Background: For most febrile respiratory tract infections (RTIs) in children, the causative pathogen is never identified. We sought to identify the causative pathogen in individual cases of pediatric outpatient with RTIs and to determine whether particular clinical features of RTIs are associated with particular viruses.

Methods: Over 3 years, we prospectively collected nasopharyngeal aspirate specimens from individual pediatric outpatients with an RTI accompanied by persistent fever (>3 days, ≥38.0°C) and peak temperature ≥39.0°C. Two methods—(1) viral culture for respiratory viruses and (2) real-time polymerase chain reaction (PCR) assays identifying 9 different respiratory viruses and 2 respiratory bacteria—were used to test specimens.

Results: For 495 specimens, viral culture and real-time PCR assays together identified at least 1 pathogen in 83.0% and ≥2 viruses alone in 79.4%. These 2 methods identified 138 children with respiratory syncytial virus, 66 with human metapneumovirus, 73 with parainfluenza viruses, 124 with adenovirus, 23 with rhinovirus, 38 with enterovirus, 11 with influenza type C virus, 15 with Mycoplasma pneumoniae and 3 with Chlamydophila pneumoniae; the coinfection rate was 19.7% among all infections. Among the patients with single-pathogen infections, the rate of lower RTI was 37.6% for respiratory syncytial virus, 40.7% for human metapneumovirus, 18.2% for parainfluenza viruses and 2.2% for adenovirus (P < 0.01).

Conclusions: Viral culture and real-time PCR assays were used together to identify causative pathogens in 83% of febrile outpatient children with RTI; specific viruses were associated with particular clinical diagnoses.

Key Words: respiratory tract infection, viral culture, real-time PCR assays, pediatric outpatients, fever

(Footnotes)

Fever is a common presenting symptom in children examined at primary-care clinics. High-grade, prolonged fevers cause discomfort to children and anxiety for parents. Respiratory tract infections (RTIs) with fever account for a substantial portion of febrile illnesses among pediatric outpatients. Respiratory viruses are the most common causes of RTI with fever. Influenza virus, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), parainfluenza virus (type 1, 2 or 3; PIV1–3), adenovirus (AdV), rhinovirus (RV), enterovirus (EV) and coronavirus are common known causes of RTI. Highly sensitive diagnostic techniques such as polymerase chain reaction (PCR) and real-time PCR generally increase the sensitivity of viral detection compared with cell culture methods. In fact, the use of PCR or real-time PCR assays are reportedly associated with high rates of viral detection among pediatric patients with RTI in various clinical settings, but few studies have been conducted on febrile outpatient children with RTI.

Hence, we sought to identify the causative viruses in cases of acute RTI with prolonged, high-grade fever in pediatric outpatients examined at one primary-care clinic. We prospectively obtained 495 respiratory specimens over a 3-year period and then used both viral culture and real-time PCR assays to test each specimen for 9 respiratory viruses (excluding only influenza A and B viruses) and 2 bacterial pathogens. Thereafter, we sought to determine differences among the viruses with regard to the clinical spectrum of symptom.

MATERIALS AND METHODS

Study Design

All studies were conducted during a 3-year period between September 2008 and August 2011 at the Hara Pediatric Clinic, a primary-care clinic, and at the Health and Environment Center of the Hiroshima Prefectural Technology Research Institute with the approval of the Ethical Committee of Ambulatory and General Pediatrics of Japan. Parents or guardians of each participant gave written informed consent. A sterile, disposable suction catheter with a mucus trap was used to collect each nasopharyngeal aspirate (NPA) specimen; each specimen was collected prospectively from each child (≤15 years old) who presented with febrile RTI at the clinic. Viral culture and real-time PCR assays for identifying respiratory viruses were then used to test each specimen. Real-time PCR assays were also used to test each specimen for 2 bacterial pathogens (Mycoplasma pneumoniae and Chlamydophila pneumoniae). Influenza has been very well studied clinically, epidemiologically and demographically; therefore, rapid influenza diagnostic tests and viral cultures were used during the winter seasons and throughout the year, respectively, to identify patients infected with influenza A or B viruses, and each such patient was then excluded from the present study. We made every effort to follow each patient until the fever resolved.

