# Viral Infections of the Lower Respiratory Tract: Old Viruses, New Viruses, and the Role of Diagnosis

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**Viral infections of the lower respiratory tract cause an enormous disease burden in children, and the role of respiratory viruses in serious lower respiratory tract infections (LRTIs) in older adults is increasingly appreciated. Although viruses are responsible for a large proportion LRTIs, antibiotics are often prescribed. New diagnostic platforms have the potential to detect a wider range of established and newly discovered viruses with greater sensitivity. This will create additional challenges. Although it is clear that influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, and adenovirus are important causes of pneumonia, the role of rhinoviruses and some of the newly described viruses, including human coronaviruses and bocavirus, is harder to determine. Better diagnostic tests that establish the cause of LRTIs in children have the potential to both reduce overall antibiotic use and to improve the targeted use of antibiotics. In addition, rapid identification of viral infections can help control nosocomial transmission.**

Children bear the heaviest burden of viral respiratory illness. Studies that used viral culture estimate that, in developed countries, infants and preschool children experience a mean of 6–10 viral infections annually and school-age children and adolescents experience 3–5 illnesses annually [1]. Because of the limited sensitivity of culture methods, this is certainly an underestimate. Although many viral infections are limited to the upper respiratory tract, viral infections of the lower respiratory tract cause an enormous disease burden in children [2]. Recently, the role of respiratory viruses in serious lower respiratory tract infections (LRTIs) in older adults has begun to be appreciated. Although this article focuses on infections in children, many of the same issues apply to older adults.

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**Clinical Infectious Diseases 2011;52(S4):S284–S289**
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1058-4838/2011/52S4-0002$14.00
DOI: 10.1093/cid/cir043

The syndromes of LRTI in children include bronchiolitis, exacerbations of asthma or wheezing, croup, and pneumonia. Although working definitions exist, there is overlap among the syndromes. Although some respiratory viruses are more strongly associated with specific syndromes, many viruses have been shown to cause each syndrome (Table 1). It is often difficult to differentiate between viral and bacterial pneumonia in children. Seven viruses have been considered to be the usual suspects for LRTI and have been sought in many studies: respiratory syncytial virus (RSV); influenza A and B; parainfluenza 1, 2, and 3; and adenovirus. In the past decade, at least 6 new viruses associated with respiratory infection have been identified, including human metapneumovirus (hMPV), severe acute respiratory syndrome coronavirus, human coronavirus NL63 and HKU1, parainfluenza 4, and bocavirus [3, 4].

## THE PROBLEM

Viruses are responsible for a large proportion of LRTIs in children, but antibiotics are often prescribed for viral illnesses. In addition, viral infections cause the majority of febrile episodes in infants <3 months of age [5].

**Table 1. Lower Respiratory Tract Infections in Children and Important Etiologic Agents**

| Syndrome | Etiologic agents |
|---|---|
| Bronchiolitis | **RSV, hMPV, PIV, adenovirus,** coronaviruses, influenza viruses, *Chlamydophila pneumoniae, Mycoplasma pneumoniae,* rhinovirus, bocavirus, |
| Exacerbations of Wheezing/Asthma | **RSV, hMPV, rhinovirus,** adenovirus, PIV, coronaviruses, influenza viruses, *Chlamydophila pneumoniae, Mycoplasma pneumoniae,* bocavirus |
| Croup | **PIV,** Influenza, adenovirus, |
| Pneumonia | **Influenza, *Streptococcus pneumoniae, Mycoplasma pneumoniae,* PIV, adenovirus, RSV,** hMPV, *Streptococcus pyogenes, Staphylococcus aureus* |
| Pneumonitis in Transplant Recipients | **RSV, PIV, influenza, hMPV,** adenovirus, rhinovirus |

**NOTE.** Pathogens in bold are thought to be the most common etiologies. hMPV, human metapneumovirus; PIV, parainfluenza virus 1, 2, 3; RSV, respiratory syncytial virus.

