International Journal of Infectious Diseases 124 (2022) 14–20

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Age-specific hospitalization risk of primary and secondary respiratory syncytial virus infection among young children

Ko Nakajo [1,2], Hiroshi Nishiura [1,*]

[1] Kyoto University School of Public Health, Kyoto, Japan
[2] Sanofi K.K. Tokyo Opera City Tower, 3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo, Japan

ARTICLE INFO

Article history:
Received 24 May 2022
Revised 31 August 2022
Accepted 5 September 2022

Keywords:
Epidemiology
Statistical model
Respiratory syncytial virus
RSV
Hospitalization
Japan

ABSTRACT

Objectives: Elucidating the infection dynamics that lead to severe respiratory syncytial virus (RSV) pneumonia and hospitalization among young children are critical. We explored the role of infection parity as well as age in months for RSV-associated hospitalization among young children in Japan.
Methods: We used a sequential transmission catalytic model to capture the transmission mechanisms of RSV among infants in an endemic state. We investigated data on the age-dependent seroprevalence and incidence rate of hospitalization in Japan, and jointly estimated the age-specific risk of hospitalization during primary RSV infection and relative risk of hospitalization during secondary infection in children aged <5 years.
Results: The estimated risk of hospitalization with primary infection was 0.08 (95% CI: 0.05-0.14) in infants aged 0-2 months. The estimated relative risk of hospitalization owing to secondary infection was 0.18 (95% CI: 0.01-2.04).
Conclusion: Our simple models successfully captured the infection dynamics of RSV among young children in Japan. The age group of early infancy may be most vulnerable to infection and hospitalization, offering key insights into future vaccinations. The burden of hospitalization from secondary infection may be less important in young children.

Introduction

Respiratory syncytial virus (RSV) is a single-stranded RNA virus belonging to the family *Pneumoviridae*. Humans are natural hosts of RSV, which is usually transmitted through respiratory droplets from infected individuals or direct contact with contaminated environmental surfaces (Karron, 2017). Manifestations of RSV infection range from mild upper respiratory symptoms to severe lower respiratory infections (e.g., bronchiolitis and pneumonia), which can sometimes lead to death, especially in low-income settings (Hall *et al.*, 1979). Nearly all children are reported to be infected with RSV by the age of 2 (Glezen *et al.*, 1986). Reinfection with RSV occurs throughout life but tends to be milder among healthy older children and adults (Hall *et al.*, 1976). There are presently no specific approved treatments or preventive measures indicated for all young children; therefore, the virus still causes seasonal epidemics in this age group, typically annually, with a substantial public health impact (Li *et al.*, 2021; Li *et al.*, 2022; Nair *et al.*, 2010; Shi *et al.*, 2017; Stein *et al.*, 2017). Among 58 countries, the median number of RSV-associated hospitalizations owing to acute lower respiratory infections in children aged < 5 years was estimated to be 8250 in 2019 (Li *et al.*, 2021), RSV is the main cause of death from lower respiratory infections in children aged < 1 year (Lozano *et al.*, 2012). In addition, antibiotic misuse in RSV treatment is common, and the risk of antimicrobial resistance represents another serious burden associated with this infection (Obolski *et al.*, 2021).

In Japan, RSV infection is designated as a category V infectious disease, and pediatric sentinel surveillance has been implemented since 2003 (Taniguchi *et al.*, 2007). RSV infections diagnosed via reverse transcriptase–polymerase chain reaction and rapid antigen tests are monitored and reported weekly (National Institute of Infectious Diseases, 2022). Before the COVID-19 pandemic in 2020, more than 100,000 infections were reported annually at approximately 3000 pediatric sentinel sites (Fig. 1a) (National Institute of Infectious Diseases, 2018; National Institute of Infectious Diseases, 2022). The majority of cases (88%) reported in 2017 occurred

* Corresponding author: Hiroshi Nishiura, Yoshidakonoecho, Sakyoku, Kyoto 6018503, Japan, Tel: +81 75 753 4456, Fax: +81 75 753 4458.
E-mail address: nishiura.hiroshi.5r@kyoto-u.ac.jp (H. Nishiura).