Definitions and Diagnoses

Each patient had to have both a fever lasting ≥3 days and a peak temperature ≥39.0°C during those ≥3 days to be enrolled in this study; the first day on which a temperature ≥38.0°C was noticed was counted as day 1. A pediatrician made a diagnosis at the time of sample collection, and a chest radiograph was ordered at the discretion of the diagnosing pediatrician. Together with a cough, each of the 4 clinical features—(1) wheezing, (2) tachypnea, (3) dyspnea and (4) abnormal breath sounds on auscultation—were considered to be signs of lower respiratory tract infection (LRTI). Croup was defined as an LRTI characterized by hoarseness, barking cough and inspiratory stridor. Bronchitis was defined as an LRTI characterized by cough and the presence of local rales on auscultation. Wheezy bronchitis, consisting of bronchiolitis and the
exacerbation of asthma, was defined as an acute LRTI characterized by cough and diffuse wheezes and rales on auscultation. Pneumonia was defined as an acute respiratory illness with cough and the presence of focal infiltrate on a chest radiograph. Upper respiratory tract infections (URTIs) were categorized as follows: (1) an URTI with cough (URTI-C) was defined as acute respiratory disease presenting with cough, but no evidence of any LRTI described above; (2) tonsillitis was defined as an URTI characterized by the presence of exudates on the tonsils and the absence of cough; (3) pharyngitis was defined as an URTI with redness on the pharynx and/or tonsils but without exudates on the tonsils or cough. Notably, URTI-C was the only URTI diagnosis that included cough.

Asymptomatic Children
Highly sensitive techniques, such as real-time PCR, have greatly improved the clinical detection of respiratory viruses. However, these techniques frequently detect respiratory viruses, such as RV and EV, in respiratory specimens from asymptomatic persons. Therefore, we collected NPAs from asymptomatic children, as well as the symptomatic patients enrolled in the present study, to determine a cutoff value for symptomatic viral load. We then used real-time PCR to quantify the viral load of RV and EV in both the symptomatic group and the asymptomatic group, and subsequently used receiver operating characteristic curves to determine the cutoff values for each virus. NPAs from asymptomatic children from any 1 of 3 categories were tested for RV or EV viral load; the 4 categories were as follows: (1) children whose parents wanted an asymptomatic child to undergo rapid diagnosis because a sibling received the diagnosis of influenza virus, AdV, RSV or hMPV infection with a rapid diagnostic test; (2) afebrile patients who presented with vomiting or diarrhea, but without respiratory symptoms, and who had undergone rapid diagnostic testing for respiratory viruses, received a negative result and thereafter were confirmed to have a gastroenteritis due to rotavirus, norovirus or enteric AdV; (3) patients who were suspected of having erythema infectiosum, rubella or mumps, but who lacked any respiratory symptoms or fever, and underwent real-time PCR testing for human parvovirus B19, rubella virus or mumps virus that produced a positive result.

Virological and Bacteriological Studies
NPAs were put into transport medium and stored at −70°C at the clinic until subsequent testing via viral culture and real-time PCR assay at the virology laboratory. A microplate method and 7 cell types—HEp2, Vero, LLC-MK2, BGM, RD-18S, FL and MDCK—were used for viral culture tests. The QIAamp Viral RNA Mini Kit (QIAGEN, Tokyo, Japan) was used to extract RNA and DNA from aliquots of NPA in transport medium. A QuantiTect Virus + ROX Vial Kit (QIAGEN) was used to perform duplex real-time reverse transcription-PCR (RT-PCR) for simultaneous detection of RSV and hMPV,24 and triplex real-time RT-PCR was used for the detection of PIV1–3.24 QuantiTect Probe RT-PCR Kits (QIAGEN) were used to detect and identify AdV,25 RV,25 EV,25 influenza C virus,25 M. pneumoniae26 and C. pneumoniae26 via individual real-time PCR assays for each pathogen. All primers and probes used for the real-time PCR assays are shown in Table, Supplemental Digital Content 1, http://links.lww.com/INF/B759.

Statistical Analysis
We used the χ² test to compare among viral types with regard to 3 discontinuous variables—(1) detection rates via culture compared versus via PCR assay, (2) rates of multiple infections and (3) spectrum of clinical diagnoses and clinical features. We used the Kruskal-Wallis test to compare the mean ages of patient groups. A P value <0.05 was considered statistically significant. All statistical tests were performed with Statcel (OMS Publishing, Tokorozawa, Japan).