However, because of the inability to accurately identify the minority of infants who have serious bacterial infections, the majority of febrile infants are hospitalized and receive antibiotics. Existing viral diagnostics, such as enzyme immunoassay–based rapid tests, are limited in sensitivity and detect only influenza and RSV or, in the case of direct fluorescent antibody detection and shell vial culture, require a sophisticated virology laboratory. Furthermore, several of the newer pathogens do not grow well in culture.

Better diagnostic tests that establish the cause of LRTIs in children have the potential to both reduce overall antibiotic use and to improve the targeted use of antibiotics. In addition, rapid identification of viral infections can help control nosocomial transmission. Studies using currently approved rapid tests or direct fluorescent antibody testing, despite the limitations of these methods, have already demonstrated improvements in clinical practice [5–10].

## BRONCHIOLITIS

Bronchiolitis is a disease in children <2 years of age that is characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, and increased mucus production, leading to bronchospasm, wheezing, hyperexpansion of the lungs, and hypoxia. Bronchiolitis causes >120,000 hospitalizations in infants <1 year of age annually; up to 3% of infants are hospitalized for bronchiolitis annually [11]. RSV is the most common cause of bronchiolitis and is detected in 43%–74% of cases. However, other viruses can cause bronchiolitis and are clinically indistinguishable from RSV-induced disease, including parainfluenza virus, adenovirus, rhinovirus, hMPV, coronavirus, and bocavirus [12, 13]. With polymerase chain reaction (PCR)–based testing, coinfection with ⩾2 viruses has been detected in 23% of children. Thus, the potential for nosocomial transmission of a variety of viruses among children hospitalized for bronchiolitis is very high. Diagnostic testing has the potential to influence cohorting, clinical management, and the prevention of health care–associated infections [13, 14].

## PNEUMONIA

Community-acquired pneumonia (CAP) is an important cause of morbidity and hospitalization in children in developed countries, and one of the leading causes of death in children in the less developed countries [15]. The large number of established and emerging pathogens that cause pneumonia and the difficulty of determining the microbial cause complicate the management of pneumonia in children. In addition, it is difficult to obtain adequate specimens from the lower respiratory tract, and nasopharyngeal carriage of potential pathogens is common in healthy children. Moreover, coinfection with ⩾2 pathogens is common.

The etiologies of pneumonia in children differ according to the age of the child, the season, and the clinical presentation. There are relatively few contemporary studies of the etiology of pediatric pneumonia [16–19]. The studies vary in the population studied, case definition, clinical specimens, test methodology, and the number of pathogens sought. In prospective studies, a potential pathogen was identified in 24%–85% of children with pneumonia.

Table 2 summarizes several recent studies of children hospitalized with CAP. Despite differences in the methods used and age groups studied, the overall results are generally similar. In these studies, at least 1 potential pathogen was identified in 77%–86% of children studied. At least 1 virus was identified in 45%–66% of children. Mixed viral and bacterial infections were identified in 23%–33%. In most studies, viral infections were most common in children <2 years of age, but viral causes of pneumonia were important in all age groups.

The use of PCR increases the proportion of children with CAP who are found to have viral infection. Tsolia et al [18] studied 75 school-age children hospitalized with CAP with use of conventional cultures and PCR assays for influenza, RSV, parainfluenza, adenovirus, *Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae.* A pathogen was demonstrated in 58 (77%) of 75, ⩾1 virus in 65%, bacterial infection in 40%, and coinfection in 35%. Adenovirus was present in 9 (12%),

