

## Seminar

## The common cold

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**Despite great advances in medicine, the common cold continues to be a great burden on society in terms of human suffering and economic losses. Of the several viruses that cause the disease, the role of rhinoviruses is most prominent. About a quarter of all colds are still without proven cause, and the recent discovery of human metapneumovirus suggests that other viruses could remain undiscovered. Research into the inflammatory mechanisms of the common cold has elucidated the complexity of the virus-host relation. Increasing evidence is also available for the central role of viruses in predisposing to complications. New antivirals for the treatment of colds are being developed, but optimum use of these agents would require rapid detection of the specific virus causing the infection. Although vaccines against many respiratory viruses could also become available, the ultimate prevention of the common cold seems to remain a distant aim.**

"I love the doctors—they are dears;  
But must they spend such years and years  
Investigating such a lot  
Of illnesses which no one's got,  
When everybody, young and old,  
Is frantic with the common cold?  
And I will eat my only hat  
If they know anything of that!"<sup>1</sup>

The common cold is a conventional term for a mild upper respiratory illness, the hallmark symptoms of which are nasal stuffiness and discharge, sneezing, sore throat, and cough. Although the term tends to imply that there is a single cause for the illness, the common cold is actually a heterogeneous group of diseases caused by numerous viruses that belong to several different families. The common cold is usually a self-limited illness confined to the upper respiratory tract. However, in some patients the viral infection spreads to adjacent organs, resulting in different clinical manifestations, and, occasionally, colds predispose to bacterial complications.

Despite the usually benign nature of the illness, the common cold is an enormous economic burden on society in terms of visits to doctors and other health-care providers, treatments, and absences from work, school, or day care. Every year, in the USA, about 25 million people visit their family doctors with uncomplicated upper respiratory infections,<sup>2</sup> and the common cold syndrome results in about 20 million days of absence from work and 22 million days of absence from school.<sup>3</sup>

## Cause

Our knowledge about the cause of the common cold is largely derived from extensive family and community follow-up studies undertaken between the 1960s and the

1980s.<sup>4–6</sup> Intensive research into the cause of respiratory illnesses during the 1950s and 1960s led to the discovery of adenovirus, parainfluenza virus, rhinovirus, respiratory syncytial virus (RSV), enterovirus, and coronavirus, in addition to the influenza viruses that had been identified earlier (figure 1). However, because during that era the techniques of viral detection were limited to virus isolation, the viral cause could be proven in only about 25% of patients with respiratory infections.<sup>7</sup> Improvements in viral detection techniques during the past two decades, including various viral antigen detection methods and particularly the advent of PCR-based assays, have substantially increased the rates of viral detection in clinical specimens.<sup>8,9</sup>

The relative proportions of different viruses in the cause of the common cold vary dependent on several factors, such as age, season, and viral sampling and detection methods. However, rhinoviruses have been consistently found to be the most common cause in all age groups, irrespective of the viral detection techniques used (panel).<sup>8–12</sup> Yearly, rhinoviruses account for about 30–50% of all respiratory illnesses,<sup>6,9</sup> but during the autumn peak season these viruses can cause up to 80% of all upper respiratory infections.<sup>8</sup> More than 100 different serotypes of rhinoviruses have been identified, the relative prevalences of which seem to vary between different geographical areas and also over the course of time.<sup>10</sup>

Although scarce, data are available on the role of coronaviruses as a cause of the common cold. These viruses are found in 7–18% of adults with upper respiratory infections.<sup>9,13,14</sup> Parainfluenza viruses, RSV,

## Search strategy

The data for this seminar were identified by computer-aided searches of PubMed and Cochrane Library databases, using keywords relevant to the different sections. We also reviewed the journal reference lists and standard textbooks and used our existing knowledge of the primary publications in this area and new data presented at international scientific meetings. We then selected reports that, in our understanding, have contributed substantially to the current knowledge of various aspects of the common cold, and that also have potential for further reading.

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Figure 1: **Timeline of discovery of the common respiratory viruses**

Transmission electron micrograph of three adenovirus particles shown in background.

adenoviruses, and enteroviruses all account for minor proportions of the common cold syndrome, but the range of illness caused by each of these viruses also includes other manifestations that can be more typical to these viruses.<sup>10,12</sup> Influenza is often regarded as a disease entity separate from the common cold. However, the clinical presentation of influenza ranges from an asymptomatic infection to severe illness and it therefore overlaps with the common cold. Mild instances of streptococcal pharyngitis are clinically indistinguishable from viral pharyngitis and can be misclassified as colds.

