

Burden and Cost of Hospitalization for Respiratory Syncytial Virus in Young Children, Singapore

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Respiratory syncytial virus (RSV) is the most common cause of pediatric acute lower respiratory tract infection worldwide. Detailed data on the health and economic burden of RSV disease are lacking from tropical settings with year-round RSV transmission. We developed a statistical and economic model to estimate the annual incidence and healthcare cost of medically attended RSV disease among young children in Singapore, using Monte Carlo simulation to account for uncertainty in model parameters. RSV accounted for 708 hospitalizations in children <6 months of age (33.5/1,000 child-years) and 1,096 in children 6–29 months of age (13.2/1,000 child-years). The cost of hospitalization was SGD 5.7 million (US \$4.3 million) at 2014 prices; patients bore 60% of the cost. RSV-associated disease burden in tropical settings in Asia is high and comparable to other settings. Further work incorporating efficacy data from ongoing vaccine trials will help to determine the potential cost-effectiveness of different vaccination strategies.

Respiratory syncytial virus (RSV) is the commonest cause of acute lower respiratory tract infection in children <5 years of age worldwide, causing an estimated 33 million cases, 3 million hospitalizations, and 60,000 deaths annually (1). In young children and infants, RSV infections can cause bronchiolitis and pneumonia requiring hospitalization. In the United States, RSV accounts for 40% of respiratory hospitalizations in all age groups (2); children <5 years of age

account for two thirds of this burden. Similarly, in the United Kingdom, RSV accounts for 28% of hospitalizations for lower respiratory tract infection in children <5 years of age (3).

Several RSV vaccines are in development. Potential immunization strategies include vaccination of children, pregnant mothers, and older adults. Assessing the potential impact and cost-effectiveness of future vaccination strategies relies on robust estimates of RSV-related health burden and cost, to inform national procurement and prioritization decisions. We present estimates of RSV-related primary care consultations, hospitalizations, and associated healthcare costs among children <30 months of age in Singapore.

Methods

Study Setting

Singapore, a high-income tropical country, has year-round RSV circulation. Compared with the distinct winter seasonal peaks in temperate settings, the RSV season is longer, peaking in May–September (4–6). Hospitalization costs in Singapore are borne by a mix of public and private insurance, out-of-pocket financing, and means-tested subsidies for lower-income patients. KK Women’s and Children’s Hospital (KKH) is the largest specialist women’s and children’s hospital in Singapore. All children admitted to KKH with respiratory symptoms, regardless of clinical severity, are tested by nasopharyngeal swab sampling for a panel of respiratory viruses using direct immunofluorescence antibody (DFA). Primary care is available through public polyclinics, private general practices, and pediatric clinics. Polyclinics are subsidized, and patients contribute a co-payment; consultations in private practices are paid out of pocket or through individual insurance. Approximately 80% of primary care consultations occur in the private sector (7).

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Approach

We used data on primary care consultations for acute respiratory illness (ARI) and hospital admissions for bronchiolitis and pneumonia in children <30 months of age, together with data on laboratory testing for RSV and healthcare bill sizes, to estimate incidence of medically attended RSV and associated healthcare costs from a societal perspective. We used Monte Carlo simulations to estimate numbers of primary care consultations and numbers of hospitalizations for bronchiolitis, pneumonia without complications, and pneumonia with complications. We developed 2 cost models: the full-cost model estimated the total cost of RSV-related healthcare, whereas the subsidized cost estimated the share of healthcare costs paid by patients after accounting for public subsidies.

Data Sources

Bronchiolitis and Pneumonia Admissions

We obtained data on bronchiolitis and pneumonia hospitalizations in children <72 months of age during 2005–2014 from electronic inpatient admission records at KKH. We selected all admissions with diagnostic codes for pneumonia and bronchiolitis in any diagnostic field (International Classification of Diseases, 9th Revision [ICD-9], codes 480–486 and 466, or ICD, 10th Revision [ICD-10], codes J12–18 and J21). We excluded records for which a pathogen other than RSV was mentioned as the cause of bronchiolitis or pneumonia in the medical code description.

RSV and Influenza Positive Identifications

We extracted data on positive identifications of RSV and influenza at KKH from laboratory diagnostic records for children <30 months of age for the period 2005–2014. Viral infections were detected using DFA for influenza A and B viruses, RSV, adenovirus, parainfluenza viruses 1–3, and human metapneumovirus (D³ Double Duet DFA Respiratory Virus Screening and ID Kit; Diagnostic Hybrids; Quidel Corporation, <https://www.quidel.com>). The positive and negative percent agreements of virus detection by this test against a predicate test are 100%.

Rotavirus Positive Identifications

We used rotavirus as a negative control, to rule out spurious associations related to secular changes in recording of diagnoses or laboratory investigations. We extracted all positive identifications of rotavirus in children <30 months of age hospitalized for gastroenteritis during 2005–2014. Rotavirus detection in stool samples was done via an immunochromatographic

assay (Simple Rotavirus/Stick Rotavirus; Operon, <https://operon.es>).

Public Primary Care Consultations

We obtained data on polyclinic consultations for ARI among children <5 years of age in 2014 from the Ministry of Health; the National Public Health Laboratory additionally tests for a range of respiratory pathogens in a subset of primary care ARI samples. We obtained data on the proportion of samples, by age group, in which RSV was detected as the sole pathogen as determined by a commercial multiplex assay (Seegene Allplex Respiratory Panel; Seegene Inc., <http://www.seegene.com>).

Costs of Hospitalization and Primary Care Consultation

Singapore Ministry of Health (MOH) standardized unit costs of hospitalization by condition, healthcare institution, and ward class, together with average length of stay (LOS), are published annually (8). Wards are categorized into 5 classes, A, B1, B2+, B2, and C, with A being unsubsidized and C being the most highly subsidized. We obtained published costs of an admission to KKH for bronchiolitis, pneumonia, and pneumonia with complications from the MOH website for the 5 different ward classes (Appendix Table 5, <https://wwwnc.cdc.gov/EID/article/26/7/19-0539-App1.pdf>). We determined the cost of a primary care consultation on the basis of the average cost of a polyclinic visit, which we obtained from the respective providers (9,10) (Appendix Table 4).

Data Analysis

Proportion of Bronchiolitis and Pneumonia Admissions Attributed to RSV

We estimated the proportion of RSV-related bronchiolitis and pneumonia admissions using a seasonal regression method (11,12). We used a negative binomial model with an identity link to model weekly counts of bronchiolitis and pneumonia admissions against weekly counts of RSV-positive identifications for the years 2005–2013. We included an intercept term to account for admissions not explained by RSV. We fitted separate models for children <6 months of age and children 6–30 months of age. We used the model coefficients to predict the proportion of bronchiolitis and pneumonia admissions in 2014 attributable to RSV. We tested the model's validity by comparing the model-predicted and observed values for 2014 and calculating the correlation coefficient (ρ), root mean squared error

(RMSE), and mean absolute error (MAE) (Appendix Figure 1). In a sensitivity analysis, we ran additional regressions individually, adjusting for the following: linear and quadratic trend terms, weekly influenza positive identifications, weekly rotavirus positive identifications, and weekly gastrointestinal admissions (Appendix).

Percentage of Admissions for Pneumonia

Of admissions for bronchiolitis and pneumonia, the percentage specifically for pneumonia-related codes increased with age, which has implications for the cost of treatment; pneumonia incurs higher treatment costs. We used a logistic regression model with natural cubic splines of age and internal knots at 9-month age intervals to predict the age-specific proportion of pneumonia-related admissions in 2014.

LOS and Pneumonia with Complications

We modeled LOS in 2005–2013 by fitting an exponential regression to the percentage distribution of LOS separately for bronchiolitis and pneumonia admissions (Appendix Figure 4). We used the model coefficients to predict the LOS distribution for 2014.

We defined pneumonia with complications as pneumonia with LOS >5 days, assuming that pneumonia with complications results in longer hospitalization. Approximately 8% of admissions for bronchiolitis and pneumonia had a LOS >5 days, matching the percentage of admissions categorized as pneumonia with complications in MOH billing data.

Burden and Cost of RSV Hospitalization

We developed a model to estimate the annual number of hospitalizations for bronchiolitis, pneumonia, and pneumonia with complications and their associated cost, estimated separately for children <6 months and 6–29 months of age (Appendix). In the model, number of RSV-positive identifications in KKH in 2014 for each age group are inputs. We used the coefficients from the 3 regressions to estimate the overall number of bronchiolitis and pneumonia admissions attributable to RSV; the number of admissions that were bronchiolitis versus pneumonia by patient's age in months; the number of admissions for pneumonia with complications, based on the predefined cutoff for LOS; and the total number of days of hospitalization for bronchiolitis, pneumonia, and pneumonia with complications. We extrapolated hospitalization estimates to the whole of Singapore by applying inflation factors to account for the proportion of hospitalizations occurring in other hospitals (Appendix Equations 4.1–4.3).

