Endemic Non–SARS-CoV-2 Human Coronaviruses in a Community-Based Australian Birth Cohort

Keith Grimwood, MBChB, FRACP, MD,a,b Stephen B. Lambert, MBBS, PhD,c Robert S. Ware, BSc, PhD

abstract

BACKGROUND AND OBJECTIVES: The coronavirus (CoV) disease 2019 pandemic has drawn attention to the CoV virus family. However, in community settings, there is limited information on these viruses in healthy children. We explored the epidemiology of the 4 endemic (non–severe acute respiratory syndrome CoV 2) human coronaviruses (HCoVs) by species, including acute illness episodes, risk factors, and health care burden in Australian children in the first 2 years of life.

METHODS: The Observational Research in Childhood Infectious Diseases community-based cohort was a prospective study of acute respiratory illnesses in children from birth until their second birthday. Parents recorded daily symptoms, maintained an illness-burden diary, and collected weekly nasal swabs, which were tested for 17 respiratory viruses, including HCoVs, by real-time polymerase chain reaction assays.

RESULTS: Overall, 158 children participating in Observational Research in Childhood Infectious Diseases provided 11,126 weekly swabs, of which 168 were HCoV-positive involving 130 incident episodes. HCoV-NL63 and HCoV-OC43 were most commonly detected, accounting for two-thirds of episodes. Whereas 30 children had different HCoVs detected on different occasions, 7 were reinfected with the same species. HCoV incidence in the first 2 years of life was 0.76 episodes per child-year (95% confidence interval [CI] 0.63 to 0.91), being greatest in the second year (1.06; 95% CI 0.84 to 1.33) and during winter (1.32; 95% CI 1.02 to 1.71). Fifty percent of HCoV episodes were symptomatic, and 24.2% led to health care contact.

CONCLUSIONS: In children, HCoV infections are common, recurrent, and frequently asymptomatic. In future studies, researchers should determine transmission pathways and immune mechanisms.

WHAT’S KNOWN ON THIS SUBJECT: Endemic (non–severe acute respiratory syndrome coronavirus [CoV] 2) human CoVs are common causes of acute respiratory illness. Few pediatric community-based studies focus on all 4 species and viral testing has been restricted to acute respiratory illness episodes.

WHAT THIS STUDY ADDS: Almost three-quarters of children had an endemic (non–severe acute respiratory syndrome CoV 2) human CoV infection by age 2 years. Incidence was 0.76 episodes per child-year. Recurrent infections involved the same or different species and half of all episodes were asymptomatic.

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Coronaviruses (CoVs) are enveloped, single-stranded RNA viruses. Four endemic human coronaviruses (HCoVs) distributed across 2 genogroups (alphacoronaviruses HCoV-229E and HCoV-NL63 and betacoronaviruses HCoV-OC43 and HCoV-HKU1) are known to circulate continuously worldwide causing mainly mild upper respiratory symptoms.\(^1\) However, 3 highly pathogenic betacoronaviruses (severe acute respiratory syndrome CoV,\(^2\) Middle East respiratory syndrome CoV,\(^3\) and severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2])\(^4\) have emerged this century, each of which have caused outbreaks and illnesses ranging from mild or asymptomatic infections to severe pneumonia with multiorgan failure and death.\(^2\)–\(^4\) Although causing severe disease, the severe acute respiratory syndrome CoV outbreak in 2002–2004 had limited scope, with <9000 confirmed cases globally.\(^1\) Middle East respiratory syndrome CoV was first identified in Saudi Arabia in 2012 and has resulted worldwide in <3000 cases to date, with <100 human cases annually, occurring almost exclusively on the Arabian Peninsula.\(^1,3\) SARS-CoV-2, which arose in China in late 2019, causes an illness termed COVID-19 and has resulted in a global pandemic.\(^5\) However, with each of these new highly pathogenic CoVs, children have milder symptoms than most adults.\(^3\)–\(^8\) The reasons for this observation are uncertain but may relate in young children to angiotensin-converting enzyme-2 receptor levels, raised lymphocyte counts, and activated innate immunity from frequent viral infections.\(^6\)–\(^9\) As SARS-CoV-2 is likely to remain circulating, at least until an effective treatment or vaccine is available, insights into its future activity might be found from examining the 4 endemic (non–SARS-CoV-2) HCoVs in children.

