Human coronaviruses (HCoVs) include the alphacoronaviruses HCoV-229E and HCoV-NL63 and the betacoronaviruses HCoV-OC43, HCoV-HKU1, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS)-CoV, and SARS-CoV-2 (1). Four of the viruses (HCoV-229E, -NL63, -OC43, and -HKU1, hereinafter designated as common HCoVs) have been recognized as respiratory viruses causing common cold (1,2). Seasonality is therefore an important factor to understand the epidemiology of common HCoV infections. Thus far, there are no longitudinal studies investigating the seasonality of common HCoV infections over a decade (3–5). Thus, we aimed to investigate the seasonality of common HCoV infections afflicting the population in the Yamagata Prefecture of Japan during 2010–2019.

The study was approved by the ethics committee of the Yamagata Prefectural Institute of Public Health (approval no. YPIPHEC 20-08) and the Yamagata University Faculty of Medicine (approval no. 2020-52).

Approximately 15–25 specimens per week were collected from patients who initially presented to Yamanobe Pediatric Clinic with acute respiratory symptoms. A total of 9,349 respiratory specimens were obtained between January 2010 and December 2019. These specimens included those described in reports of our earlier work (6–8). Reverse transcription (RT)-PCR and real-time RT-PCR methods (6–8) revealed 735 specimens as positive for common HCoVs. Because the majority of the patients who visited this pediatric outpatient clinic were children aged below 16 years, we excluded 227 specimens, including 15 specimens positive for common HCoVs, obtained from patients aged 16 and older. Of the remaining 9,122 specimens obtained from the patients aged 15 and younger, 720 (7.9%) were positive for common HCoVs. Additionally, 2 specimens were positive for both HCoV-NL63 and -229E. Therefore, we considered 722 patients as the cumulative total number of HCoV-infected patients. Among the 4 viruses detected, HCoV-OC43 was the most common (n = 286, 39.6%), followed by HCoV-NL63 (261, 36.1%), HCoV-HKU1 (120, 16.6%), and HCoV-229E (55, 7.6%).

First, we investigated the differences in patient characteristics in individuals with common HCoV infection. Statistical analyses, all performed using R (ver. 3.6.3; R Foundation for Statistical Computing, Vienna, Austria), revealed a significant difference for age but not for sex, fever, diagnosis, or usage of an influenza rapid diagnostic kit (Table 1). The results show that differences of patients with common HCoV infections other than age are difficult to ascertain. Particularly, upper respiratory tract infection was found in 80% or more cases, concordantly in all groups, suggesting that common HCoV infections cause mild illness, even in children (2). Regarding age, patients with infections caused by betacoronavirus HCoV-OC43 and -HKU1 were younger than those with infections caused by alphacoronavirus HCoV-NL63 and -229E. Significant differences were observed for the pairs HCoV-OC43 and -NL63, HCoV-OC43 and -229E, HCoV-HKU1 and -NL63, and HCoV-HKU1 and -229E (Table 1).

The monthly distributions of the common HCoV infections are shown in Fig. 1. HCoV-OC43 and -NL63 infections were observed every year. In contrast, HCoV-HKU1 and -229E infections showed marked increase after every 2 years. Furthermore, the peak of each HCoV infection tended to have a slight shift as if the respective HCoVs had caused epidemiological interference. The cumulative detection frequencies of the HCoV infections in January 2015 and June 2016
were high (i.e., 43.5% and 35.9%, respectively) because of HCoV-OC43 outbreaks (7, 8), which might contribute to a bias in the monthly distribution data. Although our investigation has a limitation of being a single-center study, results suggest that the common HCoV infections peaked in winter every year.

