Viral Acute Respiratory Illnesses in Young Infants Increase the Risk of Respiratory Readmission

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Conflicts of Interest and Source of Funding: The authors have no conflicts of interest to disclose. The study was supported by the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) [grant number 10008012] from Ministry of Education, Culture, Sport, Science & Technology in Japan; Japan Agency for Medical Research and Development (AMED) [grant number 21406028]; Grants-in-Aid for Scientific Research (Japan Society for the Promotion of Science) [grant number 15K09571]; and Morinaga Hoshikai.

Key words: Human metapneumovirus; Adenoviridae; Human rhinovirus; Pediatrics; Vietnam

Abbreviated title: Respiratory Viruses Increase Readmissions in Infants

Running head: Virus, Infants, and Respiratory Readmissions

ABSTRACT

Background: Respiratory viruses cause acute respiratory illness (ARI) in early childhood, but their effect on subsequent ARI admissions is not fully understood. This study aimed to determine the association between initial ARI admission due to viruses including human rhinovirus (HRV), respiratory syncytial virus (RSV), human adenovirus (HAdV), and human metapneumovirus (hMPV) and the risk of ARI readmission in children.

Methods: Clinical information and nasopharyngeal swab samples were collected from children <2 years old at their initial ARI admission in Nha Trang, Vietnam, from January 2007 to April 2012. The incidence of ARI readmission during the follow-up period (initial admission to 5 years of age) was compared between children with and without one of 13 respiratory viruses (influenza virus A, influenza virus B, RSV, hMPV, parainfluenza virus-1, -2, -3, and -4, HRV, human coronavirus-229E, human coronavirus-OC43, HAdV, and human bocavirus) at initial admission.

Results: A total of 1,941 children were enrolled in the study. Viruses were detected in 1,254 (64.6%) children at enrollment; HRV, RSV, HAdV, and hMPV were detected in 499 (25.7%), 439 (22.6%), 156 (8.0%), and 47 (2.4%) children, respectively. During the follow-up period (4,572.7 person-years), 277 children were readmitted with ARI. Virus-

related ARI initial admission was associated with an increased risk of ARI readmission for children who were initially admitted before 6 months of age (adjusted rate ratio, 1.6; 95%CI, 1.1-2.5). HAdV (4.6; 1.8-11.9), hMPV (20.4; 6.2-66.9), and HRV (1.6; 1.0-2.4) were independently associated with the outcome. These associations were not observed for children whose initial admission occurred after 6 months of age.

Conclusions: HAdV-, hMPV-, and HRV-related initial ARI admissions, when occurring during early infancy, increased the risk of subsequent ARI-related re-admission.

INTRODUCTION

Acute respiratory illnesses (ARIs) are common and often recurrent in young children. A wide range of respiratory viruses, including respiratory syncytial virus (RSV), human rhinovirus (HRV), influenza virus A and B (Flu A and B), human adenovirus (HAdV), parainfluenza virus (PIV), and human metapneumovirus (hMPV), are associated with childhood ARIs such as bronchiolitis and pneumonia.[1-3]

The risk of virus-related ARI is highest during early childhood and decreases with age. According to our previous study conducted in Vietnam, the annual incidence of virus-related ARI among children aged <24 months and those aged 24-59 months was 65 per 1,000 and 11 per 1,000 person-years (PY), respectively.[4] The clinical presentations of ARI vary by virus. In Vietnam, HRV, RSV and hMPV infections were found to be independent risk factors for severe ARI among children.[4]

Virus-related ARIs in early childhood are also associated with subsequent respiratory problems. Previous studies have reported that RSV-related ARI increases the risks of subsequent wheezing, asthma, and pneumonia in children.[5-7] Recent studies have shown that HRV-related wheezing is associated with recurrent wheezing and asthma in early

childhood[8-10] and that hMPV-related bronchiolitis in infancy is associated with asthma in children up to 5 years of age.[11] However, these studies did not systematically investigate the different effects of multiple viruses on later respiratory problems. Although the risk of viral infection differs by age, no study has investigated the potential changes in the effect of viruses by timing of initial infection.

In the current study, utilizing our population-based ARI surveillance system in central Vietnam, we tested 13 respiratory viruses in young children admitted with ARI and investigated the effects of initial virus-related ARI admission on subsequent ARI admission. The effects were assessed by different viruses as well as by timing of initial ARI admission.

MATERIALS AND METHODS

Study participants

The study was conducted at Khanh Hoa General Hospital in Nha Trang, central Vietnam. This hospital is the sole provider of secondary and tertiary care for children living in our catchment area (16 communes in Nha Trang). A population-based cross-sectional survey was conducted in 2006 that covered all residents of the catchment area (N=198,000)[12] and was updated in 2010. ARI surveillance was initiated in January 2007. All children admitted to the hospital who 1) presented with cough and/or difficulty breathing; 2) were aged less than 60 months; 3) and resided in the catchment area were enrolled in the study.[13] Surveillance records were linked to census sociodemographic data by the unique census identification number.

For this study, we enrolled children <2 years of age who were admitted with ARI for the first time from January 29, 2007, to April 20, 2012 (initial ARI admission). We investigated whether the enrolled children had died or left the catchment area by phone or home visit in 2013. Admission to the cohort began at the date of initial ARI admission and continued until the child was readmitted with ARI (main outcome), reached 5 years of age, died, left the area, or April 20, 2012, whichever occurred first. The Institutional

Review Boards at the National Institute of Hygiene and Epidemiology, Hanoi, and the Institute of Tropical Medicine, Nagasaki University, approved this study.