RESULTS

Study Population
We enrolled 495 pediatric outpatients whose symptoms met criteria of febrile RTI (mean age ±SD: 35.9 ± 23.6 months; boys: 260) and 119 asymptomatic children (mean ±SD, 39.0 ± 26.2 months; boys: 58) in this study. Infants constituted 7.7% (n = 38) of all 495 patients, patients aged 12 to 71 months constituted 85.5% (n = 423) and those 26 years of age constituted 6.9% (n = 34). Sample collection was conducted any time from day 3 to day 7 (mean ± SD, 3.9 ± 1.0).

Determination of Cutoff Values for Rhinovirus and Enterovirus via Testing With Real-time PCR
A real-time PCR assay was used to detect both RV and EV in 119 specimens from 119 respective asymptomatic children; 19 of these specimens were positive for RV and 24 for EV. We used RV copy numbers from 48 specimens—19 RV-positive specimens from asymptomatic children and 29 specimens from patients with febrile RTI and positive for RV alone (single-pathogen infection)—to set the receiver operating characteristic curves. Each specimen with a virus copy number larger than the cutoff value was considered truly positive for RV. Simultaneously, a cutoff value for EV infection was determined based on the EV copy numbers in 55 specimens—24 specimens from asymptomatic children and 31 specimens from patients with single EV infections.

Viral and Bacterial Etiology and Demographic Features
For the 495 specimens collected from enrolled patients, viral culture and real-time PCR assay together detected at least 1 pathogen (viral and/or bacterial) in 83.0% of all specimens (n = 411) and ≥2 viruses alone in 79.4% (n = 393); among these 393 specimens with ≥2 viruses but no bacteria, there were 317 single viral infections and 76 multiple viral infections. Testing with the real-time PCR assay and viral culture identified 138 patients with RSV, 66 with hMPV, 73 with PIV1–3 (type 1, 20; type 2, 17; type 3, 36), 124 with AdV, 23 with RV, 38 with EV, 11 with influenza C virus, 15 with M. pneumoniae and 3 with C. pneumoniae (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B760); patients with multiple infections were counted multiple times, once independently for each pathogen. The mean age of children infected with M. pneumoniae was significantly higher than that of any of the following 4 patient groups; those infected with RSV, with hMPV, with PIV1–3 or with AdV (P < 0.01); the age distribution within these patient groups is shown in Figure 1. Of 411 children infected with any pathogen, 93.2% were younger than 6 years. When the number of specimens determined as positive via the real-time PCR assay for all viruses was defined as 100%, the viral detection rate of the culture method was 51.4% for RSV, 22.7% for hMPV, 39.7% for PIV1–3, 95.2% for AdV and 0% for influenza C virus (P < 0.01) (Table 1). Among all specimens negative for RSV, hMPV, PIV1–3, AdV and influenza C virus based on real-time PCR findings, none were virus-positive for these virus groups based on culture findings. However, 35 specimens had an EV copy number greater than the cutoff value for EV, and 16 of these 35 specimens were EV-positive based on culture findings; moreover, 3 specimens not included among these 35 specimens had an EV copy number less than the cutoff value, yet each had a positive viral culture. Accordingly, we defined 38 children as being infected with EV in this study. Of 23 specimens with RV copy number greater than the RV cutoff value, 2 specimens were positive for RV based on viral culture. For the 118
The method. The multiple-pathogen infection rate was 26.8% for RSV. 13 multiple-pathogen infections were also identified by viral culture. Of the 411 children infected with any pathogen, 330 had single-pathogen infections, which were all identified by real-time PCR assay. Among the 81 multiple-pathogen infections; therefore, the overall rate of multiple-pathogen infections was 19.7% of all infections. Among the 81 multiple-pathogen infections, 101 for RSV, 54 for hMPV, 44 for PIV1–3, 88 for AdV, 10 for RV, 12 for EV, 2 for influenza C virus, 13 for M. pneumoniae for EV, 2 for influenza C virus, 13 for M. pneumoniae. We analyzed the clinical features of patients among 4 patient groups (single-pathogen RSV, hMPV, PIV1–3 or AdV). The number of patients with a single-pathogen infection was 101 for RSV, 54 for hMPV, 44 for PIV1–3, 88 for AdV, 10 for RV, 12 for EV, 2 for influenza C virus, 13 for M. pneumoniae and 1 for C. pneumoniae.