Endemic HCoVs can be isolated from 2% to 9% of children presenting with an acute respiratory illness (ARI) to hospitals, emergency departments (EDs), or clinics.\(^10\)–\(^18\) Such studies, however, are limited by their cross-sectional design and lack of suitable controls. They are also likely to be biased toward more severe illness and to underestimate the burden of mild-to-moderate disease and asymptomatic infections in the community. Seroprevalence studies indicate all 4 endemic HCoVs are usually encountered by 6 years of age.\(^15\)–\(^20\) However, outside of child care centers,\(^2\)–\(^4\) there are few community-based studies describing early infections by all 4 HCoVs in young children.\(^1,14,22\)–\(^28\) In community studies employing sensitive polymerase chain reaction (PCR) assays, authors have found that HCoVs rank between second and fourth among the major respiratory viruses detected in children with ARI\(^21\)–\(^24,27,28\) and seventh with influenza-like illness presentations.\(^26\) Nevertheless, to our knowledge, authors of only one study have collected respiratory samples between ARI episodes,\(^28\) follow-up of infants was often conducted for only 6 months to 1 year or a single respiratory season,\(^22\)–\(^28\) and some studies included older-aged cohorts and household occupants.\(^27,28\) Thus, the incidence of HCoV infections in community-dwelling children is likely to have been underestimated and seasonality and full spectrum of the disease incompletely characterized.

Using an Australian prospective birth cohort, the Observational Research in Childhood Infectious Diseases (ORChID) study, researchers attempted to address the limitations of these community-based studies.\(^29\) They showed that by age 2 years, 72% had experienced at least 1 HCoV infection, and the median age at first detection was 18 months.\(^30,31\) Our objectives of the current study were to use ORChID data to further explore the epidemiology of endemic HCoVs by species, including ARI episodes, risk factors, and health care burden for infection in the first 2 years of life.

**METHODS**

**Study Design**

The ORChID study (www. clinicaltrials.gov [identifier NCT01304914]) progressively recruited healthy term newborn infants without underlying congenital abnormalities or chronic disorders from 2 metropolitan hospitals in Brisbane, Australia, between September 2010 and October 2012 and followed them until their second birthday.\(^29\)–\(^31\) Parents provided informed consent for their child’s participation shortly after birth. Children exited the study when we stopped receiving diaries and swabs or when they had their second birthday. The human research ethics committees of Children’s Health Queensland (HREC/10/QRCH/16), Royal Brisbane and Women’s Hospital (HREC/10/QRBW125), and The University of Queensland (2010000820) approved the study.

**Study Procedures**

At recruitment, parents provided their sociodemographic and health details, including information on the pregnancy and delivery. Telephone interviews were conducted every 3 months to learn about breastfeeding and child care attendance. Exclusive breastfeeding was the period from birth to introducing solids or formula milk. Child care was classified as formal if it was outside the home conducted by a regulated child care service or informal if it was nonregulated and from friends or family. Parents completed a daily tick-box symptom diary, consisting of a set of predefined ARI symptoms they had been trained to recognize. Nasal discharge or congestion, dry cough, or physician-diagnosed otitis media were...
categorized as an upper respiratory illness (URI), and a lower respiratory illness (LRI) was defined as rattly breathing, wet (moist) cough, shortness of breath, wheeze, or physician-diagnosed pneumonia. Parents were also asked to complete an illness-burden diary, which documented health care–seeking behavior and antibiotic prescriptions, whenever the child had symptoms of an LRI or both nasal discharge or congestion and cough. To minimize parent inconvenience, we did not ask for illness-burden diary entries for either isolated nasal symptoms or a dry cough. We reasoned that under these circumstances, parents were unlikely to seek health care advice. Completed symptom and illness-burden diaries were mailed each month to the research team.

