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Association Between Preceding Viral Respiratory Infection and Subsequent Respiratory Illnesses Among Children: A Prospective Cohort Study in the Philippines

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Background. Acute respiratory infection (ARI) is of great concern in public health. It remains unclear whether viral infections can affect the host's susceptibility to subsequent ARIs.

Methods. A prospective cohort study on ARIs of children below 5 years old was conducted in the Philippines from 2014 to 2016. The respiratory symptoms were recorded daily, and nasopharyngeal swabs were collected at both household and health facilities. The specimens were tested for respiratory viruses. We then determined whether viral etiology was associated with the severity of the present ARI and whether previous viral infections was associated with subsequent ARIs.

Results. A total of 3851 children and 16 337 ARI episodes were enrolled and recorded, respectively. Samples were collected from 24% of all ARI episodes; collection rate at the healthcare facilities was 95%. Enterovirus D68, rhinovirus species C, and respiratory syncytial virus were significantly associated with severe ARIs. The risk for subsequent ARIs was significantly enhanced after infections with adenovirus, influenza A virus, parainfluenza virus type 4, and rhinovirus species C.

Conclusions. This study revealed that viral etiology plays a significant role in the severity of the present ARI and that viral infection affects the host's susceptibility to subsequent ARIs.

Keywords. acute respiratory infection; viral infection; Philippines; risk factor; prospective cohort study.

Acute respiratory infection (ARI) remains a major global health problem, with pneumonia being the leading cause of mortality among young children in low- and middle-income countries [1]. Adenovirus (AdV), enterovirus D68 (EV-D68), human metapneumovirus (hMPV), influenza virus (IFV), parainfluenza virus (PIV), and respiratory syncytial virus (RSV), which are commonly detected in hospitalized children with ARIs, are considered to play important etiological roles in the severity of infections [2–5].

Serological studies have shown that most children experience infections with common respiratory viruses such as hMPV, IFV, and RSV during their early years [6, 7]. Therefore, children are likely to experience multiple ARIs caused by a variety of viruses [8]. Previous respiratory viral infections could alter host susceptibility to subsequent ARIs. Viral infections could affect the host's immune status, including the production of cytokines, such as interferons, and the number and function of immune cells [9, 10], thus possibly altering the host's susceptibility to subsequent infections. Tissue damage and impairment of the epithelial barrier function of the respiratory tract by viral infections may also affect the host susceptibility to subsequent infections [9, 11]. Furthermore, viral infections have been found to alter the composition of respiratory tract microbiome [12, 13], the profile of which has been reported to be associated with the risk of respiratory infections [14–16].

Jartti et al [8] reported that children with recurrent respiratory infections have often been infected with a series of different viruses. However, whether viral infections affect the risk for subsequent ARIs has not been fully elucidated. The present study analyzes data from a pediatric ARI cohort study in the Philippines and assesses how prior viral infections can lead to an enhanced or decreased risk for subsequent ARIs.

METHODS

Cohort Design

A prospective cohort study on ARIs was conducted in Biliran Island, Philippines, from March 2014 to June 2016. Biliran

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Province consists of a main island (Biliran Island, 556 km^2) and small islands, with a total of 161 760 inhabitants [17]. The province consists of 8 municipalities, which are further divided into barangays. In the Philippines, the barangay is the smallest administrative unit under municipalities and is equivalent to a village in other countries. The healthcare system within the study area includes the Barangay Health Station, Rural Health Unit, and the Biliran Provincial Hospital. Barangay Health Stations provide pre- and postnatal care, health education, and public health services such as mass drug administration and immunization. Rural Health Units are primary healthcare facilities located in each municipality where a qualified doctor is assigned to provide outpatient care in addition to public health services. Biliran Provincial Hospital, a secondary level referral hospital with 20 beds allocated for the pediatric ward, is the only hospital in Biliran Province.