Variables

Clinical information, laboratory data, and nasopharyngeal swab samples were collected from all enrolled ARI children soon after their admission. Multiplex polymerase chain reaction (PCR) assays were applied to detect 13 respiratory viruses from the nasopharyngeal specimen (Flu A, Flu B, RSV, hMPV, PIV-1, -2, -3, and -4, HRV, human coronavirus-229E, human coronavirus-OC43, HAdV, and human bocavirus).[14] The primers that were used in the multiplex PCR assay targeted RSV nucleoprotein and HRV non-coding region thus the PCR assays used in this study did not distinguish between different subtypes or genotypes.

Children were classified into three groups according to their age at enrollment: <6 months, 6-11 months, and 12-23 months. ARIs were classified as no pneumonia, pneumonia, and severe pneumonia using modified algorithms from the World Health Organization Integrated Management of Childhood Illnesses.[15] The highest level of education for any household member was used as a household-level variable. Household economic status

was modelled as a wealth index based on a previously applied principal component analysis of durable assets.[16]

Statistical analysis

Baseline characteristics of the enrolled children were described by simple tabulations. The proportions of virus-positive cases at enrollment were compared between age groups using chi-squared test for trend. Readmission rates were compared between children who had tested positive for a specific virus at enrollment (virus-positive cohort) and those who had tested negative for all viruses (all virus-negative cohort). Readmission rate ratios (RRs) were estimated using Poisson regression analysis. Age, sex, type of ARI, presence of underlying diseases, household crowding, family smoking, wealth level, and household educational level were considered potential confounders and were thus included in the multivariable Poisson regression models. Age was included as an age band to allow for aging by splitting the dataset according to current age. The dataset was further divided into calendar time bands according to current year. Confidence intervals (CIs) were adjusted for the clustering of communes using robust standard errors. Further details on definition of variables used in the multivariable model can be found in Detail Methods, Supplemental Digital Content 1.

Two sensitivity analyses were performed. In the first sensitivity analysis, cohort children whose residential status was unknown at the end of follow-up were excluded. In the second, children were allowed to enter cohorts every time that they were admitted for ARI during the study period. Viruses detected at each admission were considered the exposure, and the cohorts were stratified by age group at each time of admission.

P values <0.05 were considered statistically significant. Statistical analyses were conducted using STATA version 12.0 (Stata Corp, USA).

RESULTS

Characteristics of participants at enrollment

During the study period, 1,948 children admitted with ARI were enrolled in the study, seven of whom did not have viral data. After excluding these children, a total of 1,941 participants were eligible for the analyses.

The baseline characteristics of the cohort children are shown in Table 1. Subjects were mostly male (n=1,196, 61.6%), and the median age at enrollment was 11.5 months (interquartile range, 10.6). The total duration of follow-up was 4,572.7 PY. During the follow-up period, 277 (14.3%) children were readmitted with ARI. The overall readmission rate was 60.6 per 1,000 PY. The readmission rate decreased with age; the rate for children aged <6 months, 6-11 months, and 12-23 months at enrollment was 71.5, 63.7, and 53.4 per 1,000 PY, respectively. The characteristics of children with and without readmission were similar.

Virus-positive status at enrollment

In total, 1,254 (64.6%) children tested positive for at least one virus at enrollment (Table 2). HRV was the most common virus identified (n=499 [25.7%]), followed by RSV

(n=439 [22.6%]) and Flu A (n=201 [10.4%]). HAdV and hMPV were detected in 156 (8.0%) and 47 (2.4%) children, respectively (Table 2). Two or more viruses were identified in 19.5% of the virus-positive samples. RSV was identified more frequently in the younger age group ($p<0.001$), while Flu A and HAdV were more frequently identified in the older age group ($p<0.001$ and $p<0.001$, respectively).

Effect of initial virus-related ARI admission on ARI readmission rate

The readmission rates of cohort children according to infection with different viruses at enrollment are shown in Table 3. The readmission rates with bocavirus, Flu B, PIV-1, -2, -4, and coronavirus were not calculated because of the small numbers of positive cases. The overall readmission rate among virus-positive children was 61.7 (95%CI, 53.4-71.3) per 1,000 PY: the rates among children aged <6 months, 6-11 months, and 12-23 months at enrollment were 82.7 (95%CI, 63.0-108.49), 61.3 (95%CI, 47.1-79.9), and 52.9 (95%CI, 42.3-66.2) per 1,000 PY, respectively. Among children aged <6 months, the readmission rate was highest in those positive for hMPV at enrollment (801 per 1,000 PY; 95%CI, 258.3-2483.5), followed by PIV3 (138.8 per 1,000 PY; 95%CI, 44.8-430.3) and HAdV (163.4 per 1,000 PY; 95%CI, 61.3-435.5).

The readmission rate was higher among virus-positive children than all virus-negative children for those aged <6 months (adjusted rate ratio (aRR), 1.61; 95%CI, 1.06-2.45), but the rates did not differ for those aged 6-11 months (aRR, 0.87; 95%CI, 0.63-1.19) or 12-23 months (aRR, 0.93; 95%CI, 0.61-1.41) (Table 3). For the youngest age group, hMPV- (aRR, 20.4; 95%CI, 6.22-66.87), HAdV- (aRR, 4.6; 95%CI, 1.77-11.94), and HRV-related ARI admissions (aRR, 1.55; 95%CI, 1.01-2.39) independently increased the readmission rate (Table 3). Other viruses such as RSV, Flu A, and PIV3 were also associated with an increased risk of readmission, but their effects did not reach statistical significance. The effects were stronger for children aged 3-5 months at enrollment when we broke down the age group <6 months (See Table, Supplemental Digital Content 2). Viruses were not associated with readmission rates for children aged 6-11 months or 12-23 months, with the exception of RSV, which was associated with a decreased risk of readmission for children aged 12-23 months.

Sensitivity analysis

To account for potential selection bias, we performed a sensitivity analysis restricting the analysis to children whose residential status had been confirmed at the end of follow-up (n=1,440) and found similar results (See Table, Supplemental Digital Content

3). The findings were also similar when we allowed children to enter the cohort multiple times (a total of 2,309 admissions, data not shown).