**Table 2. Etiologic Agents of Pneumonia in Hospitalized Children From 4 Recent Studies**

| Variable | Juven et al [16] ($n$ = 254) | Tsolia et al [18] ($n$ = 75) | Michelow et al [17] ($n$ = 154) | Cevey-Macherel et al [19] ($n$ = 99) |
|---|---|---|---|---|
| Age | 1 month–17 years | 5–14 years | 2 months–17 years | 2 months–5 years |
| Any pathogen identified | 215 (85) | 58 (77) | 122 (79) | 85 (86) |
| Any bacteria[a] | 134 (53) | 30 (40) | 93 (60) | 52 (52) |
| Any virus[b] | 158 (62) | 49 (65) | 65 (45) | 66 (66) |
| Bacteria and virus | 77 (30) | 21 (28) | 35 (23) | 33 (33) |
| Specific viruses | | | | |
| Influenza virus | 10 (4) | 5 (7) | 32 (22) | 14 (14) |
| Parainfluenza virus | 25 (10) | 6 (8) | 20 (13) | 13 (13) |
| Adenovirus | 19 (7) | 9 (12) | 11 (7) | 7 (7) |
| RSV | 73 (29)[a] | 2 (3) | 20 (13) | 13 (13) |
| Human metapneumovirus | Ns | 1 (1) | ns | 13 (13) |
| Rhinovirus | 58 (24) | 34 (45) | 5 (3) | 20 (20) |
| Coronavirus | 7 (3) | ns | ns | 7 (7) |
| Enterovirus | Ns | ns | 1 (<1) | 13 (13) |

**NOTE.** Ns, not sought; RSV, respiratory syncytial virus.

[a] Includes bacteria alone or with virus.

[b] Includes virus alone or with bacteria.

parainfluenza in 6 (8%), influenza virus in 5 (7%), RSV in 2 (3%), and hMPV in 1 (1%). Thirty-four children were shedding rhinovirus. The significance of detection of this virus was unclear, but the authors found rhinovirus carriage in only 1 of 27 healthy children in the hospital during the same period with use of PCR. Cevey-Macherel et al [19] studied 99 children <5 years of age who fulfilled the World Health Organization clinical criteria for pneumonia. They used PCR to detect *M. pneumonia, C. pneumonia,* and 13 respiratory viruses, including 4 coronaviruses. A potential pathogen was identified in 86%; 33% had only viral infection, 19% had only bacterial infection, and 33% had mixed viral and bacterial infection. The only clinical sign that helped identify children with bacterial infection was the presence of dehydration. Procalcitonin and C-reactive protein levels were significantly higher in children with bacterial infection, but the sensitivity of these tests was modest (72% and 88%, respectively) and the specificity was low (58% and 44%, respectively). There was no association between the radiologic description and the etiology. It remains unclear from these studies whether children with coinfection with viruses and bacteria had more severe illness.

Although it is clear that influenza, parainfluenza, RSV, human metapneumovirus, and adenovirus are important causes of CAP in the absence of bacterial coinfection, the role of rhinoviruses and some of the newly described viruses, including human coronaviruses and bocavirus is harder to determine. Rhinoviruses are the most common cause of mild upper respiratory illness, and detection of rhinovirus in asymptomatic persons is relatively common [20, 21]. Jartti et al [21] reviewed studies that reported detection of viruses from asymptomatic adults and children, although some of the participants were household contacts of ill patients. With use of conventional culture, rhinovirus detection was uncommon (mean, 1.5%; range, 0%–15%), but with use of PCR, rhinovirus was detected more frequently (mean, 14%; range, 0%–45%). The few studies that have performed sequential sampling have shown that PCR positivity is relatively brief [22, 23]. Replication of many strains of rhinovirus is limited at higher temperatures, and this was thought to prevent replication in the lower respiratory tract. However, recent studies demonstrated that rhinovirus can replicate at higher temperatures and infect the lower respiratory tract [24]. Although season- and age-matched control subjects would be helpful, detection of rhinovirus in young children hospitalized with CAP has been substantially higher in some studies than would be expected from children with uncomplicated URTI [16, 25]. PCR-based detection and sequencing of rhinoviruses has revealed a greater degree of genetic divergence than was appreciated with culture-based detection [20, 26]. It is possible that better understanding of these viruses will identify genotypes with greater capacity for lower respiratory tract disease and severe disease [27, 28].