Children younger than 5 years old from 25 barangays of 2 municipalities (Kawayan and Caibiran) in Biliran Island were recruited for this study. Children in the study area were identified by a census and household visit. An eligible child for the cohort was defined as a person who had lived in the household for at least 1 month or since birth at the time of consideration of enrollment, with no plans to move in the next month. Newborns and children who moved into the study site during the study period were also enrolled. Children whose guardians declined to participate were excluded. Children were monitored until the study ended, they reached 5 years old, or they moved out of the study area.

Demographic and other information, including date of birth, gender, family structure, socioeconomic (SES) score [18], and birthweight, were obtained through a questionnaire given upon recruitment to the cohort. Socioeconomic score was grouped by tertile for analysis: 0–24, 25–36, and 37–93. Height and weight were measured upon recruitment and updated at least every 6 months. Nutritional status was assessed using the height-for-age Z-score (HAZ) [19].

Follow-Up of Respiratory Symptoms and Sampling

The guardians or caregivers of cohort children were asked to record respiratory symptoms (a cough and difficulty breathing) and presence of fever daily. Every other week, when each household was visited, the records were collected and reviewed by trained nurses. When children developed respiratory symptoms with fever within 7 days of the visit, nasopharyngeal swabs were collected for viral detection.

All healthcare facilities where there is a medical doctor (Rural Health Units and Biliran Provincial Hospital) that the cohort children could access were included in the present study. Nurses or a medical doctor employed and trained for this study conducted physical examinations to check for chest indrawing and respiratory rate, measured blood oxygen saturation level (SpO_2) using a pulse oximeter (PalmSAT 2800; Nonin Medical, Plymouth, MN), and obtained nasopharyngeal swabs for viral detection from the cohort children who visited the healthcare facilities because of respiratory symptoms.

Definition of Acute Respiratory Infection

Acute respiratory infection was defined as the presence of a cough or difficulty breathing determined using the daily records of respiratory symptoms. Coughing or difficulty breathing that lasted >28 days were not considered an ARI in this study. At least 7 asymptomatic (no cough or difficulty breathing) days were required to distinguish each ARI episode. Therefore, the end of an ARI was defined as the last day when a child had a cough or difficulty breathing followed by 7 asymptomatic days.

Acute respiratory infection severity was assessed at the healthcare facilities during patient visit. A severe ARI was defined as an ARI that caused "tachypnea (respiratory rate of >60/min, >50/min, and >40/min for children below two months old, below one year old, and between one and four years old, respectively, according to the Integrated Management of Childhood Illness [20]) or SpO_2 < 95%" and "chest indrawing or SpO_2 < 93%" based on the proposal for definition of severe lower respiratory tract infection by the World Helath Organization [21].

Laboratory Tests

Nasopharyngeal swabs collected at the participant's home and healthcare facilities were placed in a viral transport medium, stored at 4°C in refrigerators at Rural Health Units and Biliran Provincial Hospital for 1–4 days, and transported with ice packs twice a week to the Research Institute for Tropical Medicine, Metro Manila, Philippines, for sample processing. Virological tests were performed to detect the following: AdV [22]; EV including EV-D68 [23]; hMPV [24]; IFV-A and IFV-B [25]; PIV-1, PIV-2, PIV-3, and PIV-4 [26]; rhinovirus species A, B, and C (RhV-A, RhV-B, and RhV-C) [3]; and RSV [27].

In brief, after nucleic acid extraction using the QIAamp MinElute Virus Spin Kit (QIAGEN, Hilden, Germany), polymerase chain reaction (PCR), reverse transcription-PCR, and reverse transcription-quantitative PCR were conducted. Random primer was used for reverse transcription and sequence information of primers and probes are listed in Supplementary Table 1. The PCR amplicon was sequenced to confirm PCR results and to determine the viral classification. Adenovirus serotypes were identified by both sequencing and neutralization tests with viral isolates using HEp-2 cells. When multiple viruses were detected, the ARI episodes were regarded as positive for each virus during further analyses.

