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Letters

Letters commenting on recent articles as well as letters reporting cases, outbreaks, or original research are welcome. Letters commenting on articles should contain no more than 300 words and 5 references; they are more likely to be published if submitted within 4 weeks of the original article's publication. Letters reporting cases, outbreaks, or original research should contain no more than 800 words and 10 references. They may have 1 Figure or Table and should not be divided into sections. All letters should contain material not previously published and include a word count.

Viral Etiology of Common Cold in Children, Finland

To the Editor: The common cold is regarded as a viral disease. In the first years of the 21st century, several new respiratory viruses have been identified, such as human metapneumovirus (hMPV), coronaviruses NL63 and HKU1, and human bocavirus (HBoV). Many studies have addressed the role of these viruses in hospital settings, but few studies have been conducted among outpatients. We examined the etiology of the common cold in young children who were newly symptomatic but had no need of hospital care. We hypothesized that the etiology could be detected in all cases by using modern diagnostics that test for 16 viruses in outpatients.

Between February 1996 and April 1998, we collected nasopharyngeal aspirate samples in an outpatient setting from 194 Finnish children having newly onset (<48 h) symptoms of common cold but no acute otitis media (AOM) or other symptoms demanding antimicrobial therapy (*1*). The mean age of the study population was 2.1 years (range 0.7–3.9 years), and 81% attended day care. The parents of all participants gave written informed consent, and the study protocol was approved by the Ethics Committee of Turku University Hospital in Turku, Finland.

The nasopharyngeal aspirate samples were processed freshly for antigen detection (respiratory syncytial virus [RSV]; parainfluenza viruses 1, 2, and 3; influenza A and B viruses; and adenovirus) by time-resolved fluoroimmunoassay (*2*). Stored samples were subjected to nucleic acid testing (NAT) for picornaviruses; RSV; coronaviruses 229E, OC43, NL63, and HKU1; influenza C virus; HBoV; hMPV; and adenovirus. Recently, these samples were reanalyzed for rhinovirus and enterovirus using real-time PCR for the amplification step (*1*,*3*–*6*).

At least 1 respiratory virus was detected in 179 (92%) of 194 children. Rhinovirus was the most common respiratory virus, found in 138 (71%) children (Table). Other viruses were found in varying proportions: HBoV was present in 27 (14%) children; adenovirus was found in 23 (12%) (3 were positive by antigen detection, and 23 by NAT); enterovirus was present in 20 (10%); coronaviruses were found in 11 (6%) (NL63:7; HKU1:2; 229E/OC43:2); influenza viruses were present in 11 (6%) (A:4; B:1; C:6); RSV was shown in 8 (4%) (all were positive by antigen detection and NAT); parainfluenza viruses were present in 7 (4%) (1:1; 3:6); and hMPV was found in 3 (2%). The Table shows the concomitant occurrence of all viruses. Among children with a positive viral finding, 46 (26%) had 2 viruses, and 10 (6%) had 3 or 4 viruses concomitantly. The viruses occurring most frequently with other viruses were adenovirus (100%), HBoV (81%), and enterovirus (75%).

Although our diagnostic panel was incomplete, lacking parechoviruses and parainfluenza type 4 virus, we detected ≥1 respiratory viruses in 92% of the children who had a common cold. As expected, rhinovirus was the leading cause of the common cold in these children. The role of picornaviruses was also emphasized by the abundance of enteroviruses. Enterovirus has gained attention mainly in severe infections, e.g., meningoencephalitis, and is rarely included in diagnostics for respiratory infections. However, PCR has shown that enterovirus commonly causes upper and lower respiratory infections that may be complicated by AOM or expiratory wheezing (*4*,*7*). Thus, enterovirus should be included in the diagnostic panels of respiratory infections. HBoV was the second most prevalent virus in our study population. Since its discovery in 2005, HBoV positivity has been

reported in 3%–19% of different study populations (*8*). Its pathogenic role has been questioned because most HBoV cases are co-infections with other viruses (*8*), and 81% of those testing positive for HBoV in our study had co-infections. However, adenovirus and enterovirus reached similar co-infection frequencies, likely because of prolonged postinfection viral shedding of these agents. HBoV–specific immunoglobulin (Ig) M and IgG antibody responses were recently reported in children with wheezing, suggesting that HBoV induces a systemic infection and is probably a true causative agent of lower respiratory tract disease (*9*). Our study indicates that HBoV may also be a common cause of common cold in young children. However, we found hMPV, coronaviruses NL63 and HKU1, and influenza C virus in 1%–4% of the children, suggesting that these viruses play a minor role in childhood common cold. Our study may underestimate the role of RSV and hMPV because we excluded children with AOM, which is frequently related to these viruses.

Multiple viral findings were common in our study, and 3 children had 4 viruses concomitantly, a logical finding because young children are constantly exposed to respiratory viruses, especially if they attend day care. A recent follow-up study showed that almost all viral findings were related to symptoms, thus supporting the argument that most, if not all, viruses are causative agents (*10*).

A possible causative agent of the common cold can be found in nearly all children who have a cold, and rhinovirus is the leading causative agent. In our study, HBoV was also found frequently, but the recently discovered viruses hMPV and coronaviruses NL63 and HKU1 played a minor role in the common cold of young children.