https://doi.org/10.1016/j.ijid.2022.09.008

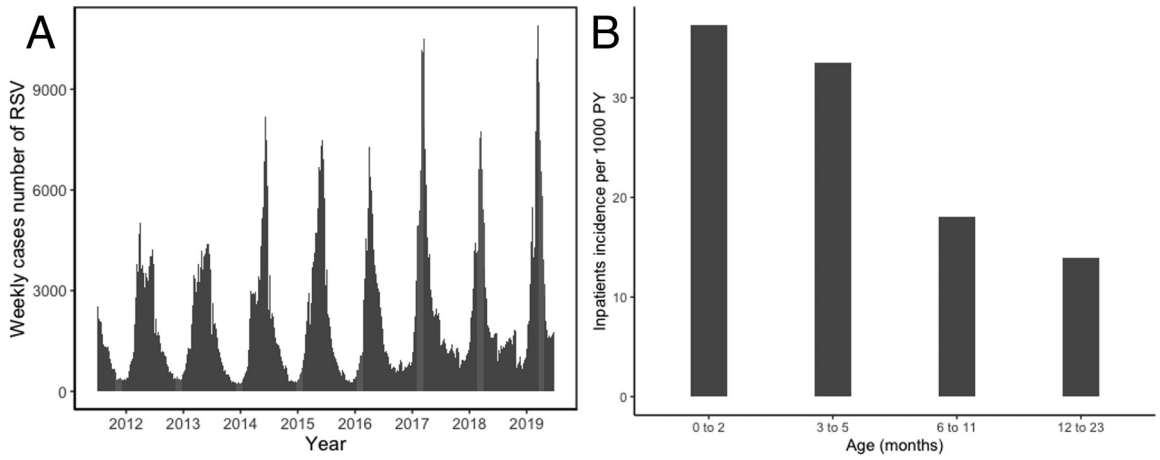

Figure 1. Incidence of RSV in Japan. (a) Weekly trend of notified RSV cases from sentinel sites, 2012–2019; (b) incidence rate of hospitalization per 1000 PY, 2017–2018. PY, person-years; RSV, respiratory syncytial virus.

in children aged < 2 years (National Institute of Infectious Diseases, 2022). The burden of disease caused by RSV among children is also considerable in developed nations other than Japan, where RSV is reported to be the leading cause of hospitalization among infants aged under 12 months (Inagaki *et al.*, 2021). The cost of hospitalization owing to RSV infection is substantial, especially in cases associated with intensive care and treatment procedures such as mechanical ventilation (Sruamsiri *et al.*, 2018).

Elucidating the infection dynamics that lead to severe RSV pneumonia and hospitalization among young children is critical. Published evidence suggests that age in months and infection parity could be effect modifiers of severity. In a recent study that examined national-level RSV-related hospitalizations in 58 countries, the proportion of RSV-associated hospitalizations was highest among infants aged < 1 year, and among all hospitalizations in children aged < 5 years (Li *et al.*, 2021). A birth cohort study indicated that the risk of RSV-associated severe lower tract infection is inversely associated with increasing age (range: 0-30 months), with statistical significance (Ohuma *et al.*, 2012). In Japan, a retrospective cohort study using a commercially available database of big data also showed that among all children aged < 2 years infants <3 months of age had the highest incidence of hospitalization for RSV (Fig. 1b) (Kobayashi *et al.*, 2022). However, the contribution of infection parity to disease severity in young children seems not as well established as age in months. A classical longitudinal study in the United States showed that illness was milder in reinfection with RSV than in cases of primary infection (Henderson *et al.*, 1979). Nevertheless, Ohuma *et al.* (2012) indicated that the risk of severe lower respiratory tract infection in reinfected individuals was not significantly different from that in primary infection, after adjustment for age class.

In the present study, we investigated the role of infection parity as well as age in months for RSV-associated hospitalizations among young children in Japan. We aimed to capture the transmission mechanisms of RSV among infants in an endemic state using a sequential transmission catalytic model. We estimated the age-specific risk of hospitalization for primary or secondary RSV infection using age-specific seroprevalence data as well as incidence data of hospitalized cases. We also jointly estimated epidemiological parameters governing the underlying dynamics, including the force of infection, i.e., the rate at which susceptible individuals experience each infection. Given the estimated parameters, we explored the impact of mass vaccination targeting young children on RSV-related hospitalization in Japan.

Methods

Epidemiological data

The present study leveraged two pieces of epidemiological information: (i) the seroprevalence of infection with RSV in Japan and (ii) the incidence of hospitalizations for RSV across multiple seasons in Japan. For the former, we revisited a published study on RSV seroprevalence carried out in Sendai city, Japan (Suto *et al.*, 1965). A total of 514 serum specimens were collected from 406 acute respiratory cases, 60 non-respiratory cases, and 48 healthy controls between January 1963 and June 1964. Neutralizing antibodies against the prototype long strain were tested and sera with titers of 1:2 or greater were defined as positive. The numerical values of the proportion in each age category (i.e., 0-3 months, 4-6 months, 7-11 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6-13 years, and high school students up to 18 years) were retrieved from the publication.

We collected data for patients hospitalized owing to RSV infection from two independent studies that adopted the same nationwide insurance claims database in Japan (Japanese Medical Data Center; JMDC) (Goto and Ispus, 2018; Kobayashi *et al.*, 2022). The database includes anonymous outpatient and inpatient claims data from health insurance in Japan. The cumulative number of insured is approximately 14 million, covering approximately 10% of the entire Japanese population (Japan Medical Data Company, 2020). Kobayashi *et al.* (2022) reported the number of RSV-related outpatients and inpatients and total person-years in the JMDC population by age group (0-2, 3-5, 6-11, and 12-23 months) from January 2017 through December 2018. Goto and Ispus (2018) reported the number of RSV-associated admissions per 1000 person-years using more granulated and older ages (i.e., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 36, and 48 months) among young children from 2006 through 2015. We reviewed the original values to identify the number of admissions per 1000 person-years and rounded them to integer values.