DISCUSSION

Virus-related ARI admission was associated with an increased risk of ARI readmission among young children who were less than 6 months of age at their initial admission. However, this association was not observed among children whose initial admission occurred after they were 6 months of age. The effect of virus-related ARI admission on ARI readmission rate differed by virus: hMPV showed the strongest effect, followed by HAdV and HRV. Thus, the effect of virus-related ARIs on later ARI by virus and timing of infection was systematically and comprehensively demonstrated.

Mid- and long-term effects of virus-related ARI

Studies have shown that virus-related ARI in early childhood is associated with both mid- and long-term respiratory problems, such as asthma and pneumonia. Singleton *et al.* showed that RSV infection in children aged <2 years increased the risks of wheezing, lower respiratory infections, and asthma until children were 4 years of age.[6] Jackson *et al.* showed that HRV-related wheezing was associated with further wheezing and asthma in early childhood.[9] On the other hand, a study conducted by Cox *et al*. failed to demonstrate an association between RSV and subsequent hospital respiratory admissions.[17]

Our findings suggested that the mid-term effect of virus-related ARI admission differed by the timing of initial infection. We found that initial virus-related ARI admission when it occurred before 6 month of age increased the risk of ARI readmission. The effect was substantial when a child had initial virus-related ARI admission at the age of 3-5 months, however, the sample size was too small to evaluate the effect for the younger age group (i.e., <3 months). The strong effect of virus-related ARI observed in the age of 3-5 months may be related to the immune system during this period. It has been reported that during this period, maternal immunoglobulins are reducing and own immunoglobulin production is still not optimal.[18] Virus infection during this period may induce inflammation in the airways which may result in deleterious changes in respiratory function and manifest as persistent wheezing and/or asthma.[19] It also may not elicit a sufficient immune response and this partial immunity may increase the risk of subsequent infection.[20] However, we could not measure immunoglobulins nor perform a subanalysis on ARI readmission with wheezing/asthma as an outcome because we could not distinguish it from all ARI admissions in this study due to the limited clinical information. These factors should be examined and investigated in future studies. We also tried to explore other factors as a potential effect modifier

surrogating the age group: nutritional status, prematurely-born, and coinfection. Number of children with malnutrition reported by parent were too small for further analysis, 1, 5, and 3 in age group <6, 6-11, and 12-23 months, respectively. There were no other indicators of nutritional status and record of prematurely-born available in the research setting. Viral co-detection rates in virus positive children were 15%, 19%, and 22% in age group <6, 6-11, and 12-23 months, respectively, and the readmission rate among children with viral co-detection did not differ from those with single viral detection (aRR, 1.07; 95%CI, 0.74-1.56). Bacterial co-infection could not be evaluated since blood culture was not performed routinely on hospitalized ARI cases in the study hospital, however, mean of white blood cell count as an indicator of bacterial infection was 11.1 x10^3/μl (SD 4.1), 13.4 (5.6), and 13.9 (7.6), respectively. Therefore, coinfection was less likely to derive difference of the effect of initial virus-related ARI admission on ARI readmission in each age group.

Virus-specific effects

Regarding virus-specific effects, hMPV showed the strongest effect on the risk of ARI readmission. In Spain, Garcı´a-Garcı´a *et al.* recruited children who had been admitted with and without hMPV-related bronchiolitis in the first two years of life and compared

their frequencies of wheezing at three and five years of age. They found that hMPV-related bronchiolitis was strongly associated with later development of asthma (odds ratio, 15.9).[11] Although our primary outcome was ARI readmission, not asthma, our observations can be considered as complementary to their findings. hMPV infection has been strongly associated with lower respiratory infection among young children,[4] and its damage to respiratory functions may persist for several years.

In the current study, HRV-related ARI admission before 6 months of age was associated with subsequent ARI admission. Previous studies have also reported that HRV-related ARI in early childhood is associated with recurrent wheezing.[8-10] Recently, HRV-A and HRV-C species have been shown to cause more severe respiratory illnesses than HRV-B in infants.[21] Cox *et al*. showed that HRV-C-related wheezing illnesses in children younger than five years of age were associated with an increased risk of subsequent hospital respiratory admissions within 12 months.[17] Our results seem consistent with their findings, however, further HRV species specific analysis will be required to clarify a more detail effect of HRV.

We also made the original observation that HAdV-related ARI admission increased the

risk of ARI readmission. HAdV infection is common in childhood ARIs: HAdV has been associated with 6-8% of ARIs in children younger than 5 years old.[4, 22] However, the epidemiology of HAdV-related respiratory infections is not fully understood. Further studies are needed to establish the effects of HAdV infection on the respiratory system.

In this study, RSV-related ARI admission did not affect the risk of ARI readmission. Previous studies have found an association between RSV-related lower respiratory tract infection and long-term respiratory morbidity, including recurrent wheeze and asthma.[5, 6, 23-26] However, some studies have failed to demonstrate this association. Cox *et al.* reported that compared with other viruses, RSV was associated with a decreased risk of subsequent respiratory admissions,[17] whereas the rate of readmission for pneumonia in RSV-related lower respiratory infections did not differ from that of non-RSV lower respiratory infections in a study by Munywoki.[7] Our finding could be explained by an acquisition of protective immunity against RSV infection resulting from the initial infection. In fact, RSV-related ARI admission was associated with a decreased risk of readmission for RSV-related ARI (aRR, 0.47; 95%CI, 0.19-1.13), and this association was particularly strong among children aged 12-23 months (aRR, 0.14; 95%CI, 0.02-

0.82) (data not shown in results). This finding may suggest that RSV immunity acquired from the index RSV infection reduced subsequent RSV infection and that the immunity was stronger when the index infection occurred after infancy. RSV infection induces mucosal and systemic virus-neutralizing antibody responses as well as cell-mediated responses, and secretory and serum antibodies play the primary role in protection against reinfection. However, with the exception of passively acquired RSV-neutralizing antibodies, the correlates of protection in young infants are difficult to measure and are poorly understood.[27] In this study, RSV genotype information was not available and we were not able to conduct RSV genotype specific analysis, however, this does not change the overall role of RSV on pediatric ARI readmission.