To estimate the full hospitalization costs, we applied the average daily bill size in a class A (unsubsidized) ward to the total hospitalization days for bronchiolitis, pneumonia, and pneumonia with complications (Appendix Equation 5). To estimate the subsidized cost (the cost borne by patients), we applied the average daily bill size for each ward class to the number of hospitalization days spent by patients in each type of ward (Appendix Equation 6). We estimated costs separately for bronchiolitis, pneumonia, and pneumonia with complications.

Burden and Cost of RSV Primary Care Consultations

Because fine age stratification of primary care consultations was not available, we used the age distribution of RSV-positive identifications from KKH to infer the number of polyclinic consultations in children <6 months and 6–29 months of age (Appendix Equation 7). To estimate the number of consultations occurring in the private sector, we used the ratio of pediatric consultations (for children <5 years of age) in polyclinics versus private GPs, published in the 2014 Primary Care Survey (7). We estimated the proportion of respiratory consultations due to RSV using National Public Health Laboratory ARI testing data, in which 8% of ARI samples from children <5 years had RSV as the sole identified pathogen. We estimated the full cost of primary care consultations for RSV by applying the cost of an unsubsidized polyclinic consultation to the estimated number of consultations. To estimate the subsidized cost, we applied the cost of a pediatric polyclinic consultation to the subset of consultations occurring in government polyclinics (Appendix Equations 8.1–8.2).

Monte Carlo Simulation

To account for uncertainty in model parameters, we used Monte Carlo methods to sample parameter values at random from their assumed distributions. We performed 10,000 simulations. For each output parameter, we used the median and 2.5th and 97.5th percentiles of the sampled distributions as the point estimate and corresponding 95% CI.

To assess the influence of our definition of pneumonia with complications, we repeated the analyses varying the LOS cutoff used to define pneumonia with complications (± 1 day). We adjusted costs to 2014 prices using the healthcare domain of the Consumer Price Index (13). We rounded cumulative healthcare costs to the nearest SGD 1,000.

We performed all analyses using Stata version 12 (Stata Corporation, <https://www.stata.com>) and R version 3.4.1 (14). The SingHealth Centralized

Institutional Review Board approved this study (application 2017/2223).

Results

During 2005–2013, there were 18,323 bronchiolitis and pneumonia admissions in children <30 months of age at KKH, an average of 39 weekly admissions, and 7,691 RSV-positive identifications, a weekly average of 16. There was substantial temporal agreement between the two time-series, with a marked peak in RSV identifications in May–September in most years (Figure 1). Model validation showed high correlation between model-predicted and observed bronchiolitis admissions for 2014 ($\rho = 0.88$ for children <6 months of age; $\rho = 0.81$ for children 6–29 months of age) (Appendix Table 1).

Hospitalizations Attributable to RSV

The negative binomial model with an intercept and a linear term for weekly RSV-positive identifications provided the best fit to the data. From this model, RSV accounted for 47.0% (95% CI 42.4%–51.5%) of bronchiolitis and pneumonia admissions among children <6 months of age, and 34.3% (95% CI 25.0%–33.1%) among children 6–29 months. The estimated yearly number of RSV-associated bronchiolitis admissions was 135–340 among children <6 months of age and 271–680 among children 6–29 months of age (Appendix Table 1).

Adjusting for linear or quadratic trend terms, influenza positive identifications, rotavirus positive identifications, and gastrointestinal admissions resulted in small changes to the RSV-attributable percentage.

However, none of these more complex models provided a better fit to the data (Appendix Table 2).

Percentage of Pneumonia Hospitalizations by Age

Based on the regression with natural cubic splines, the percentage of pneumonia admissions was estimated to be 18.6% for children hospitalized in the first month of life. This percentage decreased to 5.5% by 4 months of age but rose to 74.0% by 29 months of age (Figure 2).

Bronchiolitis and Pneumonia Hospitalization Rates

An estimated 708 (95% CI 664–765) bronchiolitis and pneumonia admissions due to RSV occurred in 2014 among children <6 months of age, a rate of 33.5 hospitalizations/1,000 child-years. For children 6–29 months, the corresponding number was 1,096 (95% CI 998–1,273), or 13.2 hospitalizations/1,000 child-years (Table 1). Among children <6 months of age, the number of admissions was 637 for bronchiolitis, 54 for pneumonia without complications, and 15 for pneumonia with complications. In children aged 6–29 months, the corresponding numbers were 826 for bronchiolitis, 203 for pneumonia without complications, and 63 for pneumonia with complications.

Primary Care Consultation Rates

The number of estimated primary care consultations for RSV among children <6 months of age was 3,600 (95% CI 3,120–4,130) or 170.5 consultations/1,000 child-years. The corresponding number of consultations in children 6–29 months was 5,700 (95% CI 5,010–6,450), for a rate of 68.6 consultations/1,000 child-years (Table 1).

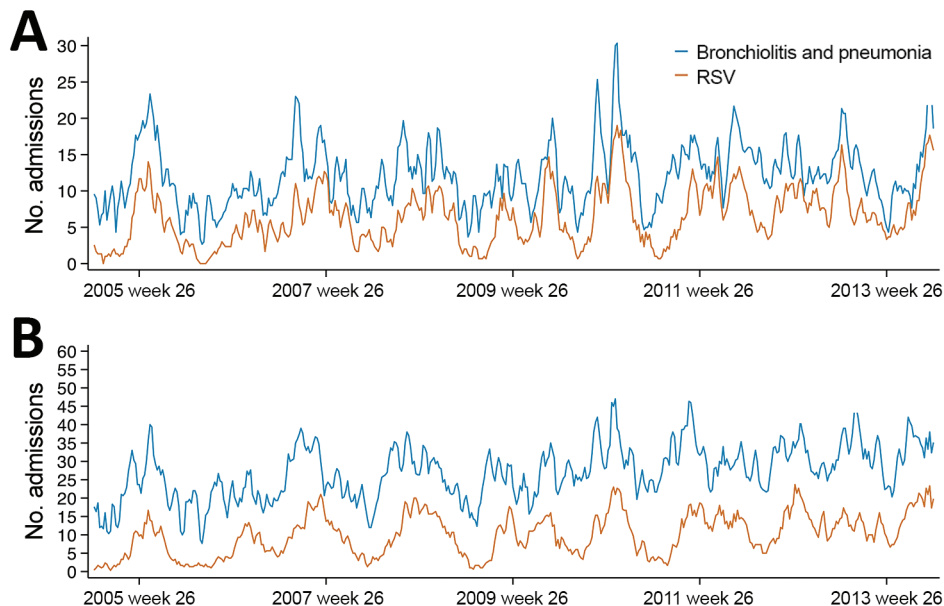


Figure 1. Hospital admissions for respiratory syncytial virus and for bronchiolitis and pneumonia over time by age group, Singapore, 2005–2013.

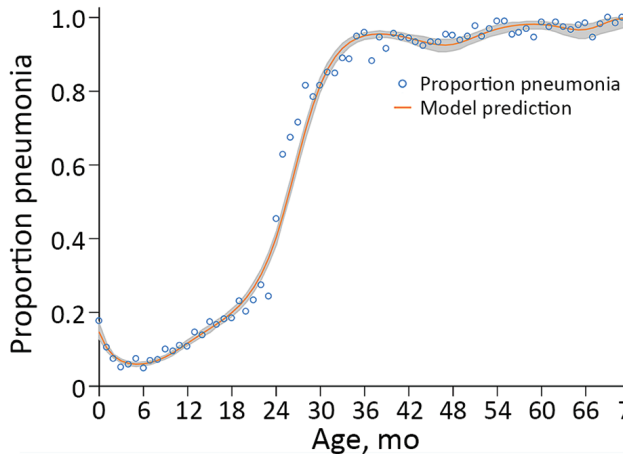


Figure 2. Proportion of bronchiolitis and pneumonia admissions for pneumonia-related codes as contrasted with model predictions by age, Singapore, 2005–2013. Gray shading along the curve indicates 95% CI.

Hospitalization Costs

The annual unsubsidized cost of RSV-associated bronchiolitis and pneumonia hospitalizations among children <30 months of age was SGD 5.7 million (95% CI SGD 5.2 – SGD 6.4 million). Patients bore SGD 3.6 million (US \$2.6 million), or 63%, of the total cost (Table 2). Approximately 40% of admissions occurred in maximally subsidized class C wards and 30% in unsubsidized class A wards (Figure 3).

Among children <6 months of age, average cost per bronchiolitis hospitalization was SGD 2,953 (US \$2,209), rising to SGD 7,944 (US \$5,942) for a hospitalization for pneumonia with complications. Among children 6–29 months of age, average costs were SGD 2,949 (US \$2,206) for bronchiolitis and SGD 8,300 (US \$6,208) for pneumonia with complications. Varying the definition of pneumonia with complications by ±1 day from the 5-day cutoff had negligible effect on estimates of case counts or overall cost (Appendix Figure 5).