Sequential transmission model of RSV infection

We developed a compartment model of the transmission dynamics of RSV among children, extending a simple catalytic S-I (susceptible-infected) model to describe two features specific to RSV infection (Fig. 2), i.e., immunity at birth derived from maternal antibodies and reinfection. Each compartment represents an age-specific state of RSV infection: $M(a)$ is the proportion of in-

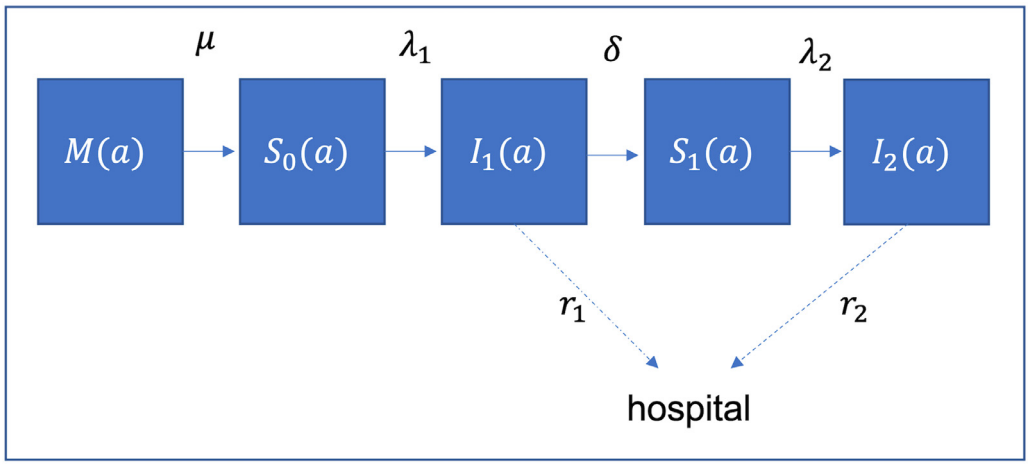

Figure 2. Sequential catalytic model. Each compartment represents an age-specific state of respiratory syncytial virus infection. $M(a)$ is the proportion of individuals with maternal immunity at age a. $S_0(a)$ and $S_1(a)$ are the proportion of individuals susceptible to primary or secondary infection, respectively. $I_1(a)$ and $I_2(a)$ are the proportion of individuals ever infected in a primary or secondary infection, respectively. λ_1 and λ_2 are the force of infection at which susceptible individuals experience a primary or secondary infection, respectively. μ is the rate of loss of maternal immunity and δ is the rate of immunity loss from the primary infection. $r_1(a)$ and $r_2(a)$ are the risks of hospitalization following primary and secondary infection, respectively.

dividuals with maternal immunity at age a, $S_0(a)$ and $S_1(a)$ are the proportion of individuals susceptible to primary or secondary infection, respectively, and $I_1(a)$ and $I_2(a)$ are the proportion of individuals ever infected in a primary or secondary infection, respectively. A similar sequential approach was adopted in several published studies (Nyiro *et al.*, 2017; Pitzer *et al.*, 2015; Weber *et al.*, 2001). Regarding reinfection with RSV, we assumed that there is one event of reinfection before achieving substantial immunity to RSV and illness during the first years of life in children, which is the same approach adopted in a modeling study (Nyiro *et al.*, 2017) and empirically supported in longitudinal studies (Kutsaya *et al.*, 2016; Yamaguchi *et al.*, 2011). We estimated the force of infection for primary and secondary infections (i.e., the rate at which susceptible individuals experience each infection), λ_1 and λ_2, respectively, and the rate of the loss of maternal immunity (μ), using age-dependent seroprevalence data (Fig. 2). The rate of loss of immunity from the first infection (δ) was assumed to be 0.33/month, according to a past study (Sande *et al.*, 2013). The following assumptions were additionally made: (i) the force of infection for each infection was age independent, for simplicity; (ii) the proposed model was not affected by a specific strain circulating in the population (i.e., RSV A or B strain); and (iii) excess risk of RSV death can be negligible compared with the per capita risk of death in the same age group. We analytically solved for the age-dependent proportion of susceptible individuals based on our sequential model. The observed number of age-dependent seropositive results was assumed to follow a binomial distribution. Supposing that there were n_a seropositive and m_a seronegative results at age a from seroprevalence data D_1 and the susceptible proportion at age a for primary and secondary infection was $S_0(a)$ and $S_1(a)$, respectively, the likelihood function to estimate λ_1, λ_2, and μ is proportional to:

$$L_s(\theta|D) = L(\lambda_1,\ \lambda_2,\ \mu|D_1) = \prod_a (1 - S_0(a) - S_1(a))^{n_a} (S_0(a) + S_1(a))^{m_a}. \quad (1)$$

Age-specific risk of hospitalization owing to RSV

In addition to the force of infection parameters, we estimated the age-specific risks of hospitalization conditional on primary and secondary infections, respectively. Letting $r_1(a)$ and $r_2(a)$ be the age-specific risks of hospitalization following primary and secondary infection, respectively (Fig. 2), the incidence of primary and secondary infection at age a is $\lambda_1 S_0(a)$ and $\lambda_2 S_1(a)$, respectively; then, the expected number of hospitalizations among children at age a would be written as $r_1(a)\lambda_1 S_0(a) + r_2(a)\lambda_2 S_1(a)$. Assuming that the observed number of hospitalizations follows a Poisson distribution, the likelihood of estimating $r_1(a)$ and $r_2(a)$ from the number of hospitalizations using two pieces of empirical data (i.e., JMDC studies by Goto and Ispus (2018) from 2006-15 and Kobayashi *et al.* (2022) from 2017-18; denoted as D_2 and D_3) is:

$$L_h(\theta|D) = L(\lambda_1,\ \lambda_2,\ \mu,\ r_1(a),\ r_2(a)|D_2,\ D_3) = \prod_a \frac{e^{-(r_1(a)\lambda_1 S_0(a) + r_2(a)\lambda_2 S_1(a))} ((r_1(a)\lambda_1 S_0(a) + r_2(a)\lambda_2 S_1(a)))^{h_{D_2}(a)}}{h_{D_2}(a)!} \frac{e^{-(r_1(a)\lambda_1 S_0(a) + r_2(a)\lambda_2 S_1(a))} (r_1(a)\lambda_1 S_0(a) + r_2(a)\lambda_2 S_1(a))^{h_{D_3}(a)}}{h_{D_3}(a)!} \quad (2)$$

where $h_{D_2}(a)$ and $h_{D_3}(a)$ are the observed number of hospitalizations at age a. Considering that the age-dependent mechanisms are governed by age-specific behaviors and other social factors, we assumed a constant proportionality between $r_1(a)$ and $r_2(a)$, i.e., $r_2(a) = kr_1(a)$, and we used a piecewise constant model for $r_1(a)$ for age categories with empirical observation, i.e., (i) 0-2 months, (ii) 3-5 months, (iii) 6-11 months, and (iv) 12-59 months. The total likelihood function, $L(\theta|D)$, is then described as a combination of (1) and (2), i.e.,

$$L(\theta|D) = L_s(\theta|D) L_h(\theta|D), \quad (3)$$

where θ and D are all the parameters and data used, respectively, e.g., θ includes λ_1, λ_2, μ, step function for $r_1(a)$, and k. Maximum likelihood estimates were obtained by minimizing the negative logarithm of (3). The 95%CIs of parameters and predicted epidemiological dynamics were computed by means of a parametric bootstrap resampling procedure: 1000 samples of parameters from a multinormal distribution with the covariance matrix, which is the inverse of the Hessian matrix, i.e., $\sigma^2 = \mathrm{diag}(H^{-1}(\theta))$. For each identical set of parameters, we assessed potential variation in the estimated parameter values. By taking the 2.5th and 97.5th percentiles of the simulated distributions, we obtained the 95% CI. More detailed mathematical descriptions are given in the Sup-

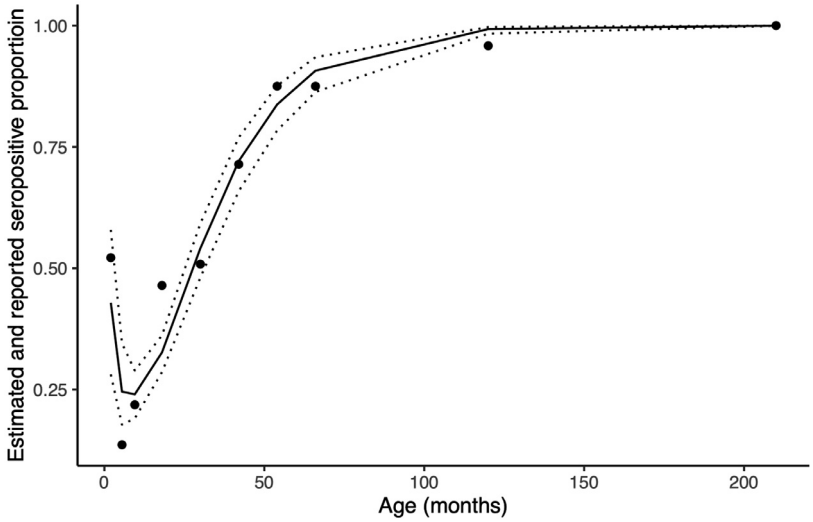

Figure 3. Age-specific seroprevalence of respiratory syncytial virus among children aged from 0 months to <19 years. Solid circles represent the observed proportion whereas the continuous black line shows the maximum likelihood estimate of the predicted proportion. Dotted lines represent lower and upper boundaries of the 95% CI based on the bootstrap method.

Table 1
Epidemiological parameters of RSV transmission.

Parameter	Description	Maximum likelihood estimate (95% CI)
μ	Rate of loss of maternal antibodies (/month)	0.50 (0.32-0.81)
λ_1	Primary force of infection (/month)	0.12 (0.07-0.18)
λ_2	Secondary force of infection (/month)	0.05 (0.04-0.06)
r_{0-2}	Risk of hospitalization during primary infection in children aged 0-2 months	0.08 (0.05-0.14)
r_{3-5}	Risk of hospitalization during primary infection in children aged 3-5 months	0.04 (0.03-0.05)
r_{6-11}	Risk of hospitalization during primary infection in children aged 6-11 months	0.03 (0.02-0.03)
r_{12-59}	Risk of hospitalization during primary infection in children aged 1 to <5 years	0.04 (0.03-0.07)
k	Relative risk of hospitalization during secondary infection	0.18 (0.01-2.04)

RSV, respiratory syncytial virus.

plement. All statistical data were analyzed using R version 4.0.3 (R Core Team, 2020).

Modeling the impact of immunization

Using the quantified system, we built a simple age-structured deterministic model to explore the impact of pediatric immunization on the incidence rate of hospitalization owing to RSV among children aged <5 years (Fig. S1). A similar method was applied to investigate varicella zoster dynamics (Brisson *et al.*, 2000); further details are available in the Supplement.