Three new coronaviruses capable of infecting humans were described recently. Severe acute respiratory syndrome coronavirus was rapidly identified after outbreaks of severe respiratory disease were detected in China, Vietnam, and Singapore in early 2003 [29]. Fortunately, only sporadic laboratory-associated cases have been detected since containment of the worldwide outbreaks by the end of 2003. Human coronavirus NL63 (HCoV-NL63) was identified in the Netherlands in 2004 [30]. It has clearly been associated with croup and bronchiolitis and

occasionally with pneumonia [31–35]. Human coronavirus HKU1 (HCoV-HKU1) was detected in an adult in Hong Kong in 2005 [36]. In one of the initial studies in Hong Kong, HCoV-HKU1 was detected in 2.4% of patients with CAP [36]. Other studies have shown slightly lower frequency. HKU1 was detected as the only respiratory pathogen in 14 (1.4%) of 1043 specimens from hospitalized children in Seattle [34]. In a prospective active surveillance study involving children <5 years of age in Nashville, coronaviruses, including HKU1, NL63, OC43, and 229E, were isolated from 2.2% of children hospitalized with respiratory disease. Thus, coronaviruses appear to be a significant but relatively uncommon cause of hospitalization among children.

Bocavirus was first isolated in 2005 in nasopharyngeal aspirate specimens from children with respiratory tract infection [37]. Unlike many other respiratory viruses, it is a single-stranded DNA virus of the family *Parvoviridae*. Bocavirus has also been isolated from stool and serum samples. Bocavirus has frequently been detected in conjunction with other pathogens and may be detected for prolonged periods. Thus, it has been challenging to demonstrate the clinical importance of bocavirus detection [38–40]. However, at least 2 studies showed that isolation of bocavirus alone was more common in ill children than in control subjects [41, 42]. Bocavirus loads were significantly higher in patients with only bocavirus than in those with co-infection [3, 43]. Thus, accumulating data support the role of bocavirus as a true pathogen, but determining the relevance of isolation from an individual patient remains difficult.

## INFECTION IN TRANSPLANT RECIPIENTS

Respiratory viral infections are an important cause of severe disease in children and adults who receive solid organ and hematopoietic stem cell transplants [44–46]. Children appear to be at increased risk of infection with respiratory viruses, compared with adult transplant recipients. Respiratory viruses can cause severe or fatal pneumonia and may trigger chronic progressive airway obstruction. The role of RSV, influenza virus, adenovirus, and parainfluenza viruses has been appreciated for several years and is reasonably well understood. The seasonal distribution parallels the epidemiology in the community. Infections may be attributable to shedding by visitors or staff or from the patients' upper respiratory tracts. Many outbreaks have been described in transplant units with horizontal transmission. In recipients of stem cell transplants, the mortality associated with lower respiratory tract infection due to the older respiratory viruses is 25%–45%.[44]

Improved molecular detection has led to increased recognition of hMPV, coronavirus, bocavirus, and rhinovirus infections in transplant recipients [47, 48]. There are reports of severe disease associated with these pathogens. However, many unanswered questions remain about the risk factors, natural history, and optimal management of these pathogens.

## POTENTIAL BENEFITS OF MULTIPLEX DIAGNOSTICS

Accurate and timely diagnosis of the cause of LRTI in children has potential benefits, including improved treatment of the individual child, decreasing the overall costs of care and reducing selection for antimicrobial organisms due to excessive antibiotic use. A specific viral diagnosis may provide reassurance to parents and providers.

A few randomized trials and case series have examined the potential for viral testing to improve management [5–7, 49] [50–54]. Bonner et al [6] conducted a randomized trial of providing emergency department physicians with the results of influenza rapid tests for febrile children. For children with influenza, access to the test results reduced the number of antibiotic prescriptions, the ordering of urinalysis, urine culture, complete blood counts, blood cultures, and chest radiographs. No differences were seen among those who did not have influenza. A quasi-randomized trial of influenza rapid testing showed similar results [51]. When the analysis included all children, the use of a rapid test did not influence clinician behavior. However, among those children who tested positive for influenza by either method, those with a rapid influenza test were less likely to have urinalysis, urine culture, or a complete blood count ordered. Doan et al [50] studied 200 children <3 years of age who were seen in the emergency department for fever and had at least 1 respiratory symptom and randomized them to have a direct fluorescent antibody test for 7 respiratory viruses or routine care. There was no statistically significant difference in duration of emergency department stay; performance of chest radiographs, blood tests, and urine analyses; or use of antibiotic prescriptions between the groups. However, children who were tested had a 64% reduction in the likelihood of receiving antibiotics from another provider within 1 week after the visit. Among those who tested positive for a virus, testing was associated with a median 69-min reduction in the duration of the emergency department stay.