Implication of the study findings

Our findings suggest that young infants with virus-related ARI, especially those with hMPV-, HRV-, and HAdV-related ARI, require careful follow-up until they are at least five years of age because of their increased risk of readmission. Rapid diagnostic tests for hMPV and HAdV may be useful for improving the clinical management of these children. Studies using hMPV proteins as subunit vaccine candidates and recombinant/non-recombinant live attenuated viruses have recently been conducted.[28, 29]

Additionally, inactivated and live attenuated HRV vaccine candidates have been studied using animal models and human trials.[30] Once these vaccines become available, they are expected to reduce the risk of ARI admission as well as subsequent ARI-related readmission. Furthermore, as the subsequent effect of these viruses was observed only during early infancy, a cocoon immunization strategy might be a preferable option.

Limitations

This study has limitations. First, to estimate the effect of virus-related ARI admission on our primary outcome, we analyzed cohort children who had tested negative for all viruses as a reference. Although we systematically screened for 13 viruses, this group may have included other pathogens that were not assessed such as enteroviruses[31] and bacteria, potentially leading to an underestimation of the true effect of viruses. Second, we conducted this study using a hospital-based surveillance system and did not conduct regular follow-ups of our cohort children in the community. This method may have introduced selection and measurement bias. However, our study hospital is the sole provider of admission care for residents in the area, and it is less likely that children with ARI who require admission care would have been missed in our study, as the free national insurance for all children up to six years of age in Vietnam facilitated good

access to hospital care. We also performed a sensitivity analysis that excluded children with an unknown residential status, and the findings did not substantially differ from the original results. Therefore, we believe that the impact of selection bias was minimal. Third, we only considered children with ARI who required hospitalization. Consequently, our findings may not be generalizable to all virus-related mild or asymptomatic ARI cases. Fourth, we did not perform HRV and RSV species or subgroup/genotype testing so we were not able to analyze HRV and RSV species or subgroup/genotype specific effect. However, this does not change our study finding and we hope to clarify it in a future study.

Conclusions

In conclusion, virus-related ARI admission among young infants increased the risk of ARI readmission in children up to five years of age. A substantial effect was observed for hMPV-, HRV-, and HAdV-related ARI admissions in particular. Our findings suggest that the use of diagnostic tests and new vaccines to manage these viruses may improve children's mid-term or long-term health outcomes.

Acknowledgements

This was a collaborative research effort between Nagasaki University (Japan), NIHE (Vietnam), Khanh Hoa Provincial Public Health Service (Vietnam) and Khanh Hoa General Hospital (Vietnam). We thank all participants and those who cooperated in this study in both Vietnam and Japan. We are also grateful to Dr. Sumihisa Honda (Department of Community-based Rehabilitation Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan) for the helpful discussions about the study design and Ms. Rina Shiramizu (Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan) who supported the virus screening PCR.

List of abbreviations

ARI: acute respiratory illness, CI: confidence interval, Flu: influenza virus, HAdV: human adenovirus, hMPV: human metapneumovirus, HRV: human rhinovirus, RR: rate ratio, PCR: polymerase chain reaction, PIV: parainfluenza virus, PY: person-years, RSV: respiratory syncytial virus

References

1. Rudan I, Boschi-Pinto C, Biloglav Z, et al. Epidemiology and etiology of childhood pneumonia. *Bull WHO*. 2008;86(5):408-416.

2. Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. *Trop Med Int Health*. 1998;3(4):268-280.

3. Juven T, Mertsola J, Waris M, et al. Etiology of community-acquired pneumonia in 254 hospitalized children. *Pediatr Infect Dis J*. 2000;19(4):293-298.

4. Yoshida LM, Suzuki M, Nguyen HA, et al. Respiratory syncytial virus: co-infection and paediatric lower respiratory tract infections. *Eur Respir J*. 2013;42(2):461-469.

5. Weber MW, Milligan P, Giadom B, et al. Respiratory illness after severe respiratory syncytial virus disease in infancy in The Gambia. *J Pediatr*. 1999;135(6):683-688.

6. Singleton RJ, Redding GJ, Lewis TC, et al. Sequelae of severe respiratory syncytial virus infection in infancy and early childhood among Alaska Native children. *Pediatrics*. 2003;112(2 I):285-290.

7. Munywoki PK, Ohuma EO, Ngama M, et al. Severe lower respiratory tract

infection in early infancy and pneumonia hospitalizations among children, Kenya. *Emerg Infect Dis*. 2013;19(2):223-229.

8. Lemanske RF, Jr., Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immun*. 2005;116(3):571-577.

9. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Resp Crit Care*. 2008;178(7):667-672.

10. Kotaniemi-Syrjanen A, Vainionpaa R, Reijonen TM, et al. Rhinovirus-induced wheezing in infancy--the first sign of childhood asthma? *J Allergy Clin Immun*. 2003;111(1):66-71.

11. Garcia-Garcia ML, Calvo C, Casas I, et al. Human metapneumovirus bronchiolitis in infancy is an important risk factor for asthma at age 5. *Pediatr Pulm*. 2007;42(5):458-464.

12. Suzuki M, Thiem VD, Yanai H, et al. Association of environmental tobacco smoking exposure with an increased risk of hospital admissions for pneumonia in children under 5 years of age in Vietnam. *Thorax*. 2009;64(6):484-489.