Primary Care Costs and Costs per Child

The annual cost of primary care consultations was SGD 0.46 million (US \$0.34 million), of which 38% was incurred for children <6 months of age. The mean cost per case was SGD 49 (US \$37).

The overall cost of RSV-related hospitalizations and primary care consultations was SGD 6.2 million (US \$4.7 million). This total is equivalent to SGD 60 annually per birth (US \$45), of which SGD 55 represents hospitalization costs.

Discussion

RSV causes substantial pediatric health and economic burden in Singapore, accounting for 33.5 hospitalizations/1,000 child-years among children <6 months of age and 13.2 hospitalizations/1,000 child-years in children 6–29 months of age. The annual healthcare cost attributable to RSV is SGD 6.2 million (US \$4.7 million), or SGD 60 (US \$45) per birth, the bulk of which is for acute hospital care. Our findings help to address the gap in information to support the cost-effectiveness evaluations of future RSV vaccination strategies in tropical settings.

Shi et al. reported similar estimates on community incidence of RSV disease (66/1,000 children) and hospitalization (26/1,000 children) for infants <6 months in high-income countries (1). RSV hospitalization rates in children <6 months from 4 East Asia and Asia-Pacific studies ranged from 14 hospitalizations/1,000 children/year in 2 rural provinces in Thailand to 42.7/1,000/year in Alice Springs, Northern Territory, Australia (1). Homaira et al., using linked administrative health data from Australia, estimated a hospitalization rate of 26/1,000 children <3 months (15). RSV hospitalization rates of ≈45/1,000 children <6 months of age have been reported in England and Wales (11) and Denmark (16). Our estimate is somewhat lower, at 33/1,000 children. This difference could reflect differences in estimation methods

Table 1. Estimated RSV-associated hospitalizations and primary care consultations, Singapore, 2014

Age, mo	Outcome	Total no. cases (95% CI)	No. cases/1,000 person-years (95% CI)
Hospitalizations			
<6	All diagnoses	708 (664–765)	33.5 (31.4–36.2)
	Bronchiolitis	637 (604–671)	30.2 (28.6–31.8)
	Pneumonia	54 (30–99)	2.6 (1.4–4.7)
	Pneumonia with complications	15 (7–29)	0.7 (0.3–1.4)
6–29	All diagnoses	1,096 (994–1,269)	13.2 (12–15.3)
	Bronchiolitis	826 (793–862)	9.9 (9.5–10.4)
	Pneumonia	203 (115–372)	2.4 (1.4–4.5)
	Pneumonia with complications	63 (38–110)	0.8 (0.5–1.3)
Primary care consultations			
<6	ARI	3,600 (3,120–4,130)	170.5 (147.8–195.6)
6–29	ARI	5,700 (5,010–6,450)	68.6 (60.3–77.6)

*Estimates are expressed as the medians from 10,000 Monte Carlo simulations. Note that the sum of medians from individual diagnoses does not equal the median for all diagnoses combined. ARI, acute respiratory illness; RSV, respiratory syncytial virus.

Table 2. Cost of RSV-associated hospitalizations and primary care consultations, Singapore, 2014*

Age, mo	Outcome	Full cost (95% CI)	Subsidized cost (95% CI)
Hospitalizations			
<6	All	\$2,160,000 (\$2,002,000–\$2,352,000)	\$1,321,000 (\$1,168,000–\$1,492,000)
	Bronchiolitis	\$1,881,000 (\$1,771,000–\$1,995,000)	\$1,127,000 (\$1,006,000–\$1,250,000)
	Pneumonia	\$152,000 (\$82,000–\$278,000)	\$106,000 (\$53,000–\$198,000)
	Pneumonia with complications	\$119,000 (\$55,000–\$220,000)	\$80,000 (\$25,000–\$167,000)
6–29	All	\$3,554,000 (\$3,175,000–\$4,118,000)	\$2,236,000 (\$1,932,000–\$2,651,000)
	Bronchiolitis	\$2,436,000 (\$2,319,000–\$2,563,000)	\$1,459,000 (\$1,328,000–\$1,600,000)
	Pneumonia	\$573,000 (\$321,000–\$1,041,000)	\$401,000 (\$217,000–\$729,000)
	Pneumonia with complications	\$523,000 (\$322,000–\$857,000)	\$358,000 (\$191,000–\$610,000)
Primary care consultations			
<6	Primary care attendances	\$177,000 (\$153,000–\$203,000)	\$118,000 (\$102,000–\$136,000)
6–29	Primary care attendances	\$280,000 (\$246,000–\$317,000)	\$187,000 (\$163,000–\$213,000)
Hospitalizations and primary care consultations			
<6	All	\$2,337,000 (\$2,175,000–\$2,530,000)	\$1,440,000 (\$1,285,000–\$1,611,000)
6–29	All	\$3,833,000 (\$3,454,000–\$4,399,000)	\$2,423,000 (\$2,115,000–\$2,838,000)
<30	All	\$6,228,000 (\$5,734,000–\$6,950,000)	\$3,899,000 (\$3,506,000–\$4,432,000)

*Estimates are expressed as the medians from 10,000 Monte Carlo simulations. Note that the sum of medians from individual diagnoses does not equal the median for all diagnoses combined. All costs are in Singapore dollars. RSV, respiratory syncytial virus.

or the lower fertility rates in Singapore, which might result in reduced transmission of RSV among very young children.

Hospitalization costs are difficult to compare because of differences between countries in health-care financing. In our analysis, the hospitalization cost per child was ≈US \$41, higher than in Denmark (≈US \$25) (16) but lower than in England and Wales (≈US \$82) (11). In our analysis, two thirds of hospitalization costs were borne by patients through personal insurance, Medisave (a national medical savings scheme), or out-of-pocket payments. In health systems with shared financing, determining the share of the cost borne by different sectors can be relevant for policy decisions. Although the healthcare costs of disease are shared by patients, insurers, and governments, it is a country's government that is generally responsible for decisions about vaccine introduction and financing. Clarifying how the costs of averted illness affect different parties can help to inform vaccine policy decisions.

A limitation of our analysis is a lack of openly available information on how closely hospital bill amounts reflect actual treatment costs for RSV disease. We used average bill sizes for services in public-sector hospitals and polyclinics, which are likely to reflect treatment costs more closely than do bills for services from private healthcare providers, which are likely to include additional profit margins. Despite the large burden and cost we identified, our figures are likely to be underestimated. First, we limited our analysis to children <30 months of age because we lacked data on positive RSV identifications in older children. Second,

our primary care estimates exclude consultations to private pediatricians, which were not included in the Primary Care Survey. Third, although we obtained detailed estimates of RSV hospitalization costs by ward class, our estimates of bill sizes in private hospitals is conservative. Because hospital billing data were not available by age group, we estimated the proportion of pediatric RSV admissions in private hospitals using the distribution of bronchiolitis admissions treated in different ward types, because bronchiolitis is primarily a pediatric diagnosis. We could not apply hospital-specific bill sizes because the cost of pneumonia admissions is usually heavily influenced by adult admissions; therefore, we applied KKH bill sizes for (unsubsidized) class A wards to all ward types as a proxy for the actual cost to providers of hospital care. Finally, we did not consider societal costs resulting from time taken off work by caretakers or nonhealthcare expenditure resulting from illness.

We did not estimate the fraction of RSV burden that occurs in higher-risk groups, such as preterm babies or children with underlying conditions, which could have implications for subsequent assessment of vaccination strategies. However, the overall healthcare cost is unlikely to be affected. Although we might have overestimated the burden attributable to RSV because of possible concurrent infections with other pathogens causally related to respiratory illness, we believe this is unlikely. We estimated RSV impact on primary care using the proportion of ARI samples in which RSV was identified as the sole pathogen (≈75% of samples in which RSV was detected). In estimating hospitalization burden, we used a regression approach