Furthermore, to elucidate the seasonal attributes associated with common HCoVs, we calculated Table 1. Characteristics of human coronavirus (HCoV)-infected patients aged 15 and younger in Yamagata Prefecture, Japan, 2010–2019.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>HCoV-OC43 ((n = 286))</th>
<th>HCoV-NL63 ((n = 261))</th>
<th>HCoV-HKU1 ((n = 120))</th>
<th>HCoV-229E ((n = 55))</th>
<th>(P) value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ((\text{yr})), median (IQR)</td>
<td>1 (1–4)</td>
<td>3 (1–6)</td>
<td>1.5 (1–3)</td>
<td>5 (2–7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>144 (50.3)</td>
<td>137 (52.5)</td>
<td>65 (54.2)</td>
<td>28 (50.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>Fever, mean ± SD</td>
<td>38.4 ± 0.8</td>
<td>38.4 ± 0.8</td>
<td>38.4 ± 0.8</td>
<td>38.4 ± 0.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Diagnosis(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>244 (85.3)</td>
<td>225 (86.2)</td>
<td>96 (80.0)</td>
<td>49 (89.1)</td>
<td></td>
</tr>
<tr>
<td>LRTI</td>
<td>18 (6.3)</td>
<td>9 (3.4)</td>
<td>8 (6.7)</td>
<td>3 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>24 (8.4)</td>
<td>27 (10.3)</td>
<td>16 (13.3)</td>
<td>3 (5.5)</td>
<td>0.36</td>
</tr>
<tr>
<td>Influenza kit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>164 (57.3)</td>
<td>148 (56.7)</td>
<td>56 (46.7)</td>
<td>33 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1 (0.3)</td>
<td>2 (0.8)</td>
<td>2 (1.7)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Not tested</td>
<td>121 (42.3)</td>
<td>111 (42.5)</td>
<td>62 (51.7)</td>
<td>21 (38.2)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

\(^1\): Kruskal–Wallis test, one-way analysis of variance, and Fisher’s exact test were applied respectively for age, fever, and sex/diagnosis/influenza kit.

\(^2\): Wilcoxon rank sum test adjusted by Holm revealed that pairs other than HCoV-OC43 and -HKU1 and HCoV-NL63 and -229E were significant \((P < 0.001)\).

\(^3\): LRTI includes patients diagnosed with bronchitis, bronchiolitis, and pneumonia. URTI includes patients diagnosed with respiratory disease other than LRTI such as pharyngitis and tonsillitis.

IQR, interquartile range; SD, standard deviation; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection.

Fig. 1. (Color online) Monthly distribution of cases of human coronavirus-OC43, -NL63, -HKU1, and -229E infection in patients with acute respiratory infection aged 15 and younger during 2010–2019 in Yamagata, Japan.
cumulative monthly trends over a decade (Fig. 2). Our results indicated January and February as the peak months of HCoV infections. The detection frequency was the highest in February (20.5%, 171 out of 836 specimens), followed by January (19.7%, 156 out of 791 specimens), and the lowest in September (0.7%, 6 out of 848 specimens) (Fig. 2B). The common HCoV infection cases started to increase considerably during November–December, then decrease considerably during March–April. Thus, on the basis of the current observations as well as earlier reports (3–5), the common HCoVs can be regarded as virus of winter and might be redesignated as “seasonal coronavirus” similar to “seasonal influenza.”

The seasonality of the common HCoV infections might overlap with that of influenza. In this study, 407 (56.4%) patients who were clinically suspected of having influenza underwent the influenza test with the rapid diagnostic kit (Table 1). To our interest, approximately 80% of HCoV-OC43-infected cases showed negative results when tested with the influenza rapid diagnostic kit during the 2014–2015 season (7). Furthermore, the median time of the influenza warning period during 2010–2019 in Yamagata was from the 3rd to 14th weeks (i.e., from mid-January to early April) (9). Taken together, the common HCoV infections in children are likely to be onerous infectious diseases that must be distinguished from influenza.

Future studies must be conducted to compare the common HCoV infections and the infection caused by SARS-CoV-2, which is the causative agent of the pandemic in 2020. Researchers must elucidate the dynamics of the epidemic, instances of cross-immunity, cross-antigenicity, and differences in symptoms among the common HCoVs and mild SARS-CoV-2 infections in children (5,10). Our investigations on the HCoV cases from the pre-pandemic period of SARS-CoV-2 might serve as an information source for additional studies on HCoV.

In conclusion, results from our longitudinal investigation suggest that winter is the major season of common HCoV infections in children. Additional
studies must be conducted to comprehensively understand the disease dynamics of HCoVs including SARS-CoV-2.

Conflict of interest None to declare.

REFERENCES