Seasonal Distribution of Individual Viral Infection

The epidemiologic pattern of febrile RTIs due to individual viruses is shown in Figure 2; all data from all 3 years were pooled. RSV infections occurred throughout the year; 81.9% of the RSV-related illnesses occurred between September and January (inclusive). A large majority of hMPV-related RTIs (97.0%) occurred from February to August (inclusive), and hMPV-related RTIs did not occur between October and January (inclusive). A large majority of PIV3-related RTIs (91.7%) occurred between May and July (inclusive), and PIV3-related RTIs did not occur between November and March (inclusive). Infections due to PIV1 (n = 20) or PIV2 (n = 17) occurred sporadically and showed no recognizable seasonality. AdV and RV infections occurred throughout the year. EV infections (n = 38) also occurred throughout the year, although a protruding peak number of EV infections (n = 10) occurred in July. There were yearly variations in the occurrence of infections due to these 6 viruses; nevertheless, infections due to each of the 6 viruses did occur in every year of the 3-year study period. Notably, all 11 illnesses due to influenza C virus occurred exclusively between February and October of 2010. Illnesses due to M. pneumoniae or C. pneumoniae showed no recognizable seasonality.

Clinical Features of Infections Caused by Individual Respiratory Virus

The table shows the demographic and clinical features of patients with single-pathogen infections. The distribution of specific clinical diagnosis was significantly different among the 4 patient groups.

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Features of 4 Patient Groups With Single-pathogen Infections due to Frequently Identified Viruses (RSV, hMPV, PIV1–3 or Adenovirus)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
</tr>
<tr>
<td>No. patients</td>
</tr>
<tr>
<td>Age (months)</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td>&lt;12</td>
</tr>
<tr>
<td>12 and &lt;72</td>
</tr>
<tr>
<td>≥72</td>
</tr>
<tr>
<td>No. boys (%)</td>
</tr>
<tr>
<td><strong>Diagnoses</strong></td>
</tr>
<tr>
<td>Croup</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>URTI with cough</td>
</tr>
<tr>
<td>Tonsillitis</td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>LRTI (%)</td>
</tr>
<tr>
<td>Cough (%)</td>
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<tr>
<td>Rhinorrhea (%)</td>
</tr>
</tbody>
</table>

*Number of patients with LRTI, cough or rhinorrhea, and the percentage of patients among each group.
among the 4 patient groups (P < 0.01) (Table 1). Patients with RSV or hMPV infection were more likely to present with bronchitis (P < 0.01) or wheezy bronchitis (P < 0.01). There was a significant difference in the rates of pneumonia among the 4 patient groups (P = 0.020), with the highest rates in the RSV and hMPV groups. The AdV group had the highest rate of tonsillitis (71.6%) among the 4 patient groups (P < 0.01). The rate of LRTI was 37.6% for the RSV group, 40.7% for the hMPV group, 18.2% for the PIV1–3 group and 2.2% for the AdV group (P < 0.01). The rate of LRTI due to AdV was significantly lower than that due to RSV (P < 0.01), hMPV (P < 0.01) or PIV1–3 (P < 0.01). The rate of LRTI due to PIV1–3 was lower than that due to RSV (P = 0.019) or hMPV (P = 0.014). Furthermore, we divided febrile RTIs into 2 groups according to the presence or absence of cough, that is, one group with cough (croup, bronchitis, wheezy bronchitis, pneumonia or URTI-C) and another group without cough (tonsillitis and pharyngitis) (Table 1). The rate of infections with cough was 95.0% for RSV, 98.1% for hMPV, 86.4% for PIV1–3 and 15.9% for AdV (P < 0.01); the rate for PIV was lower than that for hMPV (P = 0.027) and higher than that for AdV (P < 0.01). The rate of infections with rhinorrhea was 93.1% for RSV, 72.7% for PIV and 58.0% for AdV (P < 0.01).

Of the 495 patients, 484 were followed until fever resolution. Four patients were hospitalized: 1 patient had URTI with no identifiable pathogen, and the other 3 each had a single-pathogen infection due to RSV, hMPV or AdV. In addition, there was no significant difference in the duration of fever between cases of single-pathogen infection and cases of multiple-pathogen infection (P = 0.529). We did not find any evidence of increased disease severity in cases of multiple-pathogen infection.

**Causative Pathogens of Pneumonia and Detection of M. pneumoniae and C. pneumoniae**

Of the 495 patients, 166 underwent chest radiography, and 28 of these 166 were found to have pneumonia (Table 2). In the 28 respective specimens obtained from these 28 patients, no pathogen was detected in 4 specimens, and M. pneumoniae was detected in 13 specimens. These 13 specimens included 2 specimens that also contained respiratory viruses; one specimen had hMPV and another had both RV and EV. There were 11 specimens that contained ≥1 viruses, but no M. pneumoniae (Table 2).