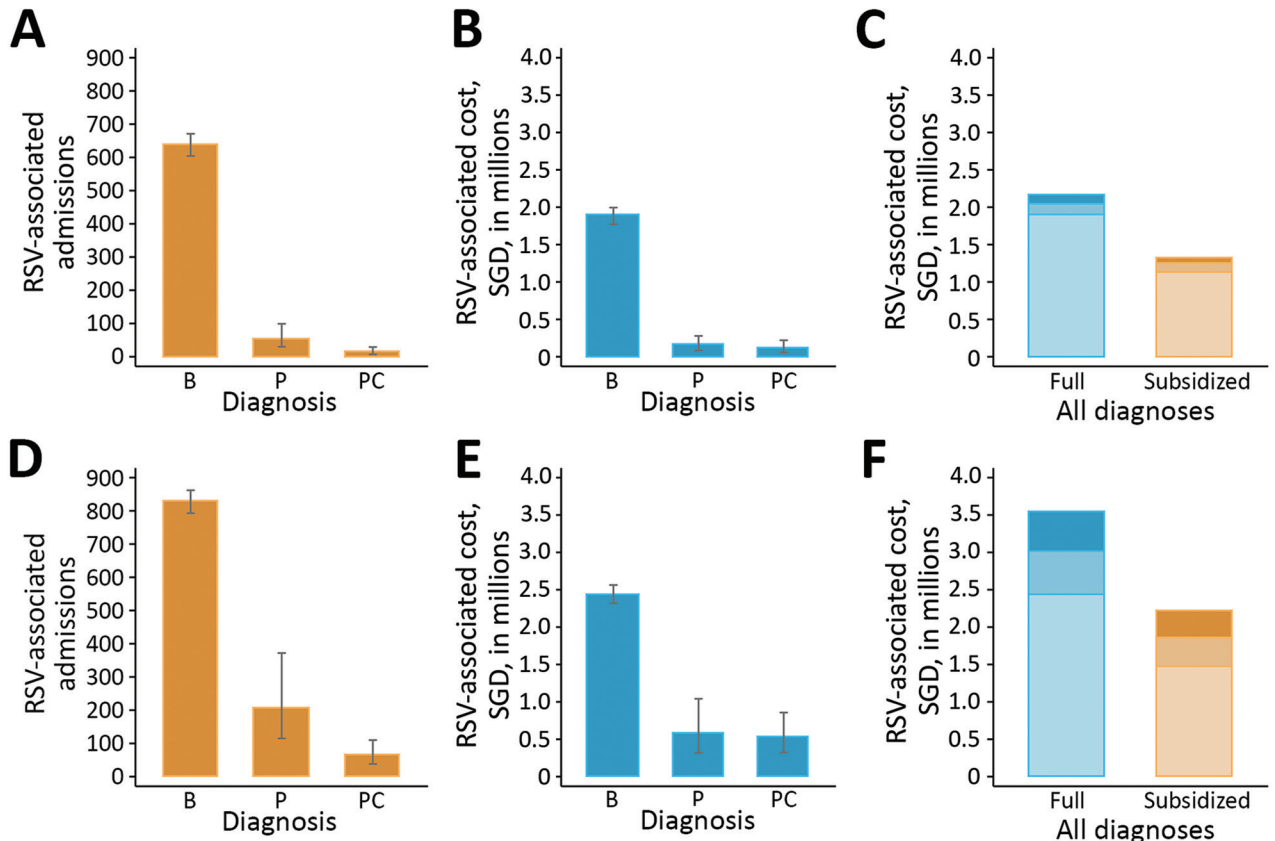


Figure 3. Estimated annual RSV-associated hospital admissions and costs for children ≤ 5 months of age (A–C) and children 6–29 months (D–F), Singapore, 2005–2013. Panels show estimated annual RSV-associated hospital admissions (panels A, D), total hospitalization costs by diagnosis (B, E), and full vs. subsidized costs (C, F). For panels C and F, shading indicates, from lightest to darkest: bronchiolitis, pneumonia without complications, pneumonia with complications. Point estimates and error bars representing medians and central 95% CI distributions were generated from 10,000 Monte Carlo simulations. B, bronchiolitis; P, pneumonia; PC, pneumonia with complications; RSV, respiratory syncytial virus; SGD, Singapore dollars.

that accounts for the seasonal correlation between hospital admissions and RSV-positive tests. To substantially affect our estimates, much of this seasonal variability would need to result from infections with other pathogens sharing similar seasonal patterns, but that is highly unlikely. Influenza showed very little correlation with bronchiolitis and pneumonia hospitalization data, whereas pneumococcal disease, also important in this age group, accounts for only a modest number of hospitalizations in Singapore (≈ 150 annually).

Strengths of our analysis include the availability of a long time-series of RSV-positive identifications based on routine, systematic diagnostic testing of pediatric respiratory admissions, and on patient-level data for diagnosis and length of hospitalization. The average hospitalization cost was US \$2,200 for bronchiolitis and \$6,000 for pneumonia. Studies of RSV-associated healthcare costs in similar Asia settings are lacking; Sruamsiri et al. estimated the

average cost of RSV-associated hospitalization in Japan at US \$3,300 (17) and Homaira et al. in Australia at US \$4,500 (15). Of note, we estimated the cost borne by patients and the health sector; in hybrid public-private healthcare financing systems, future vaccination policy options may be better informed by understanding how avoidable costs affect different sectors of society. Our results indicate that patients bear $>60\%$ of hospitalization costs either through health insurance schemes or out-of-pocket payments.

Our findings add to the increasing body of data on the burden of RSV in infants and young children in both high- and low-income settings, and point to the need and potential for RSV vaccines to reduce neonatal disease burden. As evidence for the efficacy of new RSV vaccines emerges from ongoing trials, these data will provide a much-needed baseline against which to measure the cost effectiveness of different vaccination strategies.

C.C.T. performed the analysis and drafted the manuscript. M.J. and C.F.Y. provided technical input into the development and refinement of the modeling strategy and the interpretation of results. All authors critically reviewed and contributed to the drafting of the manuscript.

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Burden and Cost of Hospitalization for Respiratory Syncytial Virus in Young Children, Singapore

Appendix

In this document, we describe the statistical methods used to estimate the burden and cost of RSV hospitalization. To simplify the notation, we limit the text to estimation methods for children <6 months of age, but the same methods were used for the older age group of 6–29 months.

Estimating RSV-attributable Hospitalizations Using Seasonal Regression

We estimated the number and proportion of hospitalizations for bronchiolitis and pneumonia attributable to RSV by regressing the weekly number of hospital admissions against the weekly number of RSV-positive identifications for the years 2005–2013 (Appendix Figure 2), using a regression model of the form:

$$H_{KKH,w} = a + \mu_r R_w \text{ (Equation 1)}$$

where H_w is the weekly number of hospitalizations for bronchiolitis and pneumonia at KK Women's and Children's Hospital (KKH) and R_w represents the number of RSV-positive identifications. The coefficient, μ_r , measures the change in weekly bronchiolitis and pneumonia hospitalizations per unit change in RSV-positive identifications; the intercept, a , captures the hospitalization burden attributable to pathogens other than RSV. The regression was fitted using a negative binomial model with identity link, as previously used by Cromer et al. (1). The estimated coefficient and associated standard error were used to estimate the RSV-attributable hospitalization burden for 2014 in subsequent simulations.

In a series of sensitivity analyses, we accounted for long-term secular trends by including both linear and quadratic terms for week in the regression model. In addition, to account for possible changes to the epidemiology of RSV during the 2009 influenza pandemic, we fitted additional models excluding data for 2009, both without a trend term, and with separate trend

terms for the years 2005–2008 and 2010–2013. We also modeled the effect of influenza by including weekly influenza positive identifications in the model. Finally, we fitted models including weekly rotavirus positive identifications and weekly gastrointestinal admissions as negative controls. For each of these models, we assessed model fit using Bayesian information criterion (BIC), favoring models with a lower BIC value.

Estimating the proportion of hospitalizations due to pneumonia by age

Preliminary analysis of hospitalization data indicated that, although the overall number of bronchiolitis and pneumonia hospitalizations decreases markedly with age, the proportion of these due to pneumonia (as opposed to bronchiolitis) increased with age (Appendix Table 3). Accounting for this is important to avoid underestimating RSV burden and cost in older age groups. We modeled age-dependent changes in the proportion of pneumonia hospitalizations between 2005–2013 with a logistic regression model:

$$\alpha_m = \ln\left(\frac{p_m}{1-p_m}\right) = b_0 + \sum_{k=1}^{k=9} b_k S_k \text{ (Equation 2)}$$

where the outcome, α_m , is the log odds of a pneumonia hospitalization at age m months and the explanatory variables, S_k , are regressors corresponding to natural cubic splines of age (over the range 0–72 months of age) with $k = 9$ equally spaced knots. The number of knots was decided based on a visual inspection of plots of observed and model-predicted values, so as to retain the minimum number of knots possible while capturing salient features in the observed data. We used model-predicted values and associated uncertainty to estimate the age-specific proportion of pneumonia hospitalizations for 2014 in subsequent simulations.