Results

Age-specific seroprevalence and the force of infection

The observed age-specific seroprevalence in Sendai city, Japan is shown in Fig. 3. The overall proportion of seropositivity was 62%. A total of 52% of infants aged 0 to 3 months were seropositive, presumably owing to the presence of maternally derived antibodies. The proportion of seropositivity then decreased to 14% in infants aged 4 to 6 months and subsequently increased with older age, reaching a plateau at more than 95% in children aged 6-13 years (Table S1). This pattern of age-dependent seroprevalence is consistent with the findings of several studies (Amaku *et al.*, 2009; Nyiro *et al.*, 2017; Sastre *et al.*, 2012). The force of infection for primary and secondary infections was estimated at 0.12 (95% CI: 0.07-0.18) and 0.05 (95% CI: 0.04-0.06) per month, respectively. The rate of loss of maternal immunity was estimated to be 0.50 (95% CI: 0.32-0.81) per month (Table 1). Thus, the average age at primary and secondary infection was estimated to be 10.6 months and 34.6 months, respectively. The predicted age-dependent seroprevalence on the basis of our sequential model qualitatively captured the observed pattern well (Fig. 3).

Age-specific risk of hospitalization

For the JMDC cohort from 2017 to 2018, the incidence rate of RSV-associated hospitalization was highest in infants aged 0 to 2 months, at 37.3 per 1000 person-years, and the average age at hospitalization among children aged <2 years was calculated as 9.0 months, from the original data (Kobayashi *et al.*, 2022) (Fig. 4a). The incidence rate of RSV-associated hospitalization was highest in infants aged 2 months at 38.0 per 1000 person-years (scanned value from an original figure) for the JMDC cohort from 2006 to 2015 (Goto and Ispus, 2018) (Fig. 4b). The age-specific risk of hospitalization conditional on primary RSV infection was estimated at 0.08 (95% CI: 0.05-0.14), 0.04 (95% CI: 0.03-0.05), 0.03 (95% CI: 0.02-0.03), and 0.04 (95% CI: 0.03-0.07) for infants or young children aged 0 to 2 months, 3 to 5 months, 6 to 11 months, and 12 to 59 months, respectively. The relative risk of hospitalization owing to secondary infection, k, was estimated at 0.18 (95% CI: 0.01-2.04) (Table 1). The observed and predicted age-dependent proportion of hospitalizations per population-year in each data set are shown in Fig. 4a and 4b. Supplementary Table S2 shows parameter estimates of the age-dependent force of infection; the age-dependent model still yielded a consistent relative risk of hospitalization during secondary infection of 0.18 (95% CI: 0.11-0.29).

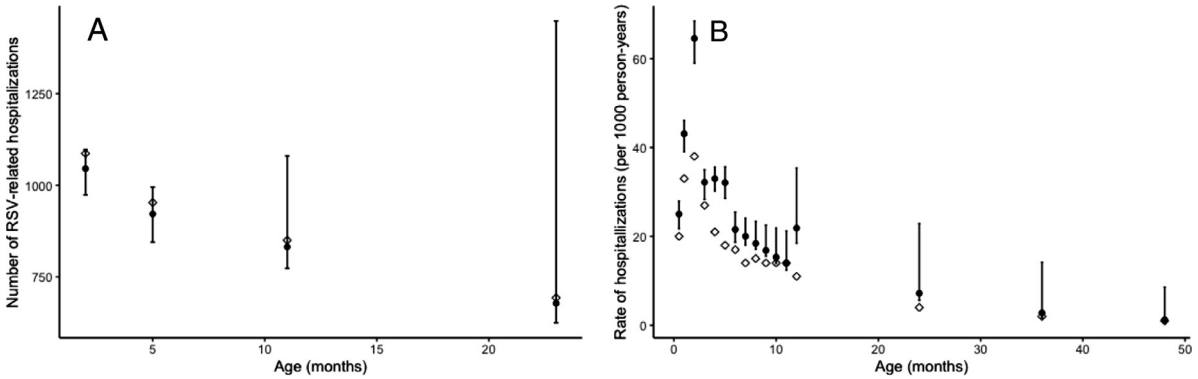

Figure 4. Age-specific incidence rate of hospitalization owing to RSV infection. (a) Incidence rate among children aged 0 to 23 months from 2017 to 2018. (b) Incidence rate among children aged 0 months to 4 years from 2006 to 2015. The open squares represent the observed incidence rate and the solid circles show the maximum likelihood estimate of the predicted incidence rate. Vertical lines represent the 95% CI based on the bootstrap method.
RSV, respiratory syncytial virus.