Parents were also taught to collect anterior nasal swabs (Virocult MW950; Medical Wire & Equipment, Co Ltd, Corsham, Wiltshire, England) from birth and then on the same day each week, irrespective of symptoms, until the child’s second birthday. These were sent by mail, taking a median of 3 days (interquartile range: 2–4) to reach the laboratory for processing and storage at −80°C. ED and hospital records of ORChID children were reviewed when the study ended.

Laboratory Testing

Swabs were batch tested for 17 respiratory viruses, including the 4 endemic HCoVs (229E, NL63, OC43, and HKU1) by using previously validated real-time PCR assays (Supplemental Table 5).29 Endogenous retrovirus-3 (ERV-3), a marker of human DNA, was used to determine nasal swab quality. Swabs with ERV-3 cycle threshold (Ct) values >38 were deemed to be of lower quality and excluded from incidence calculations to avoid underestimating incidence rates.31,32 The Ct values were used as a semiquantitative measure of HCoV loads because they are indirectly proportional to the amplified nucleic acid present in the sample. A 3.3 cycle difference represents a 10-fold difference in load.33 A new HCoV infection episode was defined as either detecting an HCoV species for the first time or the same virus detected ≥30 days from the last positive swab result. This was deemed symptomatic when symptoms were recorded within 7 days either side of a new virus detection.30,31

Data Analysis

The association between single, new HCoV episodes and both ARI symptoms and health care–seeking behavior were tabulated. Incidence rates of single, new HCoV episodes, as well as associations between predefined risk factors and single, new HCoV episodes, were calculated by using mixed-effects Poisson regression models, with the child included as a random effect and models offset by the natural logarithm of child-years at risk. The association between HCoV swabs and other respiratory virus detections was investigated by using log-binomial regression. All multivariable models adjusted for age, season of detection, presence of older children in the household, and child care attendance. All analyses were conducted by using Stata statistical software version 16 (Stata Corp, College Station, TX).

RESULTS

In total, 158 children returned 11 126 swabs, and 154 provided 87 547 symptom diary-days of observation (78% of expected observation days; Fig 1). This included 10 811 swabs (66% expected) matched to 82 036 diary-days from 154 children and 8101 higher quality swabs from 157 children. Cohort participants were predominantly the first-born child of highly educated parents living in nonsmoking households (Table 1). There were 168 HCoV-positive swabs, of which 130 were incident episodes (Table 2). The 2 most commonly detected HCoVs were HCoV-NL63 (n = 45 episodes) and HCoV-OC43 (n = 44 episodes). Most children (89.3%) shed the virus for 1 to 2 weeks. Whereas 1 child had a single dual infection episode with HCoV-229E and HCoVNL63, 30 children within the cohort had different HCoV species detected on separate occasions (26 had 2 episodes with different HCoVs; [most commonly HCoV-OC43 and HCoV-HKU1, n = 11; and HCoV-NL63 and HCoV-OC43, n = 9], whereas 4 had 3 separate episodes, each with different HCoV species [HCoV-NL63, HCoV-OC43, and HCoV-HKU1, n = 3; and HCoV-229E, HCoV-NL63, and HCoV-OC43 in 1 child]). Furthermore, 7 children infected originally between 3 and 12 months of age were reinfected with the same HCoV species a median 13 months (range 4–16) later (5 with HCoV-OC43 and 1 each with HCoV-NL63 and HCoV-HKU1). Another non-HCoV virus was codetected in 20.2% of episodes (Supplemental Table 6). Although there was a negative association between HCoV and human rhinoviruses (adjusted relative risk [RR] 0.3; 95% confidence interval [CI] 0.2 to 0.5); Supplemental Table 7), the presence of other viruses was not associated with an increased risk of ARI symptoms (RR 1.1; 95% CI 0.6 to 1.9).