Modeling length of hospital stay (LOS)

The distribution of LOS was heavily right-skewed with the mode at 2 days. Because pneumonia hospitalizations tend to be longer, we modeled LOS separately for bronchiolitis and pneumonia hospitalizations during 2005 and 2013, using an exponential regression with 2 terms to allow for the smaller proportion of hospitalization with LOS of 1 day relative to 2 days:

$$\ln(l_{o,d}) = b_{0,o} + b_{1,o}L_1 + b_{2,o}L_2 \text{ (Equation 3)}$$

where $l_{o,d}$ represents the proportion of hospitalizations for outcome o (bronchiolitis or pneumonia) that had LOS equal to d days. The terms L_1 and L_2 are defined as:

$$L_1 = \begin{cases} 1, & d = 1 \\ 2, & d \geq 2 \end{cases}$$

$$L_2 = \begin{cases} 0, & d < 3 \\ d - 2, & d \geq 3 \end{cases}$$

Estimating RSV Hospitalization Burden and Cost in 2014

RSV-Attributable Hospitalizations

We estimated age-specific hospitalizations for bronchiolitis and pneumonia attributable to RSV in 2014 by multiplying the number of RSV-positive identifications by a factor r derived from Equation 1 above:

$$H_{KKH,RSV,m} = R_m \times r$$

$$r \sim N(\mu_r, \sigma_r)$$

Hospitalizations for Bronchiolitis and Pneumonia

We estimated the age-specific number of pneumonia hospitalizations by multiplying the overall number of hospitalizations at age m months, $H_{RSV,m}$, by the the age-specific proportion of these hospitalizations that are due to pneumonia, using parameters derived from Equation 2. The number of bronchiolitis hospitalizations was derived by subtraction:

$$P_{KKH,m} = H_{KKH,RSV,m} \times p_m$$

$$B_{KKH,m} = H_{KKH,RSV,m} - P_{KKH,m}$$

$$p_m = \frac{e^{\alpha_m}}{e^{\alpha_m} + 1}$$

$$\alpha_m \sim N(\mu_{\alpha_m}, \sigma_{\alpha_m})$$

The total pneumonia and bronchiolitis hospitalizations was obtained by summing over age categories:

$$P_{KKH} = \sum_{m=0}^{m=5} P_{KKH,m}$$

$$B_{KKH} = \sum_{m=0}^{m=5} B_{KKH,m}$$

We then estimated the distribution of bronchiolitis and pneumonia cases by length of stay:

$$\begin{aligned}
P_{KKH,d} &= P_{KKH} \times l_{o=p,d} \\
B_{KKH,d} &= B_{KKH} \times l_{o=b,d} \\
\ln(l_{o,d}) &= b_{0,o} + b_{1,o}L_1 + b_{2,o}L_2 \\
b_0 &\sim N(\mu_{b_0}, \sigma_{b_0}) \\
b_1 &\sim N(\mu_{b_1}, \sigma_{b_1}) \\
b_2 &\sim N(\mu_{b_2}, \sigma_{b_2})
\end{aligned}$$

where $P_{KKH,RSV,d}$ and $B_{KKH,RSV,d}$ represent the number of RSV-related pneumonia hospitalizations with length of stay equal to d days and $l_{o=p,d}$ and $l_{o=b,d}$ are the corresponding proportions of hospitalizations with length of stay equal to d days, derived from Equation 3. In the base case scenario, we defined pneumonia with complications as pneumonia hospitalizations with LOS greater than 5 days:

$$\begin{aligned}
PN_{KKH} &= \sum_{d=1}^{d=5} P_{KKH,d} \\
PC_{KKH} &= \sum_{d=6}^{d=366} P_{KKH,d}
\end{aligned}$$

such that PN and PC represent the number of pneumonia hospitalizations with and without complications respectively.

Next, we estimated the number of admissions occurring at KKH by ward class:

$$\mathbf{B}_{KKH,w} \sim \text{Mult}(\mathbf{w}_B, B_{KKH})$$

where $\mathbf{B}_{KKH,w}$ is a vector representing the number of bronchiolitis admissions in each of 5 ward classes at KKH. $\mathbf{B}_{KKH,w}$ is drawn from a multinomial distribution with parameters \mathbf{w}_B , a vector representing the proportions of bronchiolitis admissions occurring in each ward class (Appendix Table 5), and B_{KKH} , the number of RSV-related bronchiolitis admissions as defined above. The corresponding ward-specific admissions for uncomplicated pneumonia and pneumonia with complications were obtained analogously using corresponding multinomial distributions, \mathbf{w}_{PN} and \mathbf{w}_{PC} .

To account for pediatric admissions occurring in hospitals other than KKH, we multiplied our estimates by a set of inflation factors. These factors were derived from the proportion of bronchiolitis cases in Singapore admitted to KKH, as reported in Ministry of Health (MOH) hospital billing data (2). We used bronchiolitis admissions to derive these inflation factors because billing data are not available by age group. Only a subset of public and private tertiary hospitals have pediatric departments, and bronchiolitis is likely to be almost exclusively a pediatric diagnosis. The estimated inflation factors are thus likely to reflect more accurately the ratio of pediatric admissions seen at KKH relative to other hospitals, whereas pneumonia admissions will include a large fraction of adult patients. The inflation factors were ward class-specific. This is important because the distribution of ward classes varies between hospitals; subsidized wards are only available in public-sector hospitals.

$$B_w = \sum_{w=1}^{w=5} B_{KKH,w} * I_w \text{ (Equation 4.1)}$$

$$PN_w = \sum_{w=1}^{w=5} PN_{KKH,w} * I_w \text{ (Equation 4.2)}$$

$$PC_w = \sum_{w=1}^{w=5} PC_{KKH,w} * I_w \text{ (Equation 4.3)}$$

Here, B_w is the number of bronchiolitis admissions in ward class w across all Singapore hospitals. I_w is a ward class-specific inflation factor. Estimates for pneumonia with and without complications are derived analogously.

To estimate the hospitalization costs, we first multiplied the number of admissions (for each diagnosis and ward class) by the average duration of hospitalization:

$$D_{B,w} = B_w * d_B$$

$D_{B,w}$, the total bronchiolitis hospitalization days among patients in ward class w , is obtained by multiplying the total number of bronchiolitis admissions in wards of class w by the average duration of hospitalization for bronchiolitis patients. The total days of hospitalization in each ward class for uncomplicated and complicated pneumonia admissions were derived analogously. The full (unsubsidised) cost of hospitalization was then:

$$T_B = \sum_{w=1}^{w=5} D_{B,w} * s_{B,w=1} \text{ (Equation 5)}$$

where T_B represents the total cost of bronchiolitis hospitalizations across all ward classes and $s_{B,w=1}$ is the average cost per day of hospitalization for a bronchiolitis patient admitted in

class A (private wards), obtained from MOH billing data for admissions to KKH. Ward-specific costs for uncomplicated and complicated pneumonia admissions were similarly derived.

The subsidized cost (that borne by patients through insurance or out-of-pocket payments) was estimated by applying the ward class-specific mean daily hospitalization costs, $S_{B,w}$:

$$S_B = \sum_{w=1}^{w=5} D_{B,w} * S_{B,w} \text{ (Equation 6)}$$

Costs for uncomplicated and complicated pneumonia were derived analogously.

Estimating Primary Care Consultations Due to RSV

We obtained data on the number of acute respiratory infection (ARI) consultations to government polyclinics among children <5 years of age from the Ministry of Health. We also obtained data from the National Public Health Laboratory on RSV testing results from microbiological surveillance of primary care ARI consultations. Samples from ARI patients are submitted for microbiological testing by participating sentinel primary care centers. These samples have been tested using a commercial multiplex PCR assay (Seegene Allplex Respiratory Panel Assays; <http://seegene.com>). Between 2012–2017, 3,402 samples were tested from children <5 years, of which 8.2% were positive for RSV with no other pathogen identified. To estimate the number of polyclinic consultations attributable to RSV, we applied the proportion of samples positive for RSV to the number of polyclinic consultations as follows:

$$F = \frac{K}{M} * G$$

$$K \sim \text{Binom}(\pi_1, M)$$

where π_1 is the proportion of samples testing positive for RSV, M is the total number of tests performed on samples from children aged <6 months, and G is the number of ARI consultations in polyclinics.

To account for primary care consultations in the private sector, we estimated the ratio of pediatric consultations in polyclinics versus private GPs, using data on the proportion of consultations among children <5 years in polyclinics and private GPs as reported by MOH in the 2014 Primary Care Survey (3). We assumed binomial distributions for these proportions:

$$q = \frac{Q}{G} + 1$$

$$R = q * G$$

$$Q \sim \text{Binom}(\pi_2, W)$$

Here, q is a multiplier that inflates the number of polyclinic consultations, G , to account for private sector consultations. Q represents the number of private GP consultations by children aged <6 months among GP clinics participating in the 2014 Primary Care Survey. Q is assumed to have a binomial distribution dependent on W , the daily number of private GP consultations, and π_2 , the proportion of these occurring among children <5 years. R is an estimate of the total number of primary care consultations for RSV, both among polyclinics and private GP clinics.

Because primary care ARI consultation data were not available in fine age strata, we estimated the age distribution of primary consultations among children <5 years by month of age. We assumed that this age distribution was similar to the age distribution of RSV-positive identifications at KKH. We fitted a logarithmic function to the age-related RSV data (Appendix Figure 3) and applied this function to the estimated number of RSV-related primary care consultations to estimate the proportion of primary care consultations by month of age:

$$\ln(R_m) = i_0 + i_1 R_1 + i_2 R_2 + i_3 R_3 \text{ (Equation 7)}$$

where R_m represents the number of RSV-related polyclinic consultations among children aged m months, R_1 to R_3 are age group indicators, i_1 to i_3 the corresponding regression coefficients and i_0 is a constant term. The terms R_1 to R_3 are defined as:

$$R_1 = \begin{cases} 0, m = 0 \\ 1, m \geq 1 \end{cases}$$

$$R_2 = \begin{cases} 0, m < 2 \\ 1, m = 2 \\ 2, m > 2 \end{cases}$$

$$R_3 = \begin{cases} 0, m < 3 \\ m - 3, m \geq 3 \end{cases}$$

The number of RSV-related primary care consultations among children aged <6 months is:

$$C = c * R$$

$$c = \frac{\sum_{m=0}^5 R_m}{R}$$

with c representing the proportion of RSV-related consultations that occur in children aged <6 months.

