A Retrospective Claims Study Characterizing the Association Between RSV Infection and Acute Otitis Media and Related Burden in Infants and Young Children≤5 years in Japan

Viktor Chirikov, PhD [1] ; Eric AF Simoes, MD [2]

1. OPEN Health, New York, NY, USA Contact: viktorchirikov@openhealthgroup.com
2. University of Colorado School of Medicine, Aurora, CO, USA

OPEN HEALTH

INTRODUCTION

- Acute otitis media (AOM) can occur in as many as 50% of children aged <5 years with respiratory syncytial virus (RSV) infection, it being one of the most common viruses associated with AOM.[1]
- While RSV prevention strategies are largely targeted at reducing the incidence of lower respiratory infection (LRI), reducing RSV-associated AOM may be plausible, given the success of PCV and influenza vaccines in demonstrating reductions in all-cause and vaccine-type AOM.
- Assessing RSV-associated AOM healthcare resource use and cost data would be valuable in documenting the baseline attributable costs from which the economic impact of prevention could be estimated, but no such data exist.[2]

OBJECTIVES

1. To characterize the proportion of RSV-associated uncomplicated and complicated AOM and associated economic burden compared to non-RSV controls.
2. To assess the impact of RSV on subsequent risk of AOM incidence and associated preventable healthcare resource utilization and costs.

METHODS

Study design and data source

- The study employed a longitudinal, retrospective, observational design using national employment-based medical claims from the Japan Medical Data Centre Database (JMDC).
- The JMDC was used to identify a total of 113,529 infants between February 1, 2011- January 31, 2016 and followed through December 31, 2017.
- The study cohort was derived from previously constructed longitudinal matched birth cohorts, where RSV children were matched 1:2 to non-RSV controls based on calendar year and quarter of birth, and synthetic index date of RSV diagnosis was assigned among the controls.[3]

Analysis

- Four sub-cohorts were created with respect to the timing of RSV diagnosis/index:
  I. RSV-infected without AOM within 30 days of RSV (N= 14,639),
  II. RSV-infected with uncomplicated AOM within 30 days of RSV (N= 1,885)
  III. RSV-infected with complicated AOM within 30 days of RSV (N= 498)
  IV. Controls without RSV within 30 days of index (N=96,507)
- Multivariable logistic regression modeled the odds of AOM in the 30 days post-index.
- AOM-related healthcare visits and AOM-associated costs were described over 36 months since RSV diagnosis/index and modeled using longitudinal Poisson and gamma multivariable regressions.

RESULTS

Patient groups

- Children were grouped according to whether the first RSV diagnosis occurred in the first (within 12 months), second (13 to 24 months), and third or later chronological year (24-60 months) following birth.
- Additionally, children were grouped into one of the following subgroups by gestational age: preterm (≤34 weeks of gestational age [GA]); late preterm (35-36 weeks); and term (≥37 weeks).
- Among 113,529 infants, 17,022 (15%) were ever diagnosed with RSV. Among those with an RSV diagnosis, N=498 (2.9%) had a complicated AOM and N=1,885 (11.1%) had an uncomplicated AOM within 30 days of their first RSV diagnosis.
  - Patients with complicated AOM within 30 days of RSV had higher health risk at birth (more had chronic lung disease (5.4%) and congenital heart disease (4.0%), which was at least two-fold higher than those with uncomplicated or without AOM cohorts.
  - Only 56 children with a preterm birth ever had an AOM within 30 days post-RSV

AOM within 30 days of RSV diagnosis/index

- RSV-associated AOM was the highest (~20%, of which 4-5% complicated AOM) among RSV diagnosed cohorts with an index in Year 2 **(Figure 1)**
- RSV-associated AOM was less prevalent among cohorts diagnosed with RSV in index Year 3 and later years (12.5% preterm, 14% late preterm, 18% term) and Year 1 (less than 10%) **(Figure 1)**
- The percentage of AOM in RSV diagnosed patients that was not explained by prior history of AOM was around 5-7% in Year 1 and 10-11.5% in Year 2 and Year 3-5, depending on level of prematurity.