The overall incidence of HCoV in the first 2 years of life was 0.76 episodes per child-year (95% CI 0.63 to 0.91). The incidence in the first and second years was 0.51 (95% CI 0.38 to 0.69) and 1.06 (95% CI 0.84 to 1.33) episodes per child-year, respectively. The overall incidence rate in the first 2 years of life for symptomatic HCoV infections was 0.38 (95% CI 0.26 to 0.55) per child-year and 0.20 (95% CI 0.09 to 0.49) and 0.58 (95% CI 0.42 to 0.79) symptomatic episodes per child-year in the first and second years of life, respectively.
Supplemental Table 8). HCoV-NL63 and HCoV-OC43 had the highest incidence rates overall, including symptomatic episodes. Although incidence was greatest in the winter season (incidence rate: 1.32 episodes per child-year), HCoVs were detected year-round, with HCoV-NL63 peaking some years during the summer and HCoV-HKU1 peaking during alternate winters (Supplemental Table 9, Supplemental Fig 2). Other than increasing age, there was no significant association between HCoV incidence and factors, such as sex, season of birth, type of delivery, breastfeeding duration, family history of asthma and/or atopy, tobacco smoke exposure, older children in the household, maternal education, or child care.

There were 124 incident episodes linked to symptom diaries, and 62 (50%) HCoV infections were associated with an ARI (Table 3). Of the 62 symptomatic ARI episodes, 48.4% led to a health care consultation, which included 37.1% being treated only by the family physician (Table 4, Supplemental Table 10). There were 6 ED presentations, 1 of which resulted in hospitalization. Of the 7 children reinfected with the same HCoV species, 4 had ARI symptoms with the original infection, but only 1 became symptomatic (nasal congestion) with their second episode. No significant differences in peak Ct values (reflecting viral loads) between symptomatic or asymptomatic HCoV detections were identified (mean 29.2 [SD 3.7] versus mean 30.1 [SD 4.7]; mean difference 0.9 [95% CI −0.6 to 2.5]) (Supplemental Table 11). In contrast, symptomatic children shed the virus for slightly longer periods than those without symptoms (mean 1.7 [SD 1.1] versus mean 1.1 [SD 0.6] weeks; mean difference 0.6 [95% CI 0.3 to 0.9]).

**DISCUSSION**

In agreement with seroprevalence studies, Australian children were commonly exposed to endemic (non–SARS-CoV-2) HCoVs from a young age, and 50% of the episodes were asymptomatic. Of the 17 respiratory viruses tested, endemic HCoVs ranked third in frequency behind human rhinoviruses and the 2 human polyomavirus species, WU and KI. The overall community incidence of HCoV in the first 2 years of life was greater than reported in other community-based studies. However, in their first 6 months of life, Nepalese infants experienced 0.26 (95% CI 0.23 to 0.29) symptomatic HCoV episodes per child-year, which is similar to our rate of symptomatic episodes per child-year from 0 to 12 months of age. In contrast, Queensland children had almost 3 times the incidence of HCoV-related ARIs in their second year of life than children of the same age attending full-time child care in Seattle (0.20 [95% CI 0.10 to 0.50] episodes per child-year). A much lower incidence rate of 0.04 (95% CI 0.03 to 0.05) episodes per child-year was observed in a multicountry population-based study of children aged 6 months to <10 years presenting with an influenzalike illness. In agreement with studies from temperate climates, the peak seasonal activity for HCoVs in
In subtropical South East Queensland was in winter, with HCoV-NL63 revealing a more variable pattern. In other reports from hospital- and most community-based studies, HCoV-NL63 and HCoV-OC43 were also the 2 most prevalent species detected, followed by HCoV-HKU1 and HCoV-229E. In most cases, virus shedding was transient and restricted to 1 to 2 weeks. The literature on HCoV shedding in healthy children is limited, but our results are consistent with reports from children attending child care in the United States.