Subsequent Acute Respiratory Infections

To investigate whether previous viral infection affects the incidence of subsequent ARIs in the cohort, children who had experienced ARI with viral detection were identified ("children with preceding infection"). Subsequent ARIs were defined as the next ARI that occurred after the preceding infection. When

children with preceding infection had multiple ARI episodes with the same virus, only the first episode was used to identify subsequent ARIs.

We selected matched controls among children who had not experienced infections with a virus of interest by the time their counterpart had an ARI positive for the virus. The matched controls were selected even if they had experienced infection with virus other than the virus of interest. Controls were selected from the cohort and matched for gender (male or female), number of siblings (the difference in the number of siblings should be 0 or 1), HAZ (≥−2 or <−2), prematurity (birth weight ≥2500 grams or <2500 grams), SES score (same tertile), residential area (same or neighboring barangays), and age (those with the closest date of birth among children who met all of the above criteria for matching). When the age difference between children with preceding infection and their matched controls was greater than 6 months for those below 1 year old, or the difference was greater than 1 year for those between 1 and 4 years old, the criterion for either gender, number of siblings, HAZ, prematurity, or SES score was overlooked to find another matched control whose age was closer to children with preceding infection. To minimize the effect of intrinsic susceptibility to ARI and healthcare utilization pattern between children with preceding infection and their matched controls, the number of ARIs and healthcare facility visits by the time of sampling for viral detection (in children with preceding infection) was also matched. When an appropriate control could not be found, the case was excluded from further analyses.

Follow-up for subsequent ARIs in children with preceding infection and their matched control was performed at the same time to minimize the effect of seasonal ARI fluctuations and viral circulation. The follow-up began 8 days after the last day of an ARI positive for a virus of interest in children with preceding infection because 7 asymptomatic days are required to distinguish each ARI episode, as described above. The risk for subsequent ARIs was calculated using the time from the beginning of follow-up for subsequent ARIs to the onset of the first subsequent ARI of children with preceding infection and their matched controls by Cox proportional hazards regression analysis.

Statistical Analysis

Binomial logistic regression analyses with generalized estimating equations were conducted to determine the odds ratio for demographic factors in severe vs nonsevere ARIs identified at healthcare facilities. The same was also used to determine the odds ratio for the detection of each virus in severe vs nonsevere ARIs adjusted for age, gender, HAZ, and SES score. Cox proportional hazards regression analysis was conducted to determine the hazard ratio (HR) for a subsequent ARI after a preceding ARI with viral detection (in children with preceding infection), which was compared with the first ARI in matched controls during the corresponding period. Statistical tests were performed using SPSS version 24 (IBM, Armonk, NY). Confidence intervals (CIs) of 95% were computed to test statistical significance.

Ethics Approval

Informed consent was obtained from the guardians of all participants. The study protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, Japan, and the Institutional Review Board of the Research Institute for Tropical Medicine, Philippines.

RESULTS

We recruited 4012 children, but 161 were excluded because of missing or incomplete (shorter than 28 days) daily records of respiratory symptoms. As such, 3851 children were enrolled and analyzed in this study (Table 1). The median follow-up

Table 1. Summary of Characteristics of Children Included in the Cohort

Variable	Category	Number of Children
Number of Children		3851
Gender	Female	1848 (48%)
	Male	2003 (52%)
Age group (at enrollment)	0–5 M	1053 (27%)
	6–11 M	391 (10%)
	1 Y	650 (17%)
	2 Y	643 (17%)
	3 Y	575 (15%)
	4 Y	539 (14%)
Height-for-age Z-score (at enrollment)	≥−2	2283 (59%)
	≥−3, <−2 (moderate malnutrition)	846 (22%)
	<−3 (severe malnutrition)	722 (19%)
Low birth weight	<2500 grams	455 (15%)
Socioeconomic status score[a]	37–93	1285 (33%)
	25–36	1248 (32%)
	0–24	1318 (34%)
Incidence of ARIs per year	0	599 (16%)
	>0, ≤1	180 (5%)
	>1, ≤2	462 (12%)
	>2, ≤3	587 (15%)
	>3, ≤4	532 (14%)
	>4, ≤5	410 (11%)
	>5, ≤6	344 (9%)
	>6	737 (19%)
Incidence of severe ARIs per year	0	3581 (93%)
	>0, ≤1	178 (5%)
	>1, ≤2	62 (2%)
	>2, ≤3	19 (0.5%)
	>3, ≤4	4 (0.1%)
	>4, ≤5	3 (0.1%)
	>5, ≤6	3 (0.1%)
	>6	1 (0.03%)

Abbreviations: ARIs, acute respiratory infections; M, month; Y, year.