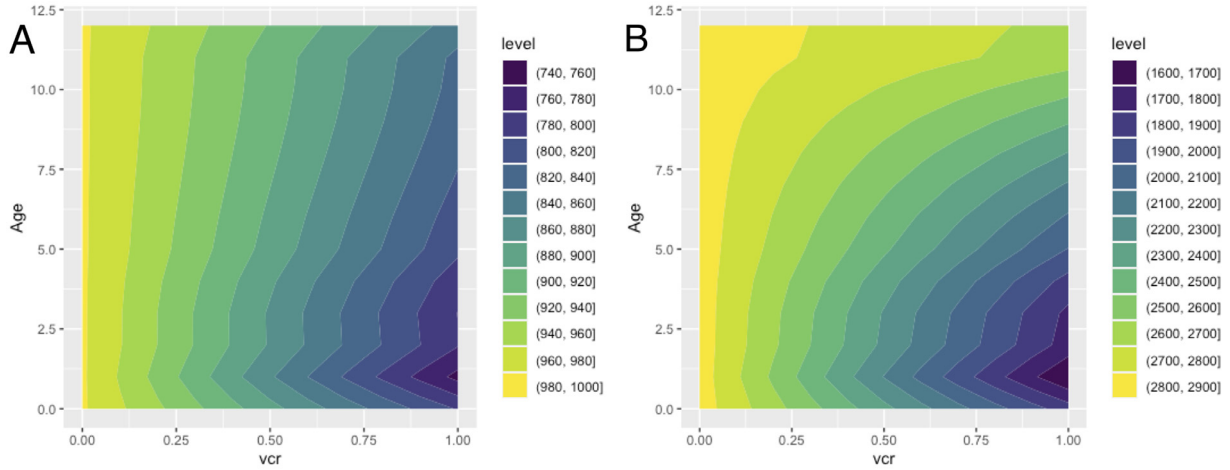

Figure 5. Incidence rate of hospitalization per 100,000 person-years at equilibrium owing to respiratory syncytial virus as a function of an effective vcr and age at vaccination in children aged <5 years (a) and in children aged <1 year (b).
vcr, vaccine coverage rate.

Pediatric vaccination against RSV

With an annual birth rate of 870,000 newborns and life expectancy of 80 years, the incidence rate of infection among children aged <5 years in Japan was predicted as 36,418 to 37,678 cases/100,000 person-years at equilibrium. The incidence of hospitalization in this age group was predicted to be 951 to 1019 cases/100,000 person-years. The incidence rate of hospitalization among infants aged <1 year was 2632 to 3147 cases/100,000 person-years.

Fig. 5 shows how the incidence rate of hospitalization in young children would behave, considering a possible range of variation in vaccination coverage and age at immunization. For the incidence rate of hospitalization in children aged <5 years, the age of immunization only had a modest impact (Fig. 5a), but immunization by age 1 to 3 months yielded a lower incidence than immunizing at older ages. The incidence rate of hospitalization in children aged <1 year was substantially affected by the age of immunization, and immunizing at approximately age 1 to 3 months was suggested to yield the minimum incidence (Fig. 5b).

Discussion

We examined data on the age-dependent seroprevalence and incidence rate of hospitalization in Japan and jointly estimated the age-specific risk of hospitalization during primary RSV infection and the relative risk of hospitalization during secondary infection in children aged < 5 years. The risk of hospitalization conditional on primary infection was highest among infants aged 0 to 2 months (0.083). The relative risk of hospitalization owing to secondary infection was small (0.18). We also jointly estimated the force of infection for primary and secondary infection with RSV as 12% and 5% per month, respectively.

To the best of our knowledge, the present study is the first to quantify epidemiological parameters governing the dynamics of RSV infection in Japan by investigating age-specific seroprevalence data. The average duration of maternal immunity was shown to be 1/0.50 (i.e., 2 months), indicating that infants become susceptible to primary RSV infection during the first months of life. Our estimate for the average age at primary infection based on seroprevalence study in Sendai city (10.6 months) is consistent with the value from a longitudinal study in Niigata city, Japan (Yamaguchi *et al.*, 2011). The average age at primary infection in Japan is younger than what has been reported in low-income countries, e.g., 15.1 months in Kenya (Nyiro *et al.*, 2017) and 1.58 years in Brazil (Amaku *et al.*, 2009). This difference may be explained by local factors that alter transmission frequency or by variations in model assumptions, e.g., M-S-I-S-I assumption (i.e. maternally immune-susceptible-primary infection-susceptible-secondary infection) in the present study versus the (M)-S-I assumed in other research.

We successfully quantified the risk of hospitalization conditional on RSV infection in granular, stratified age groups during infancy. Our predicted age-dependent proportion of hospitalizations in the JMDC data set for 2017-2018 captured the observed pattern well, whereas the predicted proportion in the JMDC data set for 2006-2015 tended to be overestimated compared with the observed data. This could be explained by the fact that bedside antigen testing for RSV was funded for all infants aged < 1 year from the 2012/2013 season and incident cases before that period may have been underreported (Jung *et al.*, 2020). Using an age-structured transmission model, van Boven *et al.* (2020) estimated the probability of hospitalization in RSV-infected infants aged less than 12 months as 1.4%. Our results suggest that there may be age-dependent heterogeneity in the risk of hospitalization, even among infants aged <1 year; the highest risk of being hospitalized (8.3%) was observed with primary infection in very early infancy (age 0-2 months). As for the contribution of parity to the risk of hospitalization, the relative risk of hospitalization because of secondary infection was small (0.18), implying that the burden of hospitalization from secondary infection may be less important in young children although more data would be needed to verify this finding considering the large variability. This is a biologically plausible finding because neutralizing antibodies after primary infection are suggested to contribute to reducing disease severity in cases of re-infection with RSV (Kawasaki *et al.*, 2004).