Table. Positive viral findings in 194 children with newly onset uncomplicated common cold, Finland, 1996–1998

Virus	No. (%) positive*
Rhinovirus	91 (47)
Rhinovirus and human bocavirus	13 (7)
Rhinovirus and adenovirus	11 (6)
Rhinovirus and enterovirus	6 (3)
Human bocavirus	5 (3)
Enterovirus	5 (3)
Respiratory syncytial virus	5 (3)
Influenza C virus	4 (2)
Parainfluenza virus 3	4 (2)
Rhinovirus, adenovirus, and enterovirus	3 (2)
Coronavirus NL63	2 (1)
Human metapneumovirus	2 (1)
Coronavirus 229E or OC43	2 (1)
Rhinovirus and parainfluenza virus 3	2 (1)
Rhinovirus and influenza A virus	2 (1)
Human bocavirus and enterovirus	2 (1)
Adenovirus and enterovirus	2 (1)
Rhinovirus, adenovirus, and coronavirus NL63	2 (1)
Rhinovirus, human bocavirus, adenovirus, and enterovirus	2 (1)
Influenza A virus	1 (1)
Influenza B virus	1 (1)
Coronavirus HKU1	1 (1)
Rhinovirus and respiratory syncytial virus	1 (1)
Rhinovirus and coronavirus NL63	1 (1)
Rhinovirus and parainfluenza virus 1	1 (1)
Human bocavirus and respiratory syncytial virus	1 (1)
Human bocavirus and coronavirus NL63	1 (1)
Human bocavirus and influenza C virus	1 (1)
Adenovirus and respiratory syncytial virus	1 (1)
Coronavirus NL63 and influenza A virus	1 (1)
Rhinovirus, human bocavirus, and influenza C virus	1 (1)
Rhinovirus, adenovirus, and human metapneumovirus	1 (1)
Rhinovirus, human bocavirus, adenovirus, and coronavirus HKU1	1 (1)
Total positive	179 (92)
Total negative	15 (8)
Total children sampled	194 (100)

*Percentages rounded to nearest whole number.

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Time from Illness Onset to Death, 1918 Influenza and Pneumococcal Pneumonia

To the Editor: Brundage and Shanks (*1*) have studied time to death from the onset of influenza symptoms during the 1918 pandemic in military and civilian populations and found a median time to death of 7–11 days. They argue that these data support the idea that the deaths may be predominantly due to bacterial superinfection after the acute phase of influenza. We observed a similar 10-day median time to death among soldiers dying of influenza in 1918 (*2*), a finding consistent with the time to death for a bacterial superinfection, specifically pneumococcal bacteremic pneumonia (*3*).

The major bacterial pathogen associated with influenza-related pneumonia in 1918 was *Streptococcus pneumoniae* (*1*,*3*). Neither antimicrobial drugs nor serum therapy was available for treatment in 1918. To further analyze the time course of death from influenza in relation to that of pneumococcal pneumonia in 1918, we examined data collected by Tilghman and Finland (*4*) from the pre–antimicrobial drug era of the 1920s and 1930s. The Figure shows the distribution of time from onset of illness to death due to influenza-related pneumonia in 1918 compared with time to death due to untreated pneumococcal pneumonia in the 1920s and 1930s. The Figure indicates a close concordance of the times to death. Similar times to death do not prove the specific bacterial etiology of the 1918 deaths. However, pneumococcal bacteremia was associated with most of the pneumonia deaths reported by Tilghman and Finland (*4*), and most 1918 influenza-related deaths were due to bacterial pneumonia (*5*). Also, up to 50% of patients dying from pneumonia in 1918 had pneumococcal bacteremia (*3*). These similar times to death provide additional evidence that the influenza-related pneumonia deaths during the 1918 influenza pandemic were largely due to the pneumococcus.

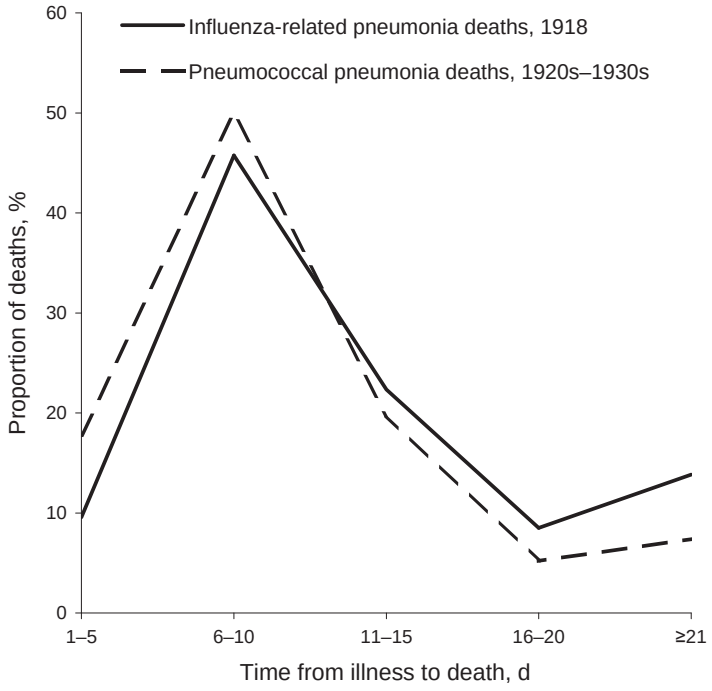

Figure. Distribution of days of illness before death from influenza-related pneumonia, 1918, and from untreated pneumococcal pneumonia, 1920s and 1930s.