[a]Socioeconomic status score is grouped by tertile.

period was 392 days (interquartile range, 168–714) with 4547 person-years of follow-up. According to the HAZ [19], 41% (1568 of 3851) of the children were classified as having moderate or severe malnutrition at the time of enrollment. Among the cohort of children, 16 337 ARI episodes were recorded, the incidence rate being 359 per 100 person–years (95% CI, 354–365). Seventeen percent of the ARI episodes (2851 of 16 337) prompted a visit to a health facility. Among these episodes, 11% (327 of 2851) and 89% (2524 of 2851) were classified as severe and nonsevere ARIs, respectively (Table 2). The incidence rate of severe ARIs was 7.2 per 100 person-years (95% CI, 6.5–8.0). All hospitalized cases (n = 85) were classified as severe ARIs, 3 of which were fatal. A comparison between severe and nonsevere ARIs revealed that the ARI episodes occurring in males and children of younger age were significantly associated with severe ARIs (Table 2).

Nasopharyngeal swabs were taken from 3971 ARI episodes (24%); samples were collected from 95% of ARI episodes at the healthcare facilities. Patients had fever in 26% of ARI episodes in households, and samples were collected from 34% of the ARI episodes with fever. There was no significant difference in patients' characteristics between ARI episodes with sample collection and those without sample collection (data not shown). At least 1 respiratory virus was detected in 56% of the samples (2204 of 3971). The most frequently detected virus was RhV (n = 867, 22%), followed by RSV (n = 489, 12%), PIV (n = 378, 10%), IFV (n = 320, 8%), hMPV (n = 129, 3%), AdV (n = 95, 2%), and EV (n = 93, 2%) (Supplementary Figure 1). Among the 93 EV-positive samples, 42 (45%) were EV-D68. Given that the serotype for some EV-positive samples could not be determined and that its etiological role in ARIs was unclear, we separated EV-D68 from other EVs (EVs other than D68) during further analyses. We identified the serotype in 62 (65%) of the 95 AdV-positive samples, serotype 7 being the most common (n = 18). Among 54 PIV-4-positive samples, 43 and 11 were types 4a and 4b, respectively. We collected samples from 2 fatal patients of the 3. One was positive for AdV serotype 7 and the other was virus negative. The codetection of multiple viruses was found in 8% of virus-positive samples (169 of 2204) (Supplementary Figure 1). Acute respiratory infection episodes with codetection of multiple viruses were not excluded for further analyses but regarded as positive for each virus.

We initially calculated the association between viral detection and disease severity. Enterovirus D68 (adjusted odds ratio [aOR], 4.6; 95% CI, 2.2–9.6), RhV-C (aOR, 2.0; 95% CI, 1.3–3.0), and RSV (aOR, 3.9; 95% CI, 2.8–5.4) were frequently detected in severe ARIs, with statistical significance (Figure 1). The codetection of different viruses was insignificantly associated with severe ARIs (aOR 1.3 compared with single-virus detection; 95% CI, 0.82–2.1).

We then investigated whether prior viral infections could affect the risk for subsequent ARIs. Risk for the next ARI in children with preceding infection was calculated by comparison of risk for the first ARI during the corresponding time in their matched controls. Matching was successful in over 89% of children with preceding infection. The characteristics of children with preceding infection and matched controls are summarized in Supplementary Table 2.