13. Vu HT, Yoshida LM, Suzuki M, et al. Association between nasopharyngeal load

of Streptococcus pneumoniae, viral coinfection, and radiologically confirmed pneumonia in Vietnamese children. *Pediatr Infect Dis J*. 2011;30(1):11-18.

14. Le MN, Yoshida LM, Suzuki M, et al. Impact of 2009 pandemic influenza among Vietnamese children based on a population-based prospective surveillance from 2007 to 2011. *Influenza Other Resp*. 2014;8(4):389-396.

15. World Health Organization. *Handbook: IMCI integrated management of childhood illness.* Geneva; World Health Organization; 2005. http://whqlibdoc.who.int/publications/2005/9241546441.pdf

16. Filmer D, Pritchett LH. Estimating wealth effects without expenditure data--or tears: an application to educational enrollments in states of India. *Demography*. 2001;38(1):115-132.

17. Cox DW, Bizzintino J, Ferrari G, et al. Human rhinovirus species C infection in young children with acute wheeze is associated with increased acute respiratory hospital admissions. *Am J Resp Crit Care.* 2013;188(11):1358-1364.

18. Lewis DB, Tu W. The physiologic immunodeficiency of immaturity. In: Stiehm ER, Ochs HD, Winkelstein JA, eds. *Immunologic Disorders in Infants and Children*. 5th ed. Philadelphia, Elsevier/Saunders; 2004:687-760.

19. Kusel MM, de Klerk NH, Kebadze T, et al. Early-life respiratory viral infections,

atopic sensitization, and risk of subsequent development of persistent asthma. *The J Allergy Clin Immun*. 2007;119(5):1105-1110.

20. Siegrist CA. Neonatal and early life vaccinology. *Vaccine*. 2001;19(25-26):3331-3346.

21. Lee WM, Lemanske RF, Jr., Evans MD, et al. Human rhinovirus species and season of infection determine illness severity. *Am J Resp Crit Care*. 2012;186(9):886-891.

22. Wold WSM, Ison MG. Adenoviruses. In: Knipe DM, Howley PM, eds. *Fields virology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:1732-1767.

23. Sigurs N. A cohort of children hospitalised with acute RSV bronchiolitis: impact on later respiratory disease. *Paediatr Respir Rev*. 2002;3(3):177-183.

24. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Resp Crit Care*. 2005;171(2):137-141.

25. Szabo SM, Levy AR, Gooch KL, et al. Elevated risk of asthma after hospitalization for respiratory syncytial virus infection in infancy. *Paediatr Respir Rev*. 2013;13 Suppl 2:S9-15.

26. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life

and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354(9178):541-545.

27. Collins PL, Karron RA. Respiratory syncytial virus and metapneumovirus. In: Knipe DM, Howley PM, eds. *Fields Virology* 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:1086-1123.

28. Ren J, Phan T, Bao X. Recent vaccine development for human metapneumovirus. *J Gen Virol*. 2015;96(Pt 7):1515-1520.

29. Wen SC, Williams JV. New Approaches for Immunization and Therapy against Human Metapneumovirus. *Clin Vaccine Immunol*. 2015;22(8):858-866.

30. Glanville N, Johnston SL. Challenges in developing a cross-serotype rhinovirus vaccine. *Curr Opin Virol*. 2015;11:83-88.

31. Renois F, Leveque N, Deliege PG, et al. Enteroviruses as major cause of microbiologically unexplained acute respiratory tract infections in hospitalized pediatric patients. *J Infection*. 2013;66(6):494-502.

List of Supplemental Digital Content

Supplemental Digital Content 1. Text: Detailed Methods

Supplemental Digital Content 2. Table: Readmission incidence rate, unadjusted rate ratio, and adjusted rate ratio according to virus detected at enrollment when children were less than 6 months old at enrollment and followed-up until 5 years of age and stratified by age group at enrollment

Supplemental Digital Content 3. Table: Readmission rate, unadjusted rate ratio, and adjusted rate ratio according to virus detected at enrollment when followed up until age of 5 years, and those stratified by age group at enrollment and children who were not asked their status and place were removed

Table 1. Characteristics of cohort children and the rate of ARI readmission.

Characteristics (n=1941)		All n (%)	Readmission n (%)	Readmission (95%CI) (per 1000 person-years)	Unadjusted rate ratio (95%CI)	p value
Total		1941 (100.0)	277 (14.3)	60.6 (53.8-68.1)		
Demographics						
Sex						
	Male	1196 (61.6)	184 (15.4)	66.0 (57.1-76.2)	1.27 (0.99-1.62)	0.10
	Female	745 (38.4)	93 (12.5)	52.1 (42.5-63.9)	reference	
Age (months)						
	<6 months	422 (21.7)	70 (16.6)	71.5 (56.6-90.4)	reference	
	6-11 months	596 (30.7)	94 (15.8)	63.7 (52.0-77.9)	0.89 (0.65-1.21)	0.46
	12-23 months	923 (47.6)	113 (12.2)	53.4 (44.4-64.2)	0.75 (0.55-1.01)	0.06
Severity						
Clinical pneumonia						
	No pneumonia	1566 (80.7)	210 (13.4)	57.1 (49.9-65.4)	reference	
	Pneumonia	245 (12.6)	45 (18.4)	73.6 (54.9-98.6)	1.29 (0.93-1.78)	0.12
	Severe pneumonia	130 (6.7)	22 (16.9)	76.9 (50.7-116.9)	1.35 (0.87-2.09)	0.18
Socioeconomic status						
Wealth level (n=1710)	Low	473 (27.7)	84 (17.8)	75.0 (60.5-92.8)	reference	
	Middle	621 (36.3)	89 (14.3)	63.2 (51.3-77.8)	0.84 (0.63-1.14)	0.26
	High	616 (36.0)	87 (14.1)	58.6 (47.5-72.3)	0.78 (0.58-1.06)	0.11
Highest education level in household (n=1443)	Low	534 (37.0)	78 (14.6)	60.7 (48.7-75.8)	reference	
	High	909 (63.0)	148 (16.3)	68.2 (58.1-80.1)	1.12 (0.85-1.48)	0.41
Daycare attendance (n=1938)	Yes	580 (29.9)	71 (12.2)	51.6 (40.9-65.1)	0.80 (0.61-1.04)	0.10
	No	1358 (70.1)	206 (15.2)	64.6 (56.4-74.1)	reference	
Home population density (number/hectare) (n=1593)	0-750	876 (55.0)	122 (13.9)	59.6 (49.9-71.2)	reference	
	>750	717 (45.0)	117 (16.3)	70.6 (58.9-84.6)	1.18 (0.92-1.53)	0.19
Family smoking						