Furthermore, M. pneumoniae was detected in 2 specimens among those obtained from the 467 patients who did not have pneumonia; these 2 patients happened to have undergone chest radiography, and one (dual infected with M. pneumoniae and RSV) was given a diagnosis of wheezy bronchitis and the other (single-pathogen infection) bronchitis. We detected C. pneumoniae in 3 specimens from among the 495: these 3 patients (3 boys) with an age range of 3 to 5 years had dual infection (n = 2) or single infection (n = 1). Each of the 3 patients received a diagnosis of URTI-C.

**DISCUSSION**

From among 495 respiratory specimens prospectively collected from 495 respective febrile pediatric outpatients with RTI, we

### TABLE 2. Causative Pathogens in 28 Children With Pneumonia

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. pneumoniae</td>
<td>11</td>
</tr>
<tr>
<td>M. pneumoniae + hMPV</td>
<td>1</td>
</tr>
<tr>
<td>M. pneumoniae + rhinovirus + enterovirus</td>
<td>1</td>
</tr>
<tr>
<td>RSV + parechovirus type 6 + influenza C virus</td>
<td>1</td>
</tr>
<tr>
<td>RSV + enterovirus 1</td>
<td>1</td>
</tr>
<tr>
<td>hMPV</td>
<td>2</td>
</tr>
<tr>
<td>hMPV + influenza C virus</td>
<td>1</td>
</tr>
<tr>
<td>PIV3</td>
<td>2</td>
</tr>
<tr>
<td>PIV3 + rhinovirus</td>
<td>1</td>
</tr>
<tr>
<td>PIV1 + enterovirus</td>
<td>1</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>2</td>
</tr>
<tr>
<td>No. pathogen</td>
<td>4</td>
</tr>
</tbody>
</table>

Of the 495 children enrolled, 166 underwent chest radiography.
identified causative respiratory pathogens in 83.0% of the specimens and more specifically causative respiratory viruses in 80.4%; specimens were collected over a period of 3 years. The use of highly sensitive diagnostic techniques, specifically real-time PCR assays, greatly enhanced the rate of viral identification because the viral culture method alone detected and identified viruses in only 50.5% of the 495 specimens. In fact, the detection rates of viral culture among RSV, hMPV and PIV1–3 ranged from 22.7% to 51.4% when compared with those of the real-time PCR assay; however, the detection rate of viral culture for AdV was noticeably higher (95.2%). In addition, the present study using real-time PCR assay to detect and identify 11 pathogens demonstrated that 19.7% (n = 81) of all 411 infections were multiple-pathogen infections; however, only 13 infections among these 81 infections were identified by the viral culture method. Accordingly, real-time PCR assay demonstrated that the multiple-pathogen infection rate was higher than previously thought. PCR or real-time PCR has been used to achieve high rates of viral detection1–4,6,7,9,10 or relatively high rates of detection of multiple-pathogen viral infections.2,4–10 Among such reports, only 2 have described a viral detection rate with those from any other study because no other study was similar enough to ours in terms of clinical setting or patient population, which was exclusively children with RTI accompanied by high-grade fever. In addition to using real-time PCR assay and studying febrile children, the NPA specimens themselves may have influenced our viral detection rate. We consider NPA a more appropriate specimen type than nasal swab or nasal wash for the identification of respiratory viruses because NPA s, unlike nasal swabs, capture ample nasal fluid that can be visually monitored in the trap, and the nasal fluid of NPA is not diluted as that in nasal washes.