We estimated the full cost of consultations by applying the unsubsidized cost of a polyclinic consultation to the estimated number of primary care visits due to RSV. To estimate the subsidized cost, we applied the cost of a pediatric consultation:

$$U = C * u \text{ (Equation 8.1)}$$

$$V = C * v \text{ (Equation 8.2)}$$

where U and V represent respectively the full and subsidized cost of all RSV-related primary care consultations in children <6 months of age, u is the full cost of a polyclinic consultation, and v is the subsidized cost of a pediatric polyclinic consultation.

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Appendix Table 1. Distribution of RSV-positive identifications at KK Women's and Children's Hospital, Singapore, by sex, age and year

Variable	No. RSV-positive identifications (N = 18,428)	% RSV positive
Sex		
M	11,488	62.3
F	6,940	37.7
Age, mo		
<1	449	2.4
1	1,154	6.3
2	1,197	6.5
3	932	5.1
4	999	5.4
5	985	5.3
6	1,077	5.8
7	1,026	5.6
8	971	5.3
9	875	4.7
10	786	4.3
11	742	4.0
12	757	4.1
13	620	3.4
14	632	3.4
15	556	3.0
16	518	2.8
17	450	2.4
18	462	2.5
19	460	2.5
20	468	2.5
21	480	2.6
22	420	2.3
23	382	2.1
24	250	1.4
25	179	1.0
26	166	0.9
27	146	0.8
28	138	0.7
29	151	0.8
Year		
2005	1,818	9.9
2006	1,480	8.0
2007	2,001	10.9
2008	2,075	11.3
2009	1,807	9.8
2010	2,236	12.1
2011	2,362	12.8
2012	2,251	12.2
2013	2,398	13.0

Appendix Table 2. Estimated bronchiolitis and pneumonia admissions in KK Women's and Children's Hospital, Singapore, by year and age group

Year	<6 mo (95% CI)	6–29 mo (95% CI)
2005	231 (209–252)	271 (209–252)
2006	149 (135–162)	257 (135–162)
2007	311 (283–340)	495 (283–340)
2008	291 (264–318)	553 (264–318)
2009	247 (225–270)	421 (225–270)
2010	334 (303–365)	501 (303–365)
2011	363 (330–397)	569 (330–397)
2012	368 (334–403)	585 (334–403)
2013	375 (340–409)	680 (340–409)

Appendix Table 3. Observed and model-predicted percentage of all bronchiolitis and pneumonia admissions due to pneumonia by age, KK Women's and Children's Hospital, Singapore, 2005–2013*

Age, mo	Observed %	Predicted % (95% CI)*
0	18.1	18.6 (15.7–21.9)
1	11.2	10.8 (9.7–12.0)
2	7.0	7.0 (6.1–8.0)
3	4.8	5.7 (5.0–6.4)
4	6.1	5.5 (4.8–6.4)
5	7.1	6.0 (5.1–7.0)
6	5.1	6.6 (5.8–7.4)
7	7.4	7.2 (6.3–8.3)
8	7.0	7.7 (6.8–8.8)
9	10.6	8.3 (7.4–9.3)
10	9.7	9.2 (8.1–10.5)
11	10.6	10.8 (9.7–12.1)
12	10.3	12.8 (11.7–14.0)
13	13.9	14.4 (13.1–15.9)
14	13.4	15.1 (13.6–16.7)
15	17.3	15.0 (13.7–16.4)
16	17.4	14.8 (13.7–16.0)
17	18.0	15.1 (13.9–16.3)
18	17.3	16.4 (15.1–17.8%)
19	23.9	18.9 (17.5–20.5)
20	22.2	22.7 (21.1–24.3)
21	24.4	27.6 (26.1–29.2)
22	28.6	33.7 (32.0–35.3)
23	25.7	40.3 (38.5–42.2)
24	45.2	47.1 (45.0–49.2)
25	61.2	53.6 (51.3–55.9)
26	66.3	59.6 (57.2–62.0)
27	69.9	65.1 (62.7–67.3)
28	79.3	69.9 (67.6–72.0)
29	74.5	74.0 (72.0–76.0)
30	81.7	77.6 (75.7–79.4)
31	84.2	80.6 (78.9–82.2)
32	83.6	83.2 (81.6–84.6)
33	88.1	85.3 (83.8–86.7)
34	87.1	87.1 (85.7–88.4)
35	94.1	88.6 (87.3–89.9)
36	95.1	89.9 (88.6–91.1)
37	87.4	91.0 (89.7–92.1)
38	93.6	91.9 (90.6–93.0)
39	89.5	92.7 (91.4–93.7)
40	96.0	93.3 (92.1–94.4)
41	94.9	93.9 (92.8–94.9)
42	93.8	94.4 (93.3–95.3)
43	92.1	94.8 (93.8–95.7)
44	91.2	95.2 (94.2–96.0)
45	92.5	95.5 (94.5–96.3)
46	92.5	95.7 (94.8–96.5)
47	94.7	96.0 (95.1–96.7)
48	94.3	96.2 (95.4–96.9)
49	92.9	96.3 (95.6–97.0)
50	94.2	96.5 (95.7–97.1)

Age, mo	Observed %	Predicted % (95% CI)*
51	98.7	96.6 (95.9–97.2)
52	94.4	96.7 (96.0–97.3)
53	96.6	96.8 (96.1–97.4)
54	98.9	96.9 (96.2–97.5)
55	98.9	96.9 (96.2–97.5)
56	94.9	97.0 (96.3–97.6)
57	96.2	97.0 (96.3–97.6)
58	98.6	97.1 (96.3–97.7)
59	93.2	97.1 (96.3–97.7)
60	98.4	97.1 (96.2–97.8)
61	97.0	97.1 (96.2–97.8)
62	98.6	97.1 (96.1–97.9)
63	97.1	97.1 (96.0–97.9)
64	96.3	97.1 (95.9–97.9)
65	97.3	97.1 (95.8–98.0)
66	98.2	97.0 (95.6–98.0)
67	93.2	97.0 (95.5–98.0)
68	97.7	97.0 (95.3–98.1)
69	100.0	96.9 (95.1–98.1)
70	98.0	96.9 (95.0–98.1)
71	100.0	96.9 (94.8–98.2)
72	100.0	96.8 (94.5–98.2)

*Percentage estimated from the regression model in Equation 2 (see also Figure 2)

Appendix Table 4. Sensitivity analysis for RSV-attributable burden by negative binomial regressions for 2005–13 data

Age group, mo	Model*	Description	β †	se(β)	BIC‡	% RSV§	No. RSV admissions¶
<6 mo	1	No trend	0.8907	0.0439	-2348.104	47.0%	5686
	2	Linear trend	0.9018	0.0461	-2341.217	47.6%	5686
	3	Quadratic trend	0.9041	0.0462	-2335.750	47.7%	5686
	4	Exclude 2009 and no trend	0.9137	0.0464	-2039.162	47.9%	5716
	5	Exclude 2009 and two trend terms	0.9174	0.0488	-2026.919	48.0%	5730
	6	Include rotavirus	0.9050	0.0444	-2343.507	47.7%	5686
	7	Include GI admissions	0.8893	0.0439	-2342.419	46.9%	5686
	8	Include influenza	0.8710	0.0448	-2346.221	45.9%	5687
6–29 mo	1	No trend	0.9238	0.0543	-2322.363	34.3%	12647
	2	Linear trend	0.7832	0.0562	-2316.329	29.1%	12646
	3	Quadratic trend	0.7834	0.0561	-2308.695	29.1%	12645
	4	Exclude 2009 and no trend	0.9600	0.0571	-2008.451	35.3%	12750
	5	Exclude 2009 and two trend terms	0.7965	0.0590	-1993.141	29.2%	12787
	6	Include rotavirus	1.0140	0.0534	-2319.427	37.6%	12647
	7	Include GI admissions	0.9100	0.0518	-2313.869	33.8%	12645

*Model descriptions: 1, includes term for RSV-positive identifications only; 2, includes a linear trend term; 3, includes quadratic trend term; 4, excludes 2009 data; 5, excludes 2009 data and includes 2 separate linear trend terms for before and after 2009; 6, includes rotavirus-positive identifications.

†Coefficient from negative binomial regression.

‡Bayes information criterion.