(n=1710)	Yes	1029 (60.2)	168 (16.3)	70.9 (61.0-82.5)	1.27 (0.98-1.63)	0.07
	No	681 (39.8)	92 (13.5)	55.9 (45.6-68.6)	reference	
Past history						
Underlying disease						
(n=1608)	Yes	505 (31.4)	95 (18.8)	73.3 (59.9-89.6)	1.14 (0.88-1.48)	0.33
	No	1103 (68.6)	135 (12.2)	64.4 (54.4-76.2)	reference	
Current breastfeeding						
(n=1713)	Yes	997 (58.2)	158 (15.9)	62.4 (53.4-72.9)	1.16 (0.89-1.50)	0.27
	No	716 (41.8)	88 (12.3)	53.9 (43.7-66.4)	reference	

CI; confidence interval

Table 2. Frequency of each respiratory virus detected at enrollment by age group.

Virus	Total (n=1941) n (%)	Single detection n=1010 (52.0%) n (%)	<6 months n=422 (21.7%) n (%)	6-11 months n=596 (30.7%) n (%)	12-23 months n=923 (47.6%) n (%)	p value*
HRV	499 (25.7)	340 (68.1)	111 (26.3)	134 (22.5)	254 (27.5)	0.35
RSV	439 (22.6)	315 (71.8)	128 (30.3)	137 (23.0)	174 (18.9)	<0.001
Flu A	201 (10.4)	125 (62.2)	26 (6.2)	58 (9.7)	117 (12.7)	<0.001
HAdV	156 (8.0)	68 (43.6)	12 (2.8)	42 (7.1)	102 (11.1)	<0.001
PIV3	69 (3.6)	52 (75.4)	15 (3.6)	16 (2.7)	38 (4.1)	0.42
hMPV	47 (2.4)	36 (76.6)	10 (2.4)	11 (1.9)	26 (2.8)	0.47
Boca	42 (2.2)	22 (52.4)	4 (1.0)	18 (3.0)	20 (2.2)	0.31
Flu B	34 (1.8)	26 (76.5)	3 (0.7)	8 (1.3)	23 (2.5)	0.01
PIV1	29 (1.5)	20 (69.0)	4 (1.0)	10 (1.7)	15 (1.6)	0.41
PIV2	7 (0.4)	5 (71.4)	2 (0.5)	1 (0.2)	4 (0.4)	0.93
PIV4	2 (0.1)	1 (50.0)	0 (0.0)	1 (0.2)	1 (0.1)	0.67
Corona	3 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.2)	0.87
Any virus	1254 (64.6)	1010 (80.5)	271 (64.2)	361 (60.6)	622 (67.4)	0.10
No virus	687 (35.4)	-	151 (35.8)	235 (39.4)	301 (32.6)	0.10

HRV; human rhinovirus, RSV; respiratory syncytial virus, Flu A: influenza virus A, HAdV; adenovirus, PIV; parainfluenza virus, hMPV; human metapneumovirus, Flu B; influenza virus B.

* Proportions of virus-positive cases were compared between age groups using chi-square test for trend

Table 3. Readmission incidence rate, unadjusted rate ratio, and adjusted rate ratio according to virus detected at enrollment when followed-up until 5 years of age and stratified by age group at enrollment.

(n=1941)

