Journal of Infection (2016) 72, S29—S33

BIAM British Infection Association

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# Respiratory viruses and children

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Available online 10 May 2016

**KEYWORDS**
Antiviral;
Bacteria;
Influenza;
Oseltamivir;
Otitis media;
Pneumonia;
Respiratory syncytial virus;
Vaccine;
Virus

**Summary** Respiratory viruses place a great disease burden especially on the youngest children in terms of high rates of infection, bacterial complications and hospitalizations. In developing countries, some viral infections are even associated with substantial mortality in children. The interaction between viruses and bacteria is probably much more common and clinically significant than previously understood. Respiratory viruses frequently initiate the cascade of events that ultimately leads to bacterial infection. Effective antiviral agents can substantially shorten the duration of the viral illness and prevent the development of bacterial complications. Viral vaccines have the potential to not only prevent the viral infection but also decrease the incidence of bacterial complications. At present, antivirals and vaccines are only available against influenza viruses, but new vaccines and antivirals against other viruses, especially for RSV, are being developed.


## Introduction

Respiratory viruses are ubiquitous organisms that can cause a wide spectrum of clinical manifestations ranging from mild or even asymptomatic upper respiratory tract infections to fatal illnesses with multi-organ failure. Fortunately, most respiratory virus infections are mild and self-limited illnesses, the main symptoms of which are nasal discharge and stuffiness, sneezing, cough, sore throat, and fever. Following the initial discovery of influenza A virus in 1933, most clinically important respiratory viruses such as adenovirus, parainfluenza virus, rhinovirus and respiratory syncytial virus (RSV) were identified during the 1950s and 1960s.[1] The development of sophisticated molecular techniques during the past two decades has led to the discovery of several new respiratory viruses such as human metapneumovirus and human bocavirus.[2,3] Nowadays, the viral etiology of respiratory infections can be determined in virtually all children.[4]

## Burden of illness

Respiratory viruses affect all age groups, but the incidence of viral illnesses is highest among young children who suffer on average 6—8 infections per year. The full economic burden of these generally benign illnesses is difficult to estimate, but e.g. in the United States, 25 million people visit their family doctors every year with uncomplicated upper respiratory infections.[5]

The clinical impact of respiratory virus infections extends far beyond the annoying symptoms in the upper respiratory tract. In developed countries, pediatric

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http://dx.doi.org/10.1016/j.jinf.2016.04.019

mortality due to respiratory viruses is low but not non-existing.[6] However, the situation is completely different in developing countries where the global annual death toll among children younger than 5 years of age is 66 000—199 000 for RSV and 28 000—111 500 for influenza viruses alone.[7,8]

The rates of hospitalization with influenza and RSV are highest in young infants and children,[9,10] and the same is true for rhinoviruses that for a long time were not considered important causes of severe infections in children.[11] However, it is obvious that hospitalized children represent only the tip of the iceberg, and the bulk of the burden of respiratory viruses is in the outpatient setting where most children with respiratory infections and their complications are treated.[12,13] Acute otitis media (AOM) is by far the most frequent bacterial complication of a viral respiratory infection in children. Practically all viruses can predispose a young child to AOM, but some of them, e.g. RSV and influenza virus, appear to be more otopathogenic than many others.[14] In a community follow-up study of respiratory infections, 40% of children <3 years of age developed AOM as a complication of influenza.[15] Other bacterial complications of respiratory virus infections that are mainly treated in primary care settings include sinusitis and pneumonia.

## Viral-bacterial interaction

One of the most interesting current topics in the field of respiratory viruses relates to our increasing understanding of the complex interplay between viruses and bacteria.[16] The tight interaction between viruses and bacteria has been most extensively described for the pathogenesis of AOM that has been conventionally considered a bacterial infection.[17] There is ample evidence to prove that respiratory viruses initiate the cascade of events that eventually leads to the development of AOM, and viruses have an important role at every step in the pathogenesis of this disease. In microbiological specimens obtained directly from the middle ear fluid, both viruses and bacteria have been detected in two-thirds of children,[18] suggesting that most cases of AOM in children are mixed viral-bacterial infections. Although the factual impact of viruses found in the middle ear still remains to be determined, the presence of viruses could at least partly explain the relatively low clinical effectiveness of antibiotics for the treatment of AOM. An important role for viruses was suggested in a study in which the highest concentrations of interleukin-8 and leukotriene B4 were measured in middle ear fluid specimens that contained both bacteria and virus.[19]

An increasing role for viruses has also been demonstrated for pneumonia that is usually regarded as a bacterial infection.[20] The tight connection between influenza and pneumonia has been appreciated since the notorious influenza A/H1N1 pandemic in 1918. However, even the ability of rhinoviruses — the most frequent causes of common cold — to infect the lower airways has been convincingly demonstrated in bronchial biopsy samples obtained from volunteers infected with rhinoviruses.[21] In clinical studies, the determination of the microbiological etiology of pneumonia is severely hampered by the difficulty of obtaining specimens directly from the infected area. Perhaps the closest one can get to obtain lower airway samples with minimum potential contamination from the upper airways is to use sputum specimens. In a recent study in which sputum production was induced by inhalation of hypertonic saline solution, both viruses and bacteria were found in 66% of children with community-acquired pneumonia.[22] Further support for the role of viruses in lower respiratory tract infections was provided by a case report of an infant with a pulmonary abscess unresponsive to treatment with antibiotics; the needle puncture of the abscess yielded *E. coli*, *S. pneumoniae* and RSV.[23]

Some recent studies have suggested that viruses may also predispose children to invasive bacterial infections. An ecological study utilizing three different datasets demonstrated a significant temporal association between the circulation of rhinoviruses and invasive pneumococcal diseases in children; no similar association was seen for either RSV or influenza viruses.[24] In another study, lower respiratory tract infections caused by RSV and influenza viruses coincided with both bacteremic and non-bacteremic pneumonia, but not with invasive pneumococcal diseases that started peaking in the autumn before the circulation of RSV and influenza viruses; however, rhinoviruses were not searched for.[25]

## Antiviral treatment

Even though most respiratory viral infections are relatively mild and self-limited, symptoms disturbing normal life may persist for up to 2—3 weeks.[26] Therefore, the possibility to treat respiratory viruses with effective antiviral agents would be most welcome. A theoretical model for the severity and duration of a respiratory viral infection with or without antiviral treatment is presented in Fig. 1. During a typical uncomplicated viral infection, the severity of the symptoms peaks around day 2—3 of the illness, and the major symptoms gradually resolve by day 7—10.[1,27,28] In case of development of a bacterial complication, both the severity and duration of symptoms are usually increased. Theoretically, an effective and specific antiviral treatment started soon after the illness onset could be expected to

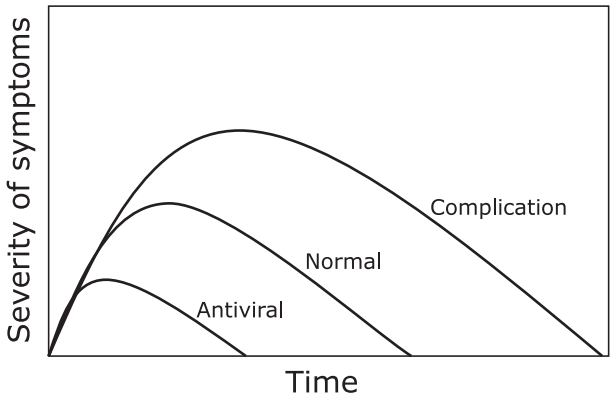


**Figure 1** Theoretical model for the severity and duration of a respiratory viral infection with or without antiviral treatment.