The Cox proportional hazards model showed that children who had preceding infections with AdV (HR, 1.5; 95% CI, 1.0–2.1), IFV-A (HR, 1.3; 95% CI, 1.1–1.7), PIV-4 (HR,

Table 2. Demographic Factors and Severity of ARIs[a]

Variable	Category	Nonsevere	Severe	Odds Ratio (Unadjusted)	95% Confidence Interval
Number		2524 (89%)	327 (11%)	-	-
Gender	Female	1270 (90%)	143 (10%)	Ref	-
	Male	1254 (87%)	184 (13%)	1.3	1.0–1.7
Age	0–5 M	342 (83%)	70 (17%)	3.4	2.0–5.8
	6–11 M	460 (88%)	64 (12%)	2.3	1.3–3.9
	1 Y	625 (84%)	116 (16%)	3.1	1.8–5.1
	2 Y	473 (92%)	41 (8%)	1.4	0.81–2.5
	3 Y	344 (95%)	19 (5%)	0.91	0.49–1.7
	4 Y	280 (94%)	17 (6%)	Ref	-
Height-for-age Z-score	≥−2	1735 (88%)	226 (12%)	Ref	-
	≥−3, <−2	453 (89%)	254 (11%)	0.91	0.66–1.3
	<−3	336 (88%)	47 (12%)	1.1	0.76–1.5
Low birth weight	No	1815 (88%)	242 (12%)	Ref	-
(<2500 grams)	Yes	289 (91%)	28 (9%)	0.73	0.44–1.2
Socioeconomic status score	37–93	706 (89%)	87 (11%)	Ref	-
	25–36	933 (91%)	96 (9%)	0.84	0.60–1.2
	0–24	885 (86%)	144 (14%)	1.3	0.96–1.8

Abbreviations: ARIs, acute respiratory infections; M, month; Ref, reference; Y, year.

[a]Odds ratios for severe ARIs were calculated by binomial logistic regression analyses with generalized estimating equations.

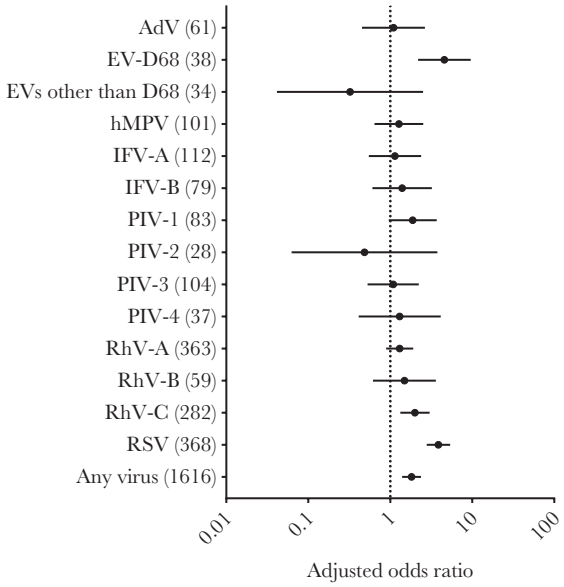

Figure 1. Viral detection and severity of acute respiratory infections (ARIs). Odds ratio and 95% confidence intervals by binomial logistic regression analyses with generalized estimating equations are shown for viral detection of severe vs non-severe ARIs adjusted for age, gender, height-for-age Z-score (HAZ), and socioeconomic (SES) score. The reference to calculate odds ratio was virus-negative ARIs. The numbers in parentheses indicate the number of ARI episodes positive for each virus. A log scale was used for the odds ratio.

1.6; 95% CI, 1.0–2.4), and RhV-C (HR, 1.3; 95% CI, 1.1–1.6) had a significantly high risk for subsequent ARIs (Figure 2 and Supplementary Figure 2). None of preceding viral infections significantly decreased the risk for subsequent ARIs. The risk for subsequent severe ARIs was not enhanced significantly after preceding infections with any viruses tested (Supplementary Figure 3).