Virus	Age at initial ARI admission		Number of readmission n(%)	Readmission rate (95%CI) (/1000 person-years)	Unadjusted rate ratio (95%CI)	Adjusted rate ratio* (95%CI)
Any virus						
	<6m	(n=271)	52 (19.2)	82.7 (63.0-108.49)	1.61 (0.94-2.75)	1.61 (1.06-2.45)†
	6-11m	(n=361)	55 (15.2)	61.3 (47.1-79.9)	0.91 (0.60-1.37)	0.87 (0.63-1.19)
	12-23m	(n=622)	77 (12.4)	52.9 (42.3-66.2)	0.97 (0.66-1.45)	0.93 (0.61-1.41)
HRV						
	<6m	(n=111)	24 (21.6)	91.3 (61.2-136.3)	1.78 (0.96-3.27)	1.55 (1.01-2.39)†
	6-11m	(n=134)	23 (17.2)	70.6 (46.9-106.3)	1.05 (0.63-1.76)	0.95 (0.58-1.53)
	12-23m	(n=254)	30 (11.8)	48.6 (34.0-69.5)	0.89 (0.55-1.45)	0.86 (0.46-1.63)
RSV						
	<6m	(n=128)	20 (15.6)	62.0 (40.0-96.2)	1.21 (0.64-2.28)	1.33 (0.71-2.48)
	6-11m	(n=137)	19 (13.9)	50.3 (32.1-78.9)	0.75 (0.43-1.29)	0.74 (0.49-1.12)
	12-23m	(n=174)	15 (8.6)	33.5 (20.2-55.5)	0.62 (0.34-1.12)	0.53 (0.34-0.81)
Flu A						
	<6m	(n=26)	7 (26.9)	103.3 (49.3-216.7)	2.01 (0.84-4.81)	2.68 (0.90-7.98)
	6-11m	(n=58)	8 (13.8)	47.9 (23.9-95.7)	0.71 (0.33-1.52)	0.75 (0.35-1.61)
	12-23m	(n=117)	19 (16.2)	71.5 (45.6-112.2)	1.32 (0.76-2.30)	1.16 (0.61-2.18)
HAdV						
	<6m	(n=12)	4 (33.3)	163.4 (61.3-435.5)	3.18 (1.08-9.40)†	4.60 (1.77-11.94)†
	6-11m	(n=42)	5 (11.9)	60.7 (25.3-145.9)	0.90 (0.36-2.29)	1.01 (0.56-1.83)
	12-23m	(n=102)	13 (12.8)	61.6 (35.8-106.1)	1.13 (0.60-2.14)	1.28 (0.80-2.05)
PIV3						
	<6m	(n=15)	4 (26.7)	175.9 (66.0-468.7)	3.42 (1.16-10.11)†	2.62 (0.35-19.58)
	6-11m	(n=16)	3 (18.8)	138.8 (44.8-430.3)	2.06 (0.64-6.67)	1.36 (0.37-4.95)
	12-23m	(n=38)	5 (13.2)	65.6 (27.3-157.7)	1.21 (0.47-3.08)	1.02 (0.36-2.87)
hMPV						
	<6m	(n=10)	3 (30.0)	801.0 (258.3-2483.5)	15.58 (4.59-52.90)†	20.40 (6.22-66.87)†
	6-11m	(n=11)	2 (18.2)	77.4 (19.4-309.4)	1.15 (0.28-4.76)	1.77 (0.18-17.14)
	12-23m	(n=26)	6 (23.1)	100.6 (45.2-223.9)	1.85 (0.78-4.39)	1.27 (0.50-3.20)
No virus						
	<6m	(n=151)	18 (11.9)	51.4 (32.4-81.6)	-	-
	6-11m	(n=235)	39 (16.6)	67.3 (49.2-92.2)	-	-
	12-23m	(n=301)	36 (12.0)	54.3 (39.2-75.3)	-	-

The data for minor viruses are not provided because of the limited number of outcome events.

* Rate ratios adjusted by age bands, calendar bands, sex, pneumonia, presence of underlying diseases, household crowding, family smoking, wealth level, and highest education level of family, considering clustering in each commune.

† $p<0.05$

CI; confidence interval, HRV; human rhinovirus, RSV; respiratory syncytial virus, Flu A; influenza virus A, HAdV; adenovirus, PIV; parainfluenza virus, hMPV; human metapneumovirus

Supplemental Digital Content 1. Definition of variables used in multivariable models

We split the follow-up time into age bands by the individual age [<6, (6-12), (12-24), >24] and into calendar bands by calendar years (2007, 2008, 2009, 2010, 2011, and 2012). Pneumonia was a variable depending on the modified algorithms from the World Health Organization Integrated Management of Childhood Illnesses,[15] classified into three categories (severe pneumonia, pneumonia and no pneumonia). Underlying diseases included all kinds of diseases that the family answered the child had. Household crowding was population density at home (number of persons/size of rooms at home (hectare)) divided into two classes (≤750, >750). Family smoking was whether any member of the family currently smoked. To assess household socioeconomic status, we constructed a wealth level using an asset index.[16] The asset index was generated from census household data of 15 main durable assets using principal component analysis. Three wealth levels were defined (low: lower than 33rd percentile of the asset index; middle: 33-67th percentile of the asset index; high: higher than 67th percentile of the asset index). Highest education level of family was regarded as highest educational background achieved in the household. It was divided into two levels (low: finished secondary school or lower, high: entered high school or higher).

Supplemental Digital Content 2. Readmission incidence rate, unadjusted rate ratio, and adjusted rate ratio according to virus detected at enrollment when children were less than 6 months old at enrollment and followed-up until 5 years of age and stratified by age group at enrollment.

(n=422)

Virus	Age at initial ARI admission		Number of readmission n(%)	Readmission rate (95%CI) (/1000 person-years)	Unadjusted rate ratio (95%CI)	Adjusted rate ratio* (95%CI)
Any virus						
	0-2m	(n=96)	10 (10.4)	40.5 (21.8-75.4)	0.50 (0.20-1.23)	0.54 (0.19-1.55)
	3-5m	(n=175)	42 (24.0)	109.8 (81.2-148.6)	2.92 (1.42-6.01)†	2.89 (1.62-5.17)†
HRV						
	0-2m	(n=39)	3 (7.7)	31.3 (10.1-97.1)	0.38 (0.10-1.42)	0.29 (0.04-2.09)
	3-5m	(n=72)	21 (29.2)	125.8 (82.0-192.9)	3.35 (1.53-7.31)†	3.34 (1.63-6.84)†
RSV						
	0-2m	(n=48)	6 (12.5)	46.2 (20.8-102.8)	0.57 (0.20-1.59)	0.87 (0.29-2.60)
	3-5m	(n=80)	14 (17.5)	72.7 (43.1-122.8)	1.94 (0.84-4.47)	1.85 (0.76-4.47)
Flu A						
	0-2m	(n=10)	1 (10.0)	33.8 (4.8-239.7)	0.41 (0.05-3.27)	0.40 (0.03-4.71)
	3-5m	(n=16)	6 (37.5)	157.3 (70.7-350.2)	4.19 (1.49-11.77)†	9.64 (1.72-53.87)†
HAdV						
	0-2m	(n=2)	0 (0.0)	0.0	-	-
	3-5m	(n=10)	4 (40.0)	262.7 (98.6-700.0)	6.99 (2.15-22.71)†	9.16 (1.97-42.66)†
PIV3						
	0-2m	(n=6)	1 (16.7)	147.6 (20.8-1048.1)	1.81 (0.23-14.32)	0.25 (0.00-34.12)
	3-5m	(n=9)	3 (33.3)	187.9 (60.6-582.6)	5.00 (1.35-18.48)	3.41 (0.52-22.54)
hMPV						
	0-2m	(n=1)	0 (0.0)	0.0	-	-
	3-5m	(n=9)	3 (33.3)	814.1 (262.6-2524.1)	21.67 (5.87-80.06)	36.39 (9.09-145.70)
No virus						
	0-2m	(n=57)	9 (15.8)	81.4 (42.3-156.4)	-	-
	3-5m	(n=94)	9 (9.6)	37.6 (19.5-72.2)	-	-

The data for minor viruses are not provided because of the limited number of outcome events.

