Correspondence

Questions Concerning the New Haven Coronavirus

To the Editor—Esper et al. present the discovery of a novel human coronavirus (HCoV) in young children and infants with respiratory tract disease in New Haven: HCoV-NH [1]. However, they also mention that the virus is very similar to HCoV-NL63, a virus that was identified previously in Amsterdam, The Netherlands [2]. Despite this, the 2 studies by Esper et al. [1, 3] and an Editorial Commentary by McIntosh [4] avoid usage of the name "HCoV-NL63" while repeatedly claiming the discovery of a novel virus.

To judge whether HCoV-NH is really a novel HCoV, a comparative analysis of HCoV-NH with a number of different features of established HCoVs should be performed. Examining the relatedness of genome sequences is one facet of such an analysis. Unfortunately, limited data on the genome sequence for HCoV-NH are available, but inspection of a 126-bp fragment clearly shows that all HCoV-NH isolates cluster together with the HCoV-NL63 Amsterdam-1 strain (figure 3 in [1]). This result strongly suggests that the viruses found by Esper et al. are New Haven isolates of HCoV-NL63. Moreover, the actual nucleotide difference between the New Haven isolates (GenBank accession nos. AY870943–AY871008) and the HCoV-NL63 isolate Amsterdam-1 (GenBank accession no. NC_005831) is 0%–6%. This degree of difference falls well within the range of genetic variation observed among different HCoV-NL63 isolates from Amsterdam [2]. We reported the presence of distinct HCoV-NL63 variants that apparently are cocirculating, as has been confirmed recently by Arden et al. [5] and Bastien et al. [6].

Esper et al. do not seem to dispute that HCoV-NH is very similar to HCoV-NL63. What then made them decide to claim the identification of a novel virus? The only argument mentioned is that the research project was initiated before the first article on HCoV-NL63 was published. Is that how it works in science? No—only the first report can claim a novel scientific finding. In fact, for HCoV-NL63, Esper et al.'s is the third article that claims its discovery. The identification of HCoV-NL63 was first announced in an article in *Nature Medicine* (which was published electronically on 21 March 2004 [2]), and an article by Fouchier et al. in the *Proceedings of the National Academy of Sciences of the United States of America* described the same virus [7]. Esper et al. submitted their manuscript to the *Journal of Infectious Diseases* on 7 September 2004, about 6 months after the initial description of HCoV-NL63 was published. Other studies on HCoV-NL63 were submitted for publication in 2004 (and some were published earlier than the one by Esper et al.), but all appropriately acknowledged the discovery of HCoV-NL63 and used its nomenclature, and none claimed the discovery of a novel virus [5–9]. In fact, the issue of the *Journal of Infectious Diseases* in which the study by Esper et al. was published also contains a survey on the prevalence of HCoV-NL63—and indeed, it appropriately names the virus—in Canada [6].

The Esper et al., Fouchier et al., and Arden et al. articles claim in their titles that HCoV-NL63 is associated with respiratory tract disease [1, 5, 7]. However, this conclusion can be drawn only when an appropriate patient control group without respiratory tract disease is included. These studies did not include such a control group, and it is therefore premature to conclude that HCoV-NL63 is associated with disease. The suggestion may be strong, but much work remains ahead of us to accurately define the spectrum of respiratory tract disease caused by HCoV-NL63. The study by Esper et al. on the association between HCoV-NH and Kawasaki disease did include the proper control group, and this finding is very intriguing indeed [3].

The detection of HCoV-NL63 in The Netherlands, Canada, Australia, Japan, and the United States convincingly demonstrates the worldwide distribution of HCoV-NL63. Proposing a different name for basically the same virus each time it is "rediscovered" needlessly complicates the HCoV literature.

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Lack of Association between New Haven Coronavirus and Kawasaki Disease

To the Editor—The new human coronavirus NL63 (HCoV-NL63) was discovered by van der Hoek et al. [1] and Fouchier et al. [2]. HCoV-NL63 has been shown to cause respiratory tract disease in young children [3, 4]. Esper et al. have reported a novel HCoV designated the "New Haven coronavirus" (HCoV-NH) that has been shown by sequence analysis to be very similar to HCoV-NL63 [5]. Esper et al. also reported that HCoV-NH was detected by reverse-transcription polymerase chain reaction (RT-PCR) in 8 (72.7%) of 11 respiratory tract samples from children with Kawasaki disease (KD) and in 1 (4.5%) of 22 age-matched samples from control subjects [6]. On the basis of these data, they suggested that HCoV-NH infection was associated with KD. To further investigate whether HCoV-NH disease is associated with KD, we performed a retrospective study.

From October 2002 to May 2003, 19 nasopharyngeal swab samples were collected from 19 children who fulfilled the criteria for KD and who were treated at Tenshi Hospital in Sapporo, Japan. All of the samples were collected after informed consent was obtained from the children's parents. All of the samples were obtained within 7 days of the onset of illness. The mean age of the children with KD was 22.6 months (range, 4 months–5 years). We used as controls 208 nasopharyngeal swab samples that were collected from children with diagnoses of respiratory tract disease who were admitted to hospitals in Sapporo, Japan, during the same period. All of these samples were examined after the possibility of infection with human respiratory syncytial virus or influenza A or B was excluded by rapid antigen-detection tests. The mean age of the children with respiratory tract disease was 21.6 months (range, 4 months–5 years). After extraction of total RNA and synthesis of cDNA, we performed RT-PCR to detect the HCoV-NH genome, as described by Esper et al. [6]. The primer set and the PCR conditions in our PCR assay were the same as those used in their PCR assays. Sequencing of the PCR products was also performed to confirm the presence of HCoV-NH.

Table 1. Detection of New Haven coronavirus (HCoV-NH) in children with Kawasaki disease (KD) and in children with respiratory tract disease (RTDs).

	No. with HCoV-NH detected/total no.	
Date	Children with KD	Children with RTD
October 2002	0/4	0/12
November 2002	0/4	0/27
December 2002	0/1	0/20
January 2003	0/2	1/20
February 2003	0/2	1/24
March 2003	0/3	3/26
April 2003	0/0	0/29
May 2003	0/3	0/50
Total	0/19 (0.0%)	5/208 (2.4%)

Although RNA sequences of HCoV-NH were detected in samples from 5 (2.4%) of the 208 control children with respiratory tract disease, we could not detect any RNA sequences of HCoV-NH in 19 samples from children with KD (table 1). On the basis of these data, we have some reservations about the findings described by Esper et al. [6]. They collected respiratory tract swab samples from children with KD as part of an ongoing epidemiological investigation of respiratory tract viruses. We collected respiratory tract swab samples from all of the patients with KD, regardless of the presence of respiratory tract symptoms, who were treated at Tenshi Hospital from October 2002 to May 2003. Because no RNA sequences of HCoV-NH were detected in samples from 19 patients with KD in our study, there is a possibility that Esper et al. tested samples from patients with KD who had respiratory tract symptoms. Our results suggest that Esper et al.'s results may be coincidental and that HCoV-NH does not play a dominant role in the etiology or pathogenesis of KD in Japan.

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