Next, we analyzed the risk for subsequent ARIs after preceding viral infections by age group to see whether the observed enhanced risk was age-dependent. The effect of age on the risk for subsequent ARIs varied among viruses (Supplementary Figure 4). The age-dependent enhanced risk for subsequent ARIs was evident for AdV, whereas the enhanced risk for subsequent ARIs was not evident for children in a specific age group for other viruses.

Finally, we determined the effect of viral etiology in subsequent ARIs. In particular, we analyzed the risk for subsequent ARIs positive for respiratory viruses in those with preceding infections with viruses that enhanced the risk for subsequent ARIs, namely, AdV, IFV-A, PIV-4, and RhV-C (Figures 2 and 3). The risk for subsequent infections with RhV increased significantly after preceding infections with AdV (HR, 2.3; 95% CI, 1.0–5.5). The risk for subsequent virus-negative ARIs was also high after preceding infections with AdV (HR, 1.8; 95% CI, 1.0–3.2). Furthermore, preceding infections with RhV-C increased the risk for subsequent RhV-positive ARIs (HR, 1.5; 95% CI, 1.0–2.1), and preceding infections with IFV-A increased the risk for subsequent virus-negative ARIs (HR, 1.7; 95% CI, 1.0–2.6). The risk for subsequent infection with specific virus did not increase after preceding infection with PIV-4. Children who had preceding infections with IFV-A were less likely to have subsequent ARIs positive for the homologous virus (HR, 0.10; 95% CI, 0.013–0.80).

DISCUSSION

This study revealed the association between viral etiology and symptom severity in children with ARIs who sought care from primary and secondary healthcare facilities in the Philippines. Enterovirus D68, RhV-C, and RSV were more prevalent in severe ARIs than in nonsevere ARIs. In addition, we evaluated the effect of viral infections on subsequent ARIs. We found that preceding infections with AdV, IFV-A, PIV-4, and RhV-C were associated with enhanced risk for acquiring subsequent ARIs.

Respiratory syncytial virus is a well known pathological agent of lower respiratory tract infections among infants and young children [28]. Besides, a surge of infections with EV-D68 and their severe clinical manifestation have been reported all over the world since 2010 [4]. The present study confirmed high positivity rate for these viruses and a strong association with severe diseases in children below 5 years old (Supplementary Figure 1 and Figure 1). Although RSV and EV-D68 played an important role in the severity of the present ARIs, preceding infections with those viruses did not significantly increase the risk for subsequent ARIs (Figure 2).

The pathological role of RhV remains unclear. The virus has been detected in respiratory specimens from healthy individuals [29–31], whereas others reported an association between the virus and severe symptoms [32–34]. In this study, infection with RhV-C was associated with severe symptoms in the present ARI (Figure 1), and the infection was a significant risk factor for subsequent ARIs (Figure 2). Rhinoviruses, especially RhV-C, are reported to trigger the development of recurrent wheezing and asthma [35–37]. This association might contribute to our finding of high susceptibility for subsequent ARIs after RhV-C infections; underlying hypersensitivity, such as allergic asthma, may be triggered by an otherwise asymptomatic respiratory infection. Still, the enhanced risk for subsequent ARIs after preceding infections with AdV and PIV-4 (Figure 2) has yet to be reported, and the mechanisms remain unclear. A high risk for subsequent ARIs after viral infections was observed a matter of months after the infections (Figure 2). This result suggests that not only temporal changes in immune status [38] but also other long-lasting factors, such as persistent modulation of immune cells [10], gene regulation [39], alterations in the respiratory tract microbiome [12–16], and tissue damage [11, 40, 41], might be responsible for the higher risk for subsequent ARIs. It is interesting to note that increased risk for subsequent ARIs after viral infections does not seem to be caused by susceptibility to a specific virus (Figure 3).