Figure 1. RSV associated AOM by year of RSV diagnosis cohort and prematurity

Percentage of AOM out of all RSV cases, by chronological year since birth and prematurity
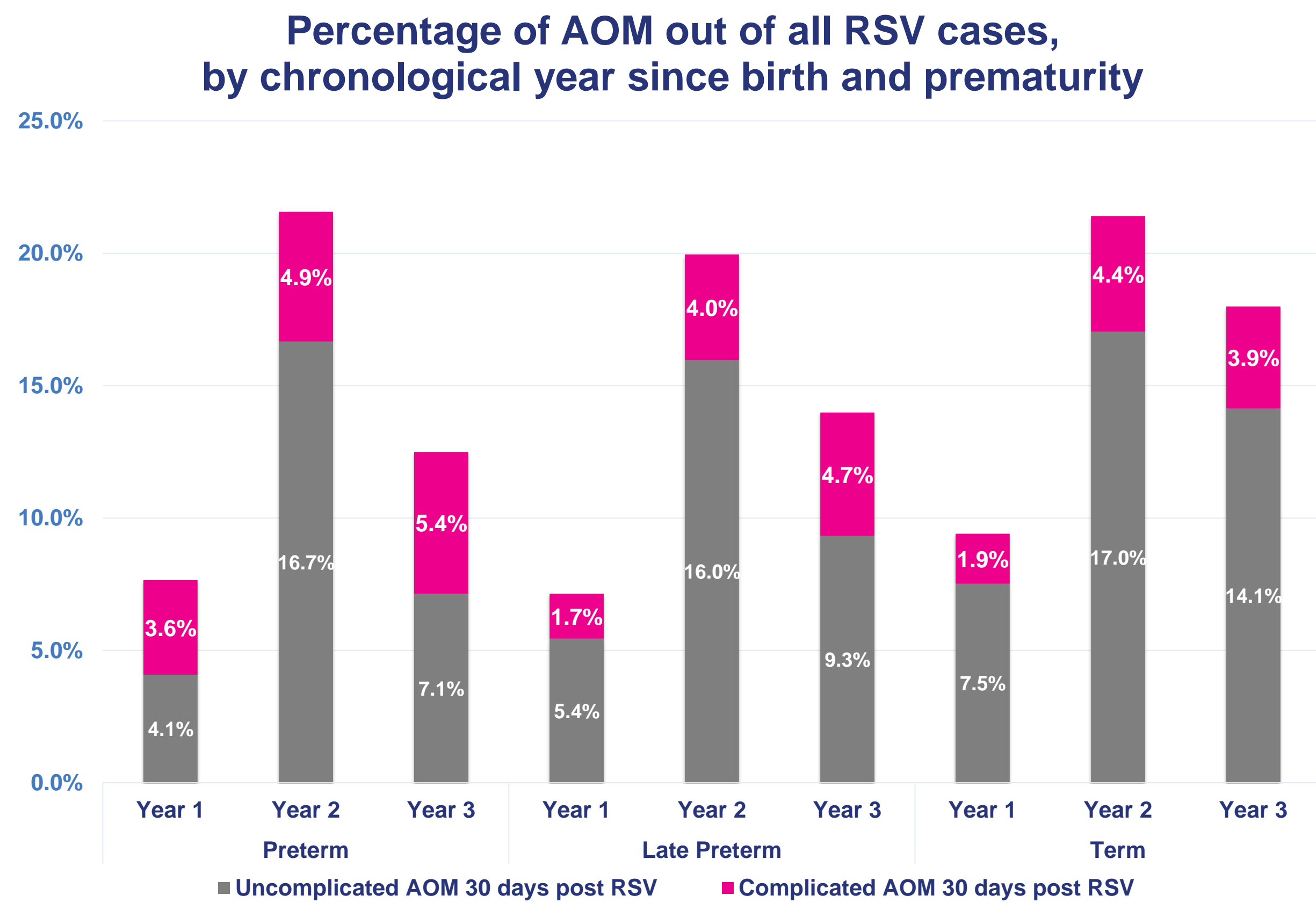
Clinical and economic burden associated with acute otitis media among children with RSV diagnosis/index in Year 1

- Among term infants with RSV in Year 1 followed by 36 months since index, the incidence of uncomplic̃ated AOM associated with RSV was 13,773 per 100 children-years and for complicated AOM it was 8,279 per 100 children-years. The incidence among term cohorts without AOM post-index were much lower (~2,000-2,500 per 100 children-years).
- Cumulative average AOM cost by prematurity is presented in **Table 1,** while complicated AOM economic burden difference is shown in **Table 2**.
- In adjusted analysis among late preterm and term children only, those with RSV had higher odds of AOM 30 days post-index (OR=3.49,p<0.001), compared to non-RSV controls; having prior AOM episode in the second 6 months of life was the most noteworthy confounder (OR=9.35, p<0.001) **(Table 3)**.
- In Poisson/gamma multivariable regressions, RSV patients had higher AOM monthly incidence over 36 months of follow-up (**Table 4A:** incidence ratio=1.52, p<0.001) and monthly cost (**Table 4B:** cost ratio=1.63, p<0.001; ¥2417 vs ¥1482) than controls.