Our simple realistic age-structured model showed that the timing of vaccination is critical in terms of reducing hospitalizations among infants aged < 1 year. Very early infancy (i.e., age 1 to 3 months) was found to be the best time for vaccination under the plausible range of vaccine coverage. In low-income countries and with the same assumption that a single vaccine shot would be administered in infants, Kinyanjui *et al.* (2015) showed that immunization against RSV in infants aged 5 to 10 months is most effective in reducing hospitalizations among infants under the age of 6 months. As discussed above, different model assumptions, as well as older age at primary infection (Nyiro *et al.*, 2017), might explain the discrepancy in conclusions.

Several limitations in our study should be noted. First, we could not assess epidemiological parameters that extend to adult groups because we had no locally available data. There is no systematic surveillance of RSV cases among all age groups in Japan at present; establishing a national RSV surveillance system is warranted. Second, we assumed random mixing in the realistically age-structured (RAS) model for simplicity and because we lacked information that would enable us to capture the mixing patterns among infants and also those involving their parents. Incorporating age-dependent contact patterns into the model is a direction for future studies (van Boven *et al.*, 2020; Yamin *et al.*, 2016). Our RAS model involved other simplistic assumptions that are subject to debate. We arbitrarily assumed the worst-case scenario, given that there was little information on pediatric vaccines, and ignored other preventive modalities (e.g., maternal/elderly vaccines, long-acting monoclonal antibodies). More information on the plausible ranges of parameters, not only for pediatric vaccines but also for these other interventions, is needed to help assess the impact of these interventions when implemented in combination at the population level. Third, despite taking reinfection into consideration, our model is simple and could be modified to increase realism, e.g., age dependence in the force of infection. We intend to extend our catalytic model by including the age-dependent force of infection. When choosing the cutoff age of 24 months, the relative risk of hospitalization owing to secondary infection was estimated to be same as the original model, but with less variability. However, the force of infection for secondary infections for ages less than 24 months was estimated to be very high (3.3), suggesting that the compartment for susceptibility to secondary infection is not substantial in the first 2 years of life.

Despite these limitations, we believe that our simple models successfully captured the infection dynamics of RSV among young children in Japan. We have elucidated the heterogeneity in the risk of hospitalization conditional on infection with RSV and determined that the age group of early infancy may be the most vulnerable to infection and hospitalization.

Funding

This work was supported by the following: HN received funding from Health and Labour Sciences Research Grants (grant numbers 19HB1001, 19HA1003, 20CA2024, 20HA2007, 21HB1002, and 21HA2016), the Japan Agency for Medical Research and Development (grant numbers JP20fk0108140, JP20fk0108535, and JP21fk0108612), the JSPS KAKENHI (grant number 21H03198), the Japan Science and Technology Agency CREST program (grant number JPMJCR1413), and the SICORP program (grant numbers JPMJSC20U3 and JPMJSC2105). We thank local governments, public health centers, and institutes for surveillance, laboratory testing, epidemiological investigations, and data collection. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical approval

The present study used publicly available data. The data sets did not contain any individual identifying information; therefore, ethical approval and informed consent were not required for this study.

Data availability statement

The epidemiological data analyzed in this study are downloadable from the online Supplement. The R code used is also available in the online Supplement.

Declaration of competing interests

K. Nakajo is employed at Sanofi K.K. This did not influence the design and analysis of the present study.

Acknowledgments

The authors thank Ryan Chastain-Gross, Ph.D., from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.09.008.

References

Amaku M, Azevedo RS, Castro RM, Massad E, Coutinho FA. Relationship among epidemiological parameters of six childhood infections in a non-immunized Brazilian community. Mem Inst Oswaldo Cruz 2009;104:897–900.

Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect 2000;125:651–69.

Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140:543–6.

Goto S, Ispus G. Evaluation on RSV disease burden in Japanese children using a nationwide claims database, Presented at the 26th ERS International Congress. https://www.researchgate.net/publication/323176262_Evaluation_on_RSV_disease_burden_in_Japanese_children_using_a_nationwide_claims_database, 2018 (accessed 28 March 2022).