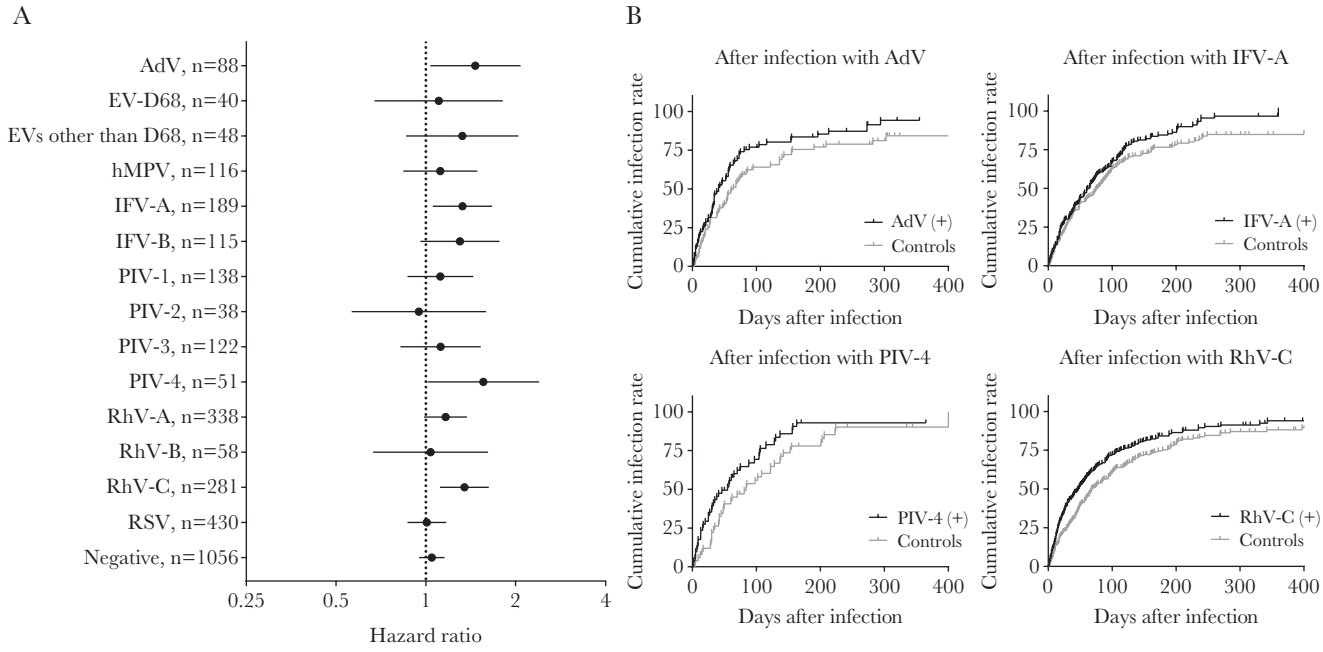

Figure 2. Preceding viral infections and subsequent acute respiratory infections (ARIs). (A) Hazard ratios and 95% confidence intervals determined using Cox proportional hazards regression analysis are shown for subsequent ARIs after preceding infections compared with the first ARIs during the corresponding time for matched controls. A log scale was used for hazard ratios. (B) Cumulative infection rates by Kaplan-Meier curves are shown for subsequent ARIs after preceding infections and ARIs in matched controls during the corresponding period. The curves were shown for preceding infections with adenovirus, influenza A virus, parainfluenza virus type 4, and rhinovirus species C. Results for all viruses can be found in Supplementary Figure 2.

Influenza is known to be associated with severe secondary bacterial infections [42, 43]. In this study, we found an enhanced risk for subsequent ARIs after preceding infection with IFV-A (Figure 2). It is notable that the risk was especially high for virus-negative ARIs (Figure 3). Although we did not test bacterial pathogens in this study, secondary bacterial infections may

