 37.3 per 1,000 patient-years for 0 to 2 months and 27.6 and 23.2 per 1,000 patient-years for all children <12 and <24 months, respectively (Table 3).

Age (months)	0 to 2	0 to 5	0 to 11	0 to 23	
All	No. of RSV infections	1,845	4,897	9,386	12,546
	Total PY	29,121	57,220	102,236	147,183
	Incidence per 1,000 PY (95% CI)	63.4 (60.5 - 66.3)	85.6 (83.2 - 88.0)	91.8 (90.0 - 93.7)	85.2 (83.8 - 86.7)
Inpatient	No. of RSV infections	1,087	2,040	2,890	3,583
	Total PY	29,146	57,592	104,641	154,174
	Incidence per 1,000 PY (95% CI)	37.3 (35.1 - 39.5)	35.4 (33.9 - 37.0)	27.6 (26.6 - 28.6)	23.2 (22.5 - 24.0)

Hospitalizations and length of stay (JMDC database)

- In the JMDC database, patients 0 to 23 months of age experienced 2,123 RSV-related hospitalizations in 2018 and 2,511 in 2017, including multiple admissions. On the average, patients stayed for about one week in the hospital across age groups and study periods (Table 4).

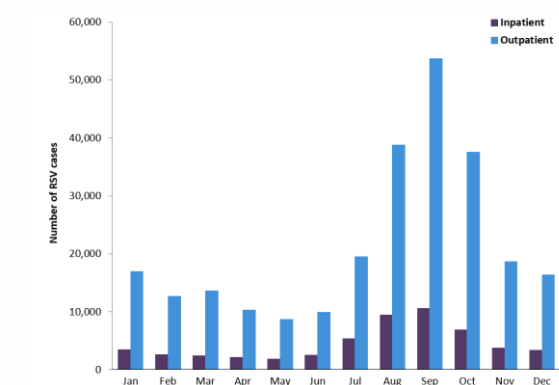
Age group (months)	0 to 2		3 to 5		6 to 11		12 to 23		
	2017	2018	2017	2018	2017	2018	2017	2018	
Total RSV inpatients	514	481	474	426	576	472	979	771	
Number of hospitalizations	516	484	447	398	569	467	979	774	
Length of hospital stay (days)									
	Mean	7.4	7.0	6.2	6.7	6.5	6.8	6.1	6.5
	Median	6	6	5	5	6	6	5	6

(For hospitalizations across age groups, the number of hospitalizations is counted as one, but patients are counted separately.)

Seasonality of RSV infections

- Extrapolating to the Japanese population, the 2017 and 2018 seasonality patterns were similar. The highest number of RSV cases, for both 2017 and 2018, were in September, which was confirmed via sensitivity analysis (Figure 2).

Figure 2. Estimated numbers of RSV cases in the Japanese population for 2018, by calendar month



CONCLUSIONS

- This study suggests that 138,059 and 119,205 RSV-related diagnoses and 33,355 and 27,339 RSV-associated hospitalizations occurred in Japan in 2017 and 2018.
- Ninety percent of children <24 months of age hospitalized with RSV infection did not have a recognized underlying medical condition.
- 3 to 4 out of every 100 Japanese children aged <6 months were hospitalized for RSV. Infants less than six months of age accounted for 39% (2017) to 42% (2018) of all RSV hospitalizations.
- The peak of hospitalizations for RSV infection occurred at 2 months of age.
- About 7% of children <24 months hospitalized for RSV infection used mechanical ventilation. Of those who used a ventilator, roughly 40% were younger than 6 months.
- About twenty percent of hospitalized patients less than one year of age experienced dehydration, and more than 10% of those younger than 6 months had acute respiratory failure.
- Current peaks of RSV infections, for both 2017 and 2018, were in September.
- Novel and broad-based prevention strategies against RSV infection targeting young infants are needed in Japan.

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