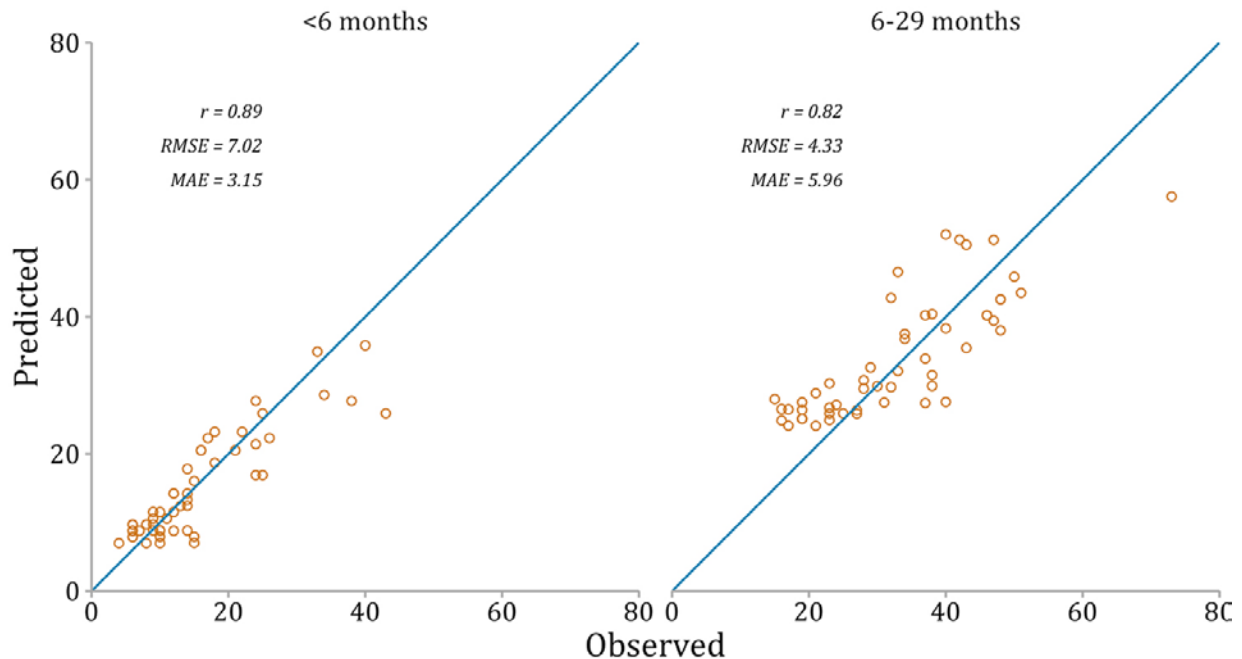
§Percentage of bronchiolitis and pneumonia admissions attributable to RSV.

¶Estimated RSV-associated admissions for bronchiolitis and pneumonia 2005–2013.

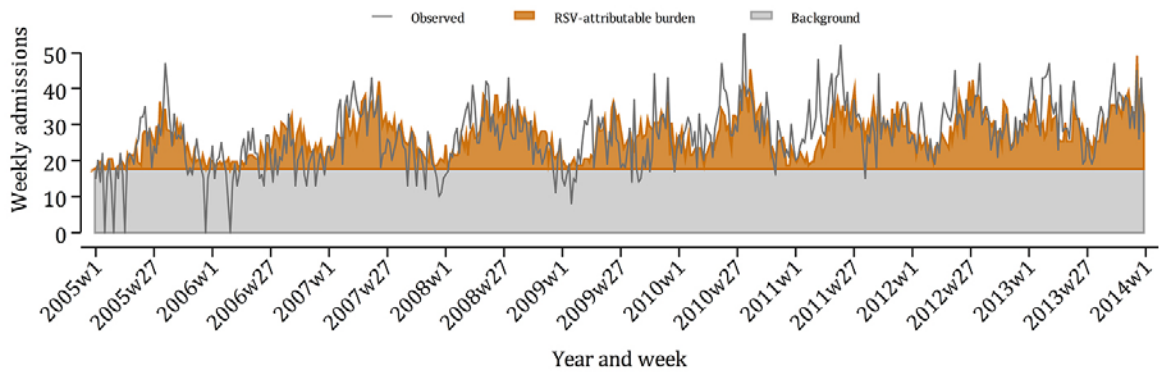
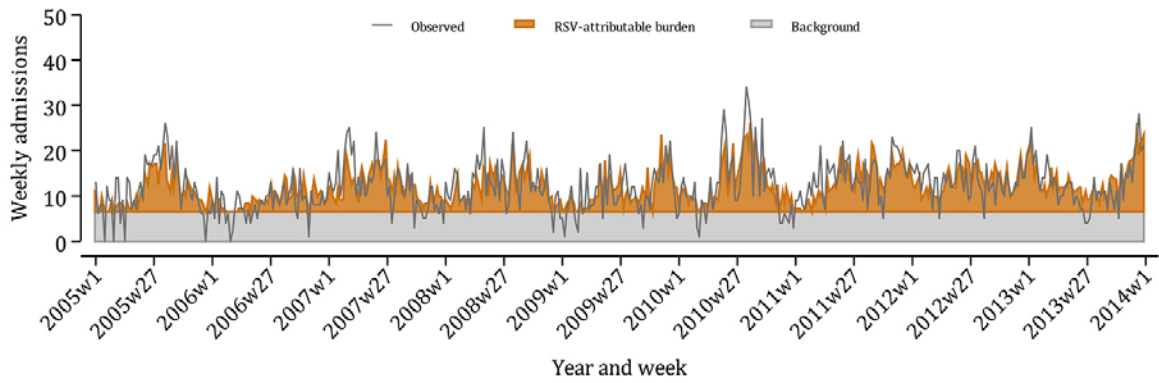
Appendix Table 5. KK Women's and Children's Hospital admissions for bronchiolitis and pneumonia by ward type*

Condition	Ward type	No. admissions (%)	Average LOS	Mean bill size, SGD	Daily bill size, SGD
Bronchiolitis	A	449 (28.4)	2.5	2,368	947
	B1	125 (7.9)	2.3	1,477	642
	B2+	244 (15.5)	2.3	925	402
	B2	98 (6.2)	2.2	554	252
	C	663 (42.0)	2.5	402	161
	Total	1,579 (100.0)			
Pneumonia (no complications)	A	378 (37.2)	2.9	2,853	984
	B1	118 (11.6)	2.6	1,696	652
	B2+	207 (20.4)	2.6	1,087	418
	B2	115 (11.3)	2.8	892	319
	C	197 (19.4)	3	544	181
	Total	1,015 (100.0)			
Pneumonia with complications	A	87 (38.3)	3.5	3,481	995
	B1	0 (0.0)	0	NA	NA
	B2+	45 (19.8)	3.5	1,295	370
	B2	0 (0.0)	0	NA	NA
	C	95 (41.9)	5.1	1,063	208
	Total	227 (100.0)			

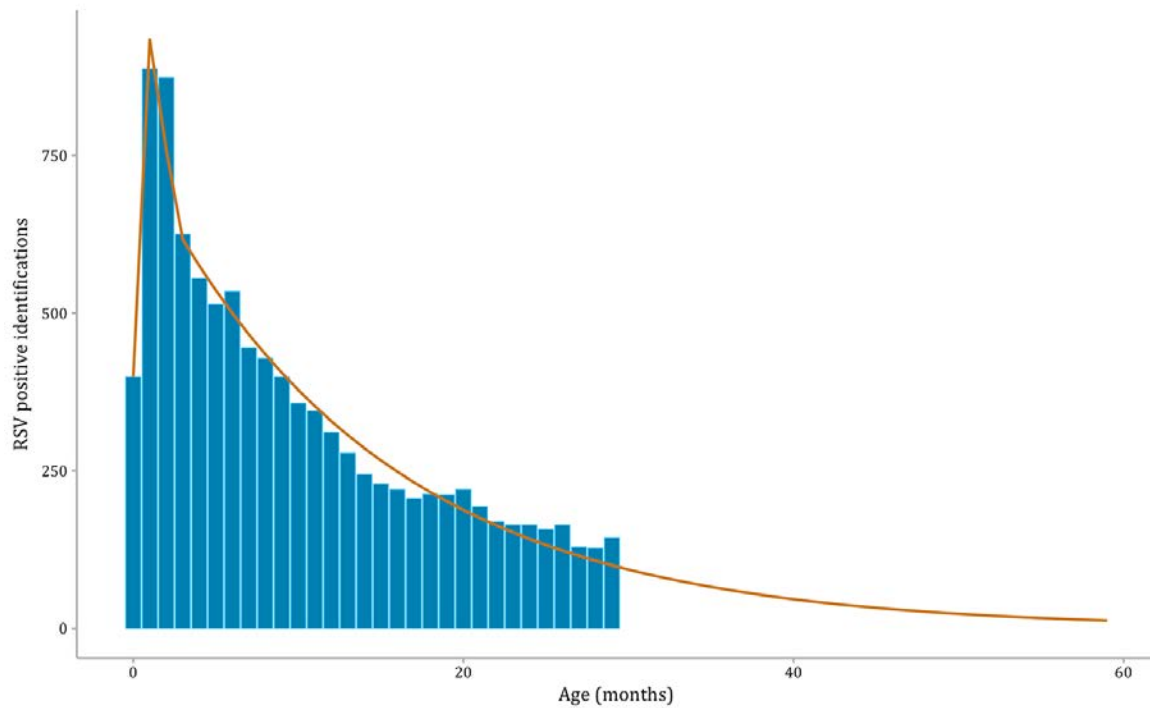
*KKH admissions for bronchiolitis and pneumonia, July 1, 2016–June 30, 2017, billing by ward type. LOS, length of stay; NA, not applicable.