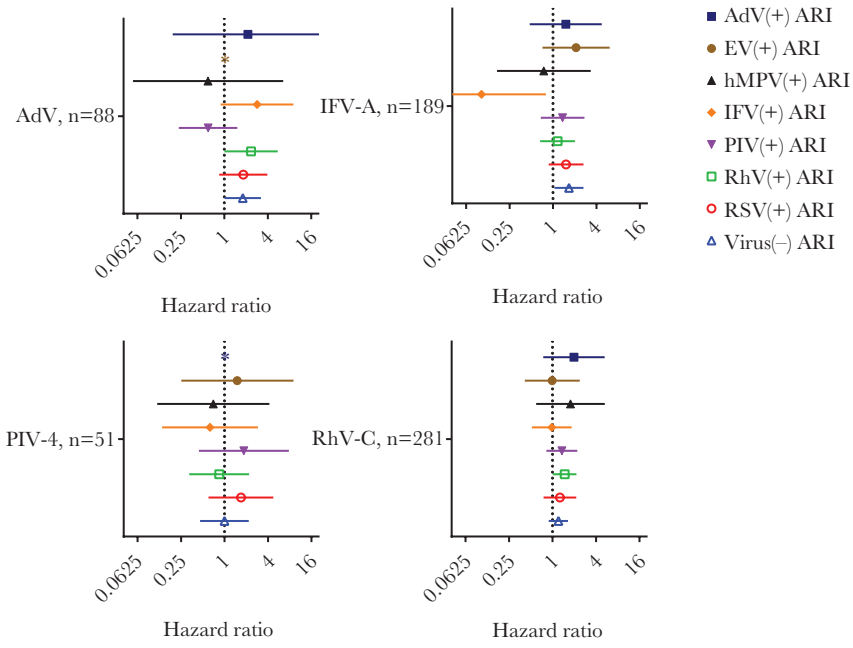

Figure 3. Risk for subsequent virus-positive and virus-negative acute respiratory infections (ARIs) after preceding viral infections. Hazard ratios and 95% confidence intervals determined using Cox regression analysis are shown for subsequent virus (+) and virus (–) ARIs after preceding adenovirus (AdV), influenza virus (IFV)-A, parainfluenza virus (PIV)-4, and rhinovirus (RhV)-C infections compared with matched controls. *, Not calculated because of the limited number of events. A log scale was used for the hazard ratios.

be attributed to the high risk for subsequent ARIs after influenza in the cohort.

A possible concern is that the high risk for subsequent ARIs after preceding viral infections resulted from children who are highly vulnerable to ARIs. Such children may have developed ARIs on multiple occasions, leading to a high possibility of virus detection from the collected samples and a high likelihood of suffering from subsequent ARIs. To reduce this possibility, we matched the incidence of ARI by the time of the preceding infection between each pair of child with preceding infection and the matched control (see Methods for detail). Seasonality of respiratory viruses reported in the study area could also affect the risk for subsequent infection [3]. To address the issue, we compared ARIs in child with preceding infection and the matched control during the same time to calculate the risk (see Methods for detail).

A limitation of this study is that the sampling of nasopharyngeal swabs was only conducted when children developed respiratory symptoms with fever within 7 days of household visit or were brought to the healthcare facilities. Undetected viral infections could confound the interpretation of the impact of specific viruses identified in our sampling on the risk for subsequent ARIs. Still, we collected samples from 95% of ARI episodes at healthcare facilities and 34% of ARI episodes with fever in households. We assume that our sampling included most of the clinically important ARI episodes. Another limitation is that matching strategy was compromised for some cases (see Methods for detail). This could cause biases in the results although matching rate was high and difference in characteristics between the case and matched control was small (Supplementary Table 2).

CONCLUSIONS

In this study, we revealed that viral etiology plays a significant role in the severity of ARIs and, more importantly, that preceding viral infection was associated with the host's susceptibility to subsequent ARIs. Interactions may exist among ARIs with different pathological agents [44–47]. Further study would be required to reveal the risk not only for subsequent ARIs but also for the development of asthma in children after viral infections. Moreover, close attention should be paid to vaccines for respiratory viruses to determine their effect on not only infection with the targeted pathogens but also other infections because the present study found high susceptibility for ARIs after natural viral infections. A better understanding of the etiological role of viral infections and the risk for subsequent ARIs is needed for the prevention and management of childhood ARIs.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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