These contrast with another community-based birth cohort study from Switzerland, in which 4 of 12 infants with an HCoV infection in the first year of life were still shedding the virus 3 weeks after an ARI involving fever with cough or wheeze. The differences between the 2 studies might be explained by small numbers and differing methodologies in which nasal swabs were collected by study nurses; additionally, the Swiss children may have been sicker. Although we have shown previously that when employing PCR assays, parent-collected nasal swabs have similar virus detection rates to those obtained by health personnel, in the current study, symptomatic children shed the virus for a small but significantly longer period than those lacking symptoms.

Codetections in our cohort at 20% were lower than those reported for other studies, which ranged from 27% to 70%. Whereas the presence of >1 virus did not impact clinical symptoms, there was a negative association between HCoV and human rhinoviruses. Others have also observed that human rhinoviruses reduce the likelihood of other RNA viruses, including HCoV, and human rhinoviruses. Others have also observed that human rhinoviruses reduce the likelihood of other RNA viruses, including HCoV.

### TABLE 1 Sociodemographic Characteristics of the ORChID Cohort (N = 158)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (Male)</strong></td>
<td>75 (47.5)</td>
</tr>
<tr>
<td><strong>Season of birth</strong></td>
<td></td>
</tr>
<tr>
<td>Summer, December to February</td>
<td>42 (26.6)</td>
</tr>
<tr>
<td>Fall, March to May</td>
<td>30 (19.0)</td>
</tr>
<tr>
<td>Winter, June to August</td>
<td>43 (27.2)</td>
</tr>
<tr>
<td>Spring, September to November</td>
<td>43 (27.2)</td>
</tr>
<tr>
<td><strong>Vaginal delivery</strong></td>
<td>107 (67.7)</td>
</tr>
<tr>
<td><strong>Gestational age at birth, wk</strong></td>
<td></td>
</tr>
<tr>
<td>36–38</td>
<td>36 (22.2)</td>
</tr>
<tr>
<td>39–41</td>
<td>122 (77.2)</td>
</tr>
<tr>
<td><strong>First-born child</strong></td>
<td>106 (67.1)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>Either parent has asthma and/or eczema</td>
<td>80 (50.6)</td>
</tr>
<tr>
<td>Mother smoked during pregnancy (n = 156)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Household smoke exposure at birth (n = 158)</td>
<td>19 (12.1)</td>
</tr>
<tr>
<td>Maternal education status (n = 157)</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>99 (63.1)</td>
</tr>
<tr>
<td>Diploma or certificate</td>
<td>38 (24.2)</td>
</tr>
<tr>
<td>Primary and secondary school</td>
<td>20 (12.7)</td>
</tr>
<tr>
<td><strong>Mode of feeding (n = 147)</strong></td>
<td></td>
</tr>
<tr>
<td>Exclusive breastfeeding beyond age 4 mo</td>
<td>83 (56.5)</td>
</tr>
<tr>
<td><strong>Child care attendance at 6 mo8 (n = 133)</strong></td>
<td></td>
</tr>
<tr>
<td>No child care</td>
<td>102 (76.7)</td>
</tr>
<tr>
<td>Informal child care only</td>
<td>14 (10.5)</td>
</tr>
<tr>
<td>Formal child care</td>
<td>17 (12.8)</td>
</tr>
<tr>
<td><strong>Child care attendance at 12 mo8 (n = 116)</strong></td>
<td></td>
</tr>
<tr>
<td>No child care</td>
<td>44 (37.9)</td>
</tr>
<tr>
<td>Informal child care only</td>
<td>21 (18.1)</td>
</tr>
<tr>
<td>Formal child care</td>
<td>51 (44.0)</td>
</tr>
<tr>
<td><strong>Child care attendance at 18 mo8 (n = 108)</strong></td>
<td></td>
</tr>
<tr>
<td>No child care</td>
<td>16 (14.8)</td>
</tr>
<tr>
<td>Informal child care only</td>
<td>23 (21.3)</td>
</tr>
<tr>
<td>Formal child care</td>
<td>69 (63.9)</td>
</tr>
<tr>
<td><strong>Child care attendance at 24 mo8 (n = 103)</strong></td>
<td></td>
</tr>
<tr>
<td>No child care</td>
<td>17 (16.5)</td>
</tr>
<tr>
<td>Informal child care only</td>
<td>18 (17.5)</td>
</tr>
<tr>
<td>Formal child care</td>
<td>68 (66.0)</td>
</tr>
</tbody>
</table>