For transplant recipients with respiratory infection, the ability to detect the full range of viral pathogens is critical. The known respiratory viral pathogens should be sought in addition to cytomegalovirus, Epstein Barr virus, human herpesvirus type 6, and herpes simplex virus. Highly sensitive multiplex platforms offer obvious advantages over the combination of direct fluorescent antibody testing (DFA), culture, and individual PCR assays.

Nosocomial viral infections impose a substantial burden in children's hospitals and pose a particular risk to immunocompromised children [55]. Early identification allows effective cohorting and isolation. The inability to distinguish among the multiple viral causes of bronchiolitis means that the practice of cohorting children by syndrome without a viral diagnosis exposes them to substantial risk of acquiring a new virus

during hospitalization. Virus-specific cohorting should reduce this risk.

The largest potential societal benefit may come from reduction in the unnecessary use of antibiotics for LRTI in children [56]. Although many factors contribute to the rapid emergence of antimicrobial resistance, respiratory tract infections remain the most common reason for prescribing antibiotics, and each course of antibiotics adds selective pressure [57].

## REMAINING CHALLENGES

The clinical interpretation of the detection of a virus from nasopharyngeal secretions in a child with LRTI can be challenging. It is possible that the virus is from a resolving upper respiratory infection and not the cause of the lower respiratory tract disease. Detection of influenza, adenovirus, RSV, and probably, human metapneumovirus can generally be assumed to correlate with infection of the lower respiratory tract, but coinfection or superinfection with bacteria is not rare. A biphasic illness, focal consolidation on chest radiograph, and elevated inflammatory markers increase the likelihood of bacterial coinfection. More research is needed to help determine when isolation of rhinovirus, bocavirus, or coronavirus is the only cause of pneumonia. Viral quantification may prove helpful to determine when an isolate is associated with severe disease. Preliminary results are encouraging [43, 58–62], but more data using consistent samples and methods are needed to validate the usefulness and to establish cutoff values.

In evaluating new diagnostic platforms, it is not enough to demonstrate that the new test correctly identifies the presence of a large number of respiratory pathogens. The clinician must be able to interpret a positive test result in the context of the clinical illness and determine the appropriate management. It is unreasonable to expect that advanced molecular diagnostic tests will be able to do this in isolation. Instead, as with all tests, the result will need to be interpreted with knowledge of the epidemiology of the pathogen, pretest probability of infection, the patient's symptoms, and other clinical information. Additional epidemiologic studies are needed to establish the importance and presentation of several of the more recently diagnosed pathogens. We need to better understand the role of multiple infections in LRTI.

It is also not enough to demonstrate improved diagnostic accuracy. The tests must ultimately change the behavior of clinicians and improve patient outcomes. Although the preliminary results of the aforementioned trials are promising, the tests studied are limited in breadth and accuracy, and none incorporate detection of bacterial causes of LRTI. Studies are needed that use newer multiplex platforms and that address hospitalized children with pneumonia. Ideally, diagnostic tests should be able to rapidly identify viral and bacterial pathogens and to simultaneously detect antibiotic resistance.

## Acknowledgments

***Financial support.*** This work was supported by National Institutes of Health (NIH; 1U01AI082184-01 to A. T. P.) and the Centers for Disease Control and Prevention (1U181P000303 to A. T. P.). A. T. P. received travel support from the Food and Drug Administration to attend this meeting. He is also a co-investigator on NIH-funded research in which scientists from Idaho Technologies are co-investigators.

***Supplement sponsorship.*** This article was published as part of a supplement entitled "Workshop on Molecular Diagnostics for Respiratory Tract Infections." The Food and Drug Administration and the Infectious Diseases Society of America sponsored the workshop. AstraZeneca Pharmaceuticals, Bio Merieux, Inc., Cepheid, Gilead Sciences, Intelligent MDX, Inc., Inverness Medical Innovations, and Roche Molecular Systems provided financial support solely for the purpose of publishing the supplement.

***Potential conflicts of interest.*** Author certifies no potential conflicts of interest.

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