Table 1. Cumulative average AOM cost (¥2018) over 36-month follow-up by study group, Year 1 diagnosis cohort.

Total cost by prematurity group	I. RSV with no AOM in first 30 days since index			II. RSV with uncomplicated AOM in first 30 days since index			III. RSV with complicated AOM in first 30 days since index			IV. Controls		
	Mean	95% LCI	95% UCI	Mean	95% LCI	95% UCI	Mean	95% LCI	95% UCI	Mean	95% LCI	95% UCI
PRETERM	¥115,680	-168,790	400,150	¥227,365	-57,105	511,835	¥401,563	117,093	686,034	¥163,281	-121,210	447,772
LATE PRETERM	¥82,077	-276,015	440,168	¥337,100	-21,005	695,205	¥583,752	225,647	941,857	¥68,460	-289,646	426,566
TERM	¥68,986	24,334	113,639	¥280,780	236,120	325,439	¥381,183	336,450	425,915	¥53,612	8,879	98,345

LCI – lower confidence interval; UCI – upper confidence interval

Table 2. Cumulative average complicated AOM cost (¥2018) over 36-month follow-up by study group, Year 1 diagnosis cohort.

Total cost by prematurity group	I. RSV with no AOM in first 30 days since index			II. RSV with uncomplicated AOM in first 30 days since index			III. RSV with complicated AOM in first 30 days since index			IV. Controls		
	Mean	95% LCI	95% UCI	Mean	95% LCI	95% UCI	Mean	95% LCI	95% UCI	Mean	95% LCI	95% UCI
PRETERM	¥52,718	-165,706	271,142	¥2,901	-215,522	221,325	¥363,164	144,741	581,588	¥112,103	-106,347	330,554
LATE PRETERM	¥34,972	-319,196	389,140	¥102,101	-252,067	456,269	¥519,039	164,871	873,207	¥37,995	-316,174	392,164
TERM	¥26,772	-15,431	68,976	¥84,979	42,773	127,185	¥333,925	291,644	376,207	¥24,290	-17,992	66,572

LCI – lower confidence interval; UCI – upper confidence interval

Table 3. Multivariable regression on the odds of RSV-associated AOM 30 days post-index, Year 1 cohort, late preterm & term.

Variable	Odds ratio	Confidence limits		P value
		95% LCI	95% UCI	
RSV vs non-RSV	3.49	3.07	3.98	<.0001
Full vs No Passive Immunization	0.83	0.40	1.76	0.63
Partial vs No Passive Immunization	0.66	0.35	1.26	0.21
Index in 7-12 vs 0-6 months	3.71	3.18	4.34	<.0001
Prior AOM in 7-12 vs 0-6 months	9.35	7.21	12.1	<.0001
Prior complicated AOM vs not	3.71	2.56	5.36	<.0001
Late Preterm vs Term	0.82	0.62	1.08	0.16
Male vs Female	1.02	0.90	1.16	0.75
Each 100,000 JPY increase in birth month cost	0.995	0.980	1.011	0.54

Additional baseline characteristics were not included in the multivariate model as they were not statistically significant and interfered with the model convergence.

Table 4A. Multivariable Poisson regression modelling the risk of AOM over 36-months of follow-up post-index, Year 1 cohort.

Variable	Incidence ratio	Confidence limits		P value
		95% LCI	95% UCI	
RSV vs non-RSV	1.52	1.49	1.55	<.0001

Table 4B. Multivariable gamma regression modelling the cost of AOM over 36-months of follow-up post-index, Year 1 cohort.

Variable	Cost ratio	Confidence limits		P value
		95% LCI	95% UCI	
RSV vs non-RSV	1.63	1.61	1.65	<.0001

* Models in Table 4A and 4B adjusted for full or partial passive immunization or not, history of prior AOM, timing of prior AOM with relation to birth, prior complicated AOM episode, late preterm vs term, sex, multiple pregnancy, cost and NICU admission in first birth month, comorbidities.

DISCUSSIONS AND CONCLUSION

- RSV infection in the first year of life, examined as possibly the highest priority for intervention and prevention, was associated with 3.5 greater odds of RSV-associated AOM post-diagnosis as well as up to 1.6 times greater long-term burden of recurrent AOM over 36-months of follow-up, compared to those without RSV.
- Study findings are useful in supporting efforts investigating whether immunization against RSV could result in reduction in AOM.

REFERENCES
1. Heikinnen T et al. *J Infect Dis.* 2017 Jan 1;215(1):17-23. **2.** Phillips M et al. *J Pediatric Infect Dis Soc.* 2020 Nov 10;9(5):544-550. **3.** Chirikov V et al. *Clinicoecon Outcomes Res.* 2022 Nov 9:14:699-714