* Two participants were born between 38.0 and 38.6 days' gestation.

** Formal child care was defined as outside home care from a regulated child care service, whereas informal care comprised nonregulated care by relatives, friends, or neighbors.

### TABLE 2 Endemic (Non–SARS-CoV-2) HCoV-Positive Swabs and Shedding Duration (N = 158 Children and 11 126 Swabs)

<table>
<thead>
<tr>
<th></th>
<th>HCoV Overall</th>
<th>HCoV-229E</th>
<th>HCoV-NL63</th>
<th>HCoV-OC43</th>
<th>HCoV-HKU1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive swabs</strong></td>
<td>168*</td>
<td>16</td>
<td>62</td>
<td>54</td>
<td>38</td>
</tr>
<tr>
<td><strong>Episodes</strong></td>
<td>130</td>
<td>11</td>
<td>45</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td><strong>Shedding duration, wk, No. (%)</strong></td>
<td>99 (76.2)</td>
<td>7 (53.6)</td>
<td>31 (83.6)</td>
<td>63 (81.8)</td>
<td>36 (80.6)</td>
</tr>
<tr>
<td>2</td>
<td>17 (13.1)</td>
<td>2 (18.2)</td>
<td>8 (17.8)</td>
<td>5 (11.4)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>3</td>
<td>8 (6.2)</td>
<td>1 (8.1)</td>
<td>4 (8.9)</td>
<td>2 (4.5)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>4</td>
<td>2 (1.5)</td>
<td>1 (8.1)</td>
<td>0 (2.2)</td>
<td>0 (0.0)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>5</td>
<td>4 (3.1)</td>
<td>0 (0.0)</td>
<td>2 (4.4)</td>
<td>1 (2.3)</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

* One episode (2 consecutive swabs) positive for both HCoV-229E and NL63.
suggesting limited crossprotective immunity exists in young children. Importantly, reinfections with the same HCoV species also occurred at a median 13 months after the original infection. However, these reinfections were either mild or asymptomatic. This observation is consistent with HCoVs remaining prevalent across all age groups and with challenge trials in adult volunteers in which reinfection from either HCoV-229E or HCoV-OC43 was successful a year after the original inoculation when serum antibodies had declined to prechallenge levels. The reasons for reinfection are unknown, but possibilities include incomplete homotypic immunity and exposure to a new genotypic variant of the same HCoV species. The latter is especially relevant as endemic HCoVs continue to evolve with the potential to cause outbreaks and severe LRIs.

Although in hospital-based studies, authors report most children with HCoV had LRIs, such as bronchiolitis, pneumonia, and croup, authors of community-based cohort studies are more likely to describe symptoms of a URI. However, illnesses vary between cohort studies because different criteria were used for collecting respiratory samples. These ranged from mild nasal symptoms alone for infants to combinations of fever, cough, wheeze, or breathing difficulties. By collecting weekly nasal swabs, we were able to identify the underlying HCoV infection rate among young children outside of a clinical setting. Our findings are in agreement with those of the Better Identification of Germs-Longitudinal Viral Epidemiology family study in which children had relatively high rates of asymptomatic infection. This suggests other community-based studies may have underestimated the true rate of HCoV infections. Among those with symptoms, almost two-thirds had only URIs and almost all were managed in the community without hospital involvement.