Approximately 90% of the virus-positive specimens were associated with at least 1 of the 4 most common viruses—RSV, hMPV, PIV1–3 or AdV. We may have had so few patients infected with EV in our study, in part, because patients with herpangina, which can be clinically diagnosed, were prospectively excluded from the study and because children with no identifiable source of fever were not included in the study. It is generally assumed that some EV-infected patients present with fevers that have no focus.28 We may have had so few patients with RV infection in this study because the number of patients with RV who meet the inclusion criteria for fever grade and duration is generally small. Among several studies that investigated respiratory viruses in pediatric outpatients,1–3,9,9 only 1 included febrile patients with RTI, and the clinical setting in that study had only a marginal similarity to the clinical setting in our study. In that study, Wang et al4 reported that the most frequent causative virus was RSV, followed by human bocavirus, influenza A and B viruses, PIV1–4, RV, hMPV, AdV, coronavirus and EV. The rates of respiratory viruses in our study were somewhat similar to those in their report, except that we did not include human bocavirus, influenza A and B viruses or coronavirus in our study. Furthermore, 4 other studies included numerous pediatric patients with acute RTI in various clinical settings, and each of these studies demonstrated that RSV, hMPV, PIVs, AdV, coronavirus and influenza A and B viruses were the leading causes of acute RTI.2,3,9,10 Notably, coronaviruses (229E, NL63, OC43 or HKU1) accounted for 4.9% to 22.5% of virus-positive specimens in these 5 prospective studies.2,3,8–10 Among these 5 prospective studies,1–10 only 3 monitored influenza C virus,4,6 and the rates of influenza C virus were negligible, as was the case in our study. Similarly, rates of M. pneumoniae and C. pneumoniae were relatively (3.0%) and extremely low (0.6%), respectively, among all specimens tested, especially when compared with the rates of viral infection that we found in the present study. Among several studies described above that evaluated causative viruses,1–10 only 3 studies also included tests for these 2 bacteria; in those 3 studies, the rates of M. pneumoniae infection ranged from 0.4% to 2.2% and that of C. pneumoniae infection from 0% to 1.8%.2,4,10 In each study, the rate of M. pneumoniae infection was higher than that of C. pneumoniae infection. These findings were in concordance with our findings. Accordingly, the number of pediatric patients infected with C. pneumoniae is considered to be negligible in any clinical setting.

Analysis of the ages of patients with particular viral infections showed that a large majority of patients infected with one of the most common viruses (RSV, hMPV, PIV1–3 or AdV) were younger than 6 years. This age distribution was in near accordance with that from the study by Wang et al4 performed on febrile pediatric outpatients.3 The mean age of patients infected with M. pneumoniae was significantly higher than that of any of the 4 patient groups. Seasonal occurrence differed for each type of viral infection monitored in our study. The particular seasonal patterns of RSV, hMPV and PIV3 were similar to the respective patterns described by Mizuta et al32,33 Patterns of seasonal distribution of AdV, RV and EV were also similar to the respective patterns described in other studies.2,4,8,9,12

We studied clinical features of each single-pathogen infection due to each of the 4 most common viruses; we found that both RSV (37.6%) and hMPV (40.7%) infections were more likely to be associated with LRTI than were AdV (2.2%) or PI (18.2%) infections; AdV infections were more likely to be associated with URTI, especially tonsillitis, than were the other viral infections. We consider that patients with URTI-C might experience less viral infiltration into the lower respiratory tract and that the difference between URTI-C and LRTI might depend on the degree of this infiltration. Hence, we also classified febrile RTIs according to the presence or absence of cough. This classification system revealed that the rates of RSV or hMPV infections associated with cough were greater than 95%, even though the rate of LRTI was 37.6% for RSV and 40.7% for hMPV. The rates of PI and AdV infections associated with cough were 86.4% and 15.9%, respectively. The rate of PIV infections associated with cough also occupied an intermediate position between those of RSV and hMPV infections and that of AdV infections. In other words, manifestations of PIV infections were intermediate between LRTI and URTI when the rates of LRTI and disease with cough were factored into the analysis. Therefore, physicians might distinguish more distinctly among these 4 infections due to the 4 most common viruses not only by separating URTI and LRTI but also by taking the presence or absence of cough into consideration. With respect to the rates of LRTI or the spectrum of clinical diagnoses, our findings among the 4 virus groups were similar to findings from other studies.3,10,12,34

There are a few limitations to our study. First, the number of patients was relatively small because the study was conducted at a single center. Second, other common respiratory viruses (eg, coronaviruses4,8–10,24,25,26,35–37 and PI type 41,4,6,8–10,13,15,38,39) were not tested via the real-time PCR assay. Finally, it is necessary to determine more reliable cutoff values for RV and EV infections. Nevertheless, insights into both the viral cause of febrile RTIs and the clinical characteristics of individual types of single virus infection provided by the present study should be helpful when physicians attempt to determine viral causes for febrile children with RTI at a primary-care center. Taking into account the patient’s age, seasonal occurrence and the spectrum of clinical diagnoses of individual viral infections, physicians should be able to speculate appreciably accurately on the causative virus.
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