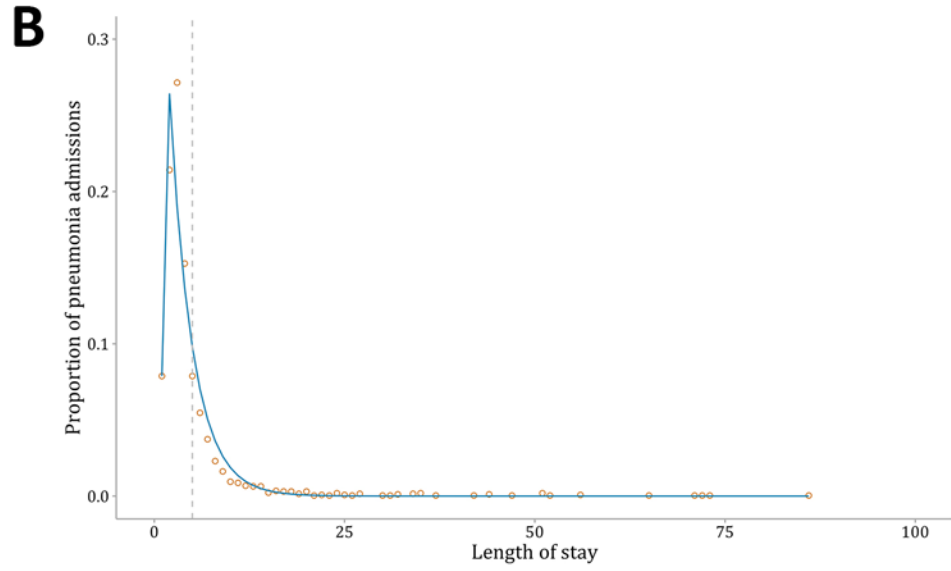
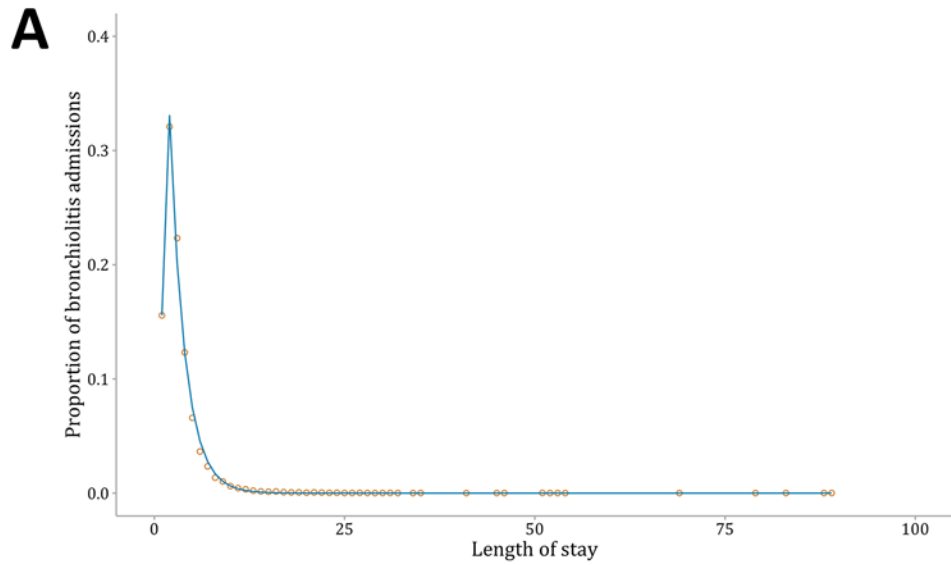
Appendix Figure 1. Correlation between observed and model-predicted weekly bronchiolitis and pneumonia admissions at KK Women's and Children's Hospital in 2014, by age group. R, correlation coefficient; RMSE, root mean squared error; MAE, mean absolute error.



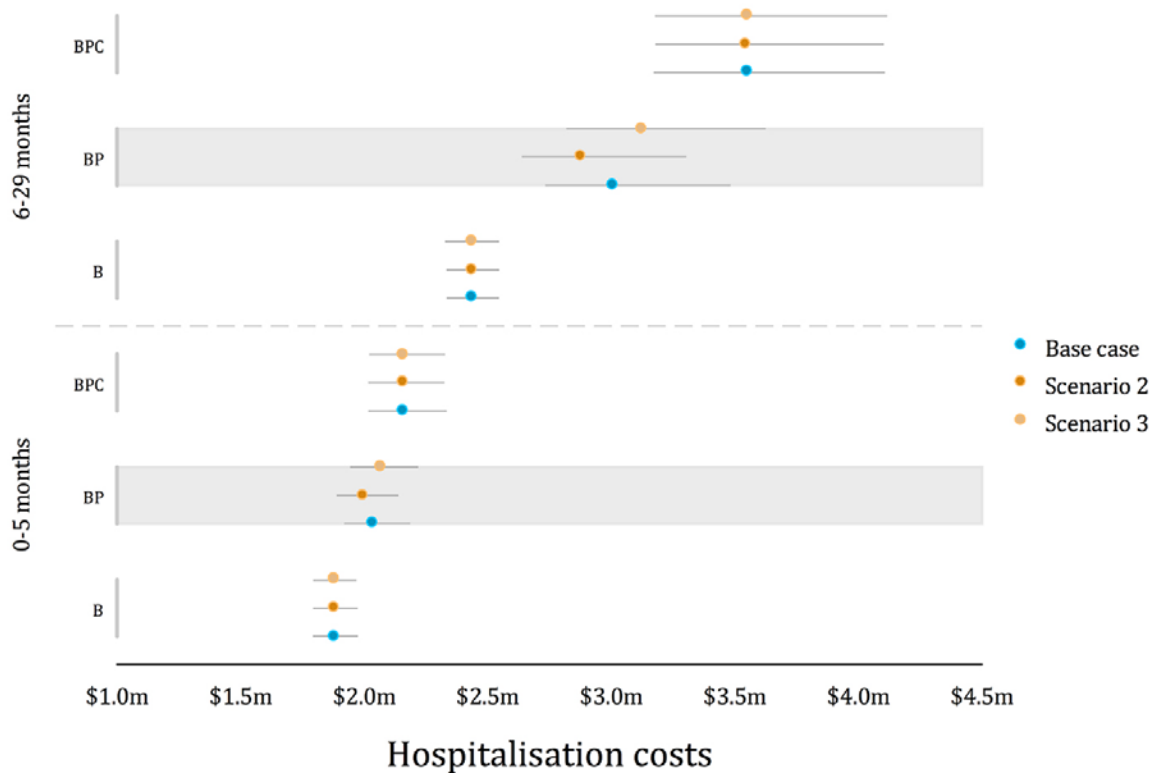
Appendix Figure 2. Observed and model-predicted weekly hospitalizations for bronchiolitis and pneumonia, KKH Women’s and Children’s Hospital, Singapore, 2005–2013. A) Children <6 months of age. B) Children 6–29 months of age. Gray line represents observed weekly bronchiolitis and pneumonia hospitalizations; orange area represents model-estimated RSV-attributable hospitalizations; gray area represents admissions attributable to other pathogens.



Appendix Figure 3. Age distribution of RSV-positive identifications at KK Women's and Children's Hospital. Blue bars indicate observed data; orange line indicates predicted values up to the age of 59 months from a logarithmic model.



Appendix Figure 4. Distribution of length of stay at KK Women’s and Children’s Hospital for bronchiolitis (A) and pneumonia (B) admissions among children <30 months of age. Orange circles indicate observed data; blue lines indicate predicted values from a logarithmic model; dashed line (panel B) indicates cutoff of 5 days used to define pneumonia with complications. A total of 5 observations with length of stay >100 days were omitted from panel A.



Appendix Figure 5. Impact of varying the definition of pneumonia with complications on estimated hospitalization costs. Pneumonia with complications is defined for 3 scenarios: base case, length of stay (LOS) >5 days; Scenario 2, LOS >4 days; Scenario 3, LOS >6 days.

Varying the definition of pneumonia with complications has little effect on the overall cost estimates because the daily hospitalization bill size is similar for pneumonia admissions with and without complications; the higher overall unit cost of admissions for pneumonia with complications is largely driven by longer hospital stays. B, bronchiolitis only; BP: bronchiolitis and pneumonia without complications, BPC, bronchiolitis, uncomplicated pneumonia, and pneumonia with complications.