Despite researchers of a large hospital-based study observing no association between severe LRI and HCoV species, in some community-based studies, including our own, authors have reported HCoV-OC43 to be more strongly associated with LRI episodes.

The ORCHID study has several strengths. Progressive recruiting of unselected healthy newborns and following them over multiple seasons allowed better estimates of infection and disease burden within the community while allowing for both seasonal and annual fluctuations in virus circulation. Comprehensive surveillance by daily symptom diaries and weekly nasal swabs provided good returns of 78% and 66%, respectively, considering the intense and prolonged nature of the study for participating families. Having parents collect nasal swabs avoids the need for research personnel to make home visits that might otherwise prove prohibitively resource intensive and costly in many settings. Taking weekly swabs also ensured sampling before, during, and after each ARI episode, which, with sensitive PCR assays, should assist detection rates and assessment of viral shedding kinetics. The longitudinal design allowed asymptomatic infections to be detected.

There are, however, important limitations. First, symptom
recognition, other than physician-diagnosed otitis media and pneumonia, was not validated. Although parents were trained before the study to recognize respiratory symptoms and entered these in a simple tick-box diary, it is possible some mild symptoms were missed or others were misclassified. Nevertheless, our rates of ARI in the ORChID study are similar to other cohort studies of children in the first 1 to 2 years of life. Second, despite showing previously that parents could reliably collect respiratory specimens from their children, we excluded 3025 (27.2%) lower-quality swabs when analyzing incidence rates to avoid these rates being underestimated if there were any false-negative results. Third, we may have also underestimated viral shedding duration because of missing swabs or because they were collected only weekly. Fourth, our study was not designed to determine who introduced HCoVs into the household. Finally, as often occurs with such intense longitudinal studies, our cohort comprised more advantaged and smaller household–sized urban families, and results may not generalize to other settings. However, the exposures within the cohort on the study outcomes remain valid.

CONCLUSIONS
Infection by 1 of the 4 endemic (non–SARS-CoV-2) HCoVs was common in young and otherwise healthy Australian children. Of these, HCoV-NL63 and HCoV-OC43 were the most prevalent. Repeat infections by different and the same HCoV species suggests protective immunity in children is species specific but incomplete. Incidence was higher in the second year of life and during winter, although most infections were either asymptomatic or resulted in URIs managed within the community. Future studies are needed to determine the transmission pathways and immune mechanisms induced by these viruses. Currently, it is too early to predict whether SARS-CoV-2 will transition from a pandemic to a seasonal, endemic HCoV species. Should this happen, the current study suggests most SARS-CoV-2 infections in children are still likely to be subclinical or mild but depending on the duration of immunity, repeated infections may also occur. The latter is supported by serum anti–SARS-CoV-2 immunoglobulin G antibodies decaying rapidly after mild infections. Although the true nature of protective immunity is unknown, antibodies are considered a reasonable correlate of antiviral immunity and their loss may have important implications for SARS-CoV-2 vaccine programs. We need to learn much more about this increasingly important family of viruses.

ACKNOWLEDGMENTS
We acknowledge the generosity of the families who participated in the ORChID study and the enthusiasm of the research assistants and volunteer staff who helped ensure its success. We also thank Claire Wang for her invaluable assistance with preparing Supplemental Fig 2.

ABBREVIATIONS
ARI: acute respiratory illness
CI: confidence interval
CoV: coronavirus
Ct: cycle threshold
ED: emergency department
ERV-3: endogenous retrovirus-3
HCoV: human coronavirus
LRI: lower respiratory illness
ORChID: Observational Research in Childhood Infectious Diseases
PCR: polymerase chain reaction
RR: relative risk
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
URI: upper respiratory illness

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