Hall CB, Geiman JM, Biggar R, Kotok DI, Hogan PM, Douglas Jr GR. Respiratory syncytial virus infections within families. N Engl J Med 1976;294:414–19.
Hall CB, Kopelman AE, Douglas Jr RG, Geiman JM, Meagher MP. Neonatal respiratory syncytial virus infection. N Engl J Med 1979;300:393–6.
Henderson FW, Collier AM, Clyde Jr WA, Denny FW. Respiratory-syncytial virus infections, reinfections and immunity: a prospective, longitudinal study in young children. N Engl J Med 1979;300:530–4.
Inagaki A, Kitano T, Nishikawa H, Suzuki R, Onaka M, Nishiyama A, et al. The epidemiology of admission-requiring paediatric respiratory infections in a Japanese community hospital using multiplex PCR. Jpn J Infect Dis 2021;74:23–8.
Japan Medical Data Company. JMDC database. https://phm.jmdc.co.jp/en/, 2020 (accessed 28 March 2022).
Jung SM, Lee H, Yang Y, Nishiura H. Quantifying the causal impact of funding bedside antigen testing on the incidence of respiratory syncytial virus infection in Japan: a difference-in-differences study. Ann Transl Med 2020;8:1441.
Karron RA. Respiratory syncytial virus vaccines. Plotkin's vaccines. Amsterdam: Elsevier; 2017. p. 943–9.
Kawasaki Y, Hosoya M, Katayose M, Suzuki H. Role of serum neutralizing antibody in reinfection of respiratory syncytial virus. Pediatr Int 2004;46:126–9.
Kinyanjui TM, House TA, Kiti MC, Cane PA, Nokes DJ, Medley GF. Vaccine induced herd immunity for control of respiratory syncytial virus disease in a low-income country setting. PLoS One 2015;10.
Kobayashi Y, Togo K, Agosti Y, McLaughlin JM. Epidemiology of respiratory syncytial virus in Japan: a nationwide claims database analysis. Pediatr Int 2022;64:e14957.
Kutsaya A, Teros-Jaakkola T, Kakkola L, Toivonen L, Peltola V, Waris M, et al. Prospective clinical and serological follow-up in early childhood reveals a high rate of subclinical RSV infection and a relatively high reinfection rate within the first 3 years of life. Epidemiol Infect 2016;144:1622–33.
Li Y, Johnson EK, Shi T, Campbell H, Chaves SS, Commaille-Chapus C, et al. National burden estimates of hospitalisations for acute lower respiratory infections due to respiratory syncytial virus in young children in 2019 among 58 countries: a modelling study. Lancet Respir Med 2021;9:175–85.
Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet 2022;399:2047–64.
Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2095–128.
Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375:1545–55.
National Institute of Infectious Diseases. Infectious agents surveillance report;39:207–26, https://www.niid.go.jp/niid/images/idsc/iasr/39/466.pdf, 2018 (accessed 28 March 2022).
National Institute of Infectious Diseases. *Infectious Diseases Weekly Report, as of 7th week*. https://www.niid.go.jp/niid/images/idsc/idwr/IDWR2022/idwr2022-07.pdf, 2022 (accessed 28 March 2022).
Nyiro JU, Kombe IK, Sande CJ, Kipkoech J, Kiyuka PK, Onyango CO, et al. Defining the vaccination window for respiratory syncytial virus (RSV) using age-seroprevalence data for children in Kilifi, Kenya. PLoS One 2017;12.
Obolski U, Kassem E, Na'amnih W, Tannous S, Kagan V, Muhsen K. Unnecessary antibiotic treatment of children hospitalised with respiratory syncytial virus (RSV) bronchiolitis: risk factors and prescription patterns. J Glob Antimicrob Resist 2021;27:303–8.
Ohuma EO, Okiro EA, Ochola R, Sande CJ, Cane PA, Medley GF, et al. The natural history of respiratory syncytial virus in a birth cohort: the influence of age and previous infection on reinfection and disease. Am J Epidemiol 2012;176:794–802.
Pitzer VE, Viboud C, Alonso WJ, Wilcox T, Metcalf CJ, Steiner CA, et al. Environmental drivers of the spatiotemporal dynamics of respiratory syncytial virus in the United States. PLoS Pathog 2015;11.
R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2020 https://www.R-project.org/ (accessed 28 March 2022).
Sande CJ, Mutunga MN, Okiro EA, Medley GF, Cane PA, Nokes DJ. Kinetics of the neutralizing antibody response to respiratory syncytial virus infections in a birth cohort. J Med Virol 2013;85:2020–5.
Sastre P, Ruiz T, Schildgen O, Schildgen V, Vela C, Rueda P. Seroprevalence of human respiratory syncytial virus and human metapneumovirus in healthy population analyzed by recombinant fusion protein-based enzyme linked immunosorbent assay. Virol J 2012;9:130.
Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390:946–58.
Sruamsiri R, Kubo H, Mahlich J. Hospitalization costs and length of stay of Japanese children with respiratory syncytial virus: a structural equation modeling approach. Med (Baltim) 2018;97:e11491.
Stein RT, Bont LJ, Zar H, Polack FP, Park C, Claxton A, et al. Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. Pediatr Pulmonol 2017;52:556–69.
Suto T, Yano N, Ikeda M, Miyamoto M, Takai S, Shigeta S, et al. Respiratory syncytial virus infection and its serologic epidemiology. Am J Epidemiol 1965;82:211–24.
Taniguchi K, Hashimoto S, Kawado M, Murakami Y, Izumida M, Ohta A, et al. Overview of infectious disease surveillance system in Japan, 1999–2005. J Epidemiol 2007;17:S3–13.
van Boven M, Teirlinck AC, Meijer A, Hooiveld M, van Dorp CH, Reeves RM, et al. Estimating transmission parameters for respiratory syncytial virus and predicting the impact of maternal and paediatric vaccination. J Infect Dis 2020;222:S688–94.
Weber A, Weber M, Milligan P. Modeling epidemics caused by respiratory syncytial virus (RSV). Math Biosci 2001;172:95–113.
Yamaguchi M, Sano Y, Dapat IC, Saito R, Suzuki Y, Kumaki A, et al. High frequency of repeated infections due to emerging genotypes of human respiratory syncytial viruses among children during eight successive epidemic seasons in Japan. J Clin Microbiol 2011;49:1034–40.
Yamin D, Jones FK, DeVincenzo JP, Gertler S, Kobiler O, Townsend JP, et al. Vaccination strategies against respiratory syncytial virus. Proc Natl Acad Sci U S A 2016;113:13239–44.