* Rate ratios adjusted by age bands, calendar bands, sex, pneumonia, presence of underlying diseases, household crowding, family smoking, wealth level, and highest education level of family, considering clustering in each commune.

† $p<0.05$

CI; confidence interval, HRV; human rhinovirus, RSV; respiratory syncytial virus, Flu A; influenza virus A, HAdV; adenovirus, PIV; parainfluenza virus, hMPV; human metapneumovirus

Supplemental Digital Content 3. Readmission rate, unadjusted rate ratio, and adjusted rate ratio according to virus detected at enrollment when followed up until age of 5 years, and those stratified by age group at enrollment and children who were not asked their status and place were removed.

(n=1440)

Virus	Age at initial ARI admission	No. of readmission n(%)	Readmission rate (95%CI) (/1000 person-years)	Unadjusted rate ratio (95%CI)	Adjusted rate ratio* (95%CI)
Any virus					
<6m	(n=259)	50 (19.3)	86.2 (65.4-113.8)	1.75 (1.00-3.07)†	1.78 (1.23-2.58)†
6-11m	(n=277)	42 (15.2)	72.3 (53.4-97.8)	0.90 (0.56-1.44)	0.85 (0.58-1.24)
12-23m	(n=363)	42 (11.6)	64.6 (47.8-87.5)	1.28 (0.76-2.17)	1.18 (0.69-2.00)
HRV					
<6m	(n=103)	23 (22.3)	100.0 (66.5-150.5)	2.03 (1.07-3.84)†	1.63 (1.14-2.33)†
6-11m	(n=109)	19 (17.4)	80.9 (51.6-126.8)	1.01 (0.57-1.79)	0.99 (0.57-1.71)
12-23m	(n=141)	15 (10.6)	57.9 (34.9-96.0)	1.15 (0.59-2.23)	1.18 (0.58-2.41)
RSV					
<6m	(n=127)	20 (15.8)	62.9 (40.6-97.6)	1.28 (0.66-2.47)	1.55 (0.81-2.98)
6-11m	(n=96)	13 (13.5)	59.0 (34.2-101.5)	0.73 (0.38-1.41)	0.70 (0.38-1.30)
12-23m	(n=96)	8 (8.3)	41.1 (20.5-82.1)	0.82 (0.36-1.84)	0.71 (0.33-1.54)
FluA					
<6m	(n=21)	6 (28.6)	128.2 (57.6-285.3)	2.60 (1.02-6.65)†	3.20 (1.15-8.86)†
6-11m	(n=32)	4 (12.5)	59.7 (22.4-159.1)	0.74 (0.26-2.11)	0.76 (0.31-1.83)
12-23m	(n=66)	9 (13.6)	75.9 (39.5-146.0)	1.51 (0.69-3.30)	1.64 (0.76-3.50)
HAdV					
<6m	(n=11)	4 (36.4)	202.6 (76.0-539.8)	4.11 (1.38-12.30)†	4.71 (1.57-14.13)†
6-11m	(n=38)	5 (13.2)	76.3 (31.7-183.3)	0.95 (0.37-2.44)	1.24 (0.63-2.44)
12-23m	(n=78)	12 (15.4)	92.6 (52.6-163.0)	1.84 (0.91-3.74)	1.78 (1.01-3.15)†
PIV3					
<6m	(n=15)	4 (26.7)	175.9 (66.0-468.7)	3.57 (1.19-10.68)†	3.66 (0.52-25.94)
6-11m	(n=14)	2 (14.3)	133.2 (33.3-532.5)	1.66 (0.40-6.93)	1.60 (0.18-13.90)
12-23m	(n=20)	2 (10.0)	89.4 (22.4-357.6)	1.78 (0.42-7.58)	1.34 (0.26-6.82)
hMPV					
<6m	(n=10)	3 (30.0)	801.0 (258.3-2483.5)	16.26 (4.74-55.81)†	29.42 (8.84-97.86)†
6-11m	(n=8)	2 (25.0)	149.5 (37.4-597.7)	1.86 (0.44-7.78)	3.19 (0.47-21.61)
12-23m	(n=6)	1 (16.7)	255.6 (36.0-1814.5)	5.08 (0.68-37.77)	5.11 (0.86-30.50)
No virus					
<6m	(n=144)	16 (11.1)	49.3 (30.2-80.4)	-	-
6-11m	(n=179)	30 (16.8)	80.4 (56.2-115.0)	-	-
12-23m	(n=218)	21 (9.6)	50.3 (32.8-77.2)	-	-

* Rate ratios adjusted by age bands, calendar bands, sex, pneumonia, presence of underlying diseases, household crowding, family smoking, wealth level, highest education level of family, and presence of non-objective viruses detected, with clustering in each commune.

† $p<0.05$

CI; confidence interval, HRV; human rhinovirus, RSV; respiratory syncytial virus, Flu; influenza virus, HAdV; human adenovirus, PIV; parainfluenza virus, hMPV; human metapneumovirus.