Despite the availability of sophisticated diagnostic methods, about 20–30% of colds remain without a proven viral cause,<sup>6,9</sup> probably due in part to suboptimum methods used in the collection, transportation, and assay of clinical specimens, resulting in underdetection of viruses known to exist. However, many colds could also be caused by infectious agents yet to be identified. This explanation gained much support after the recent discovery of a new virus in young

children with respiratory infections.<sup>15</sup> The relative effect of this virus, tentatively named human metapneumovirus, by comparison with other respiratory viruses is still undetermined. Findings of serological studies<sup>15</sup> indicate that the virus has been circulating in human beings for at least 50 years, and by the age of 5 years virtually all children in the Netherlands are infected by it. Reports<sup>16,17</sup> from other countries suggest that human metapneumovirus has a worldwide distribution.

Two or more viruses are found simultaneously in about 5% of patients with colds.<sup>18</sup> However, the rate of dual viral infection increases proportionally with the number of different diagnostic methods used,<sup>18</sup> and whether or not all of these cases really represent simultaneous infections by two viruses is unclear. Positive findings by PCR, for instance, do not require the presence of live viruses, and viral genomic materials can be detected in patients long after the subsidence of clinical symptoms.<sup>19,20</sup>

### Epidemiology

The occurrence of the common cold shows clear seasonality. In temperate regions of the northern hemisphere, the frequency of respiratory infections increases rapidly in the autumn, remains fairly high throughout the winter, and decreases again in the spring. In tropical areas, most colds arise during the rainy season. The incidence of upper respiratory infections is inversely proportional to age (figure 2). On average, the youngest children have 6–8 and adults 2–4 colds per year.<sup>5,7</sup> During the first years of life, boys seem to have more respiratory infections than girls, but this difference is reversed later in life.<sup>5</sup> Women who work outside the home have fewer infections than those who do not, which might be explained by greater exposure to children in those who stay at home.<sup>6</sup> Day-care attendance is another major risk

#### Viral cause of the common cold<sup>6,9,12</sup>

Virus	Estimated annual proportion of cases
Rhinoviruses	30–50%
Coronaviruses	10–15%
Influenza viruses	5–15%
Respiratory syncytial virus	5%
Parainfluenza viruses	5%
Adenoviruses	<5%
Enteroviruses	<5%
Metapneumovirus	Unknown
Unknown	20–30%

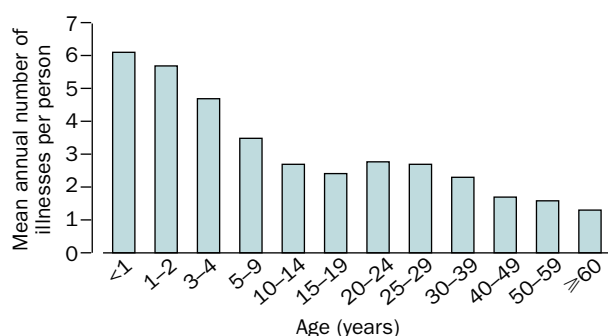


Figure 2: **Mean annual incidence of respiratory illnesses per person by age group<sup>5</sup>**

factor for respiratory illnesses in children, and the frequency of colds increases with the number of children in the group.<sup>21-23</sup> However, frequent infections in the preschool years could lower the frequency of the common cold during school years.<sup>23</sup> Some genetic factors might also affect an individual's susceptibility to respiratory infections, but any potential mechanisms remain largely unidentified.<sup>24,25</sup> Psychological stress is associated with susceptibility to the common cold in a dose-dependent manner.<sup>26</sup> Finally, some reports<sup>27</sup> indicate that heavy physical training increases the risk of respiratory infections, whereas moderate physical activity could decrease risk.

Because of the central role of rhinoviruses in the cause of the common cold, the epidemiology of this condition largely parallels that of rhinoviruses. Although rhinoviruses can be detected throughout the year, the incidence of rhinovirus infections peaks during autumn, with a subsequent smaller outbreak in the spring.<sup>28,29</sup> Results of a follow-up study<sup>30</sup> showed the high incidence of rhinovirus infections in children during the first years of life. By age 6 months, more than 20% of children had had a laboratory-confirmed rhinovirus infection. By age 2 years, rhinovirus infection had been documented by virus culture or PCR in 79% of the children, and 91% had antibodies against rhinoviruses. The average annual rate of rhinovirus infection is estimated at about 0.8 per person.<sup>28</sup> However, this figure is likely an underestimate, and calculations based on PCR data might yield a substantially higher rate.

Many other viruses that cause the common cold tend to have their own patterns of seasonality. In most temperate countries, RSV usually causes outbreaks around the turn of the year,<sup>31</sup> but other patterns have also been documented.<sup>32</sup> Influenza epidemics also typically occur in the winter in the northern hemisphere, often overlapping with RSV.<sup>31,33</sup>

The transmission of viruses that cause upper respiratory infections can occur by any of the three major mechanisms: 1) hand contact with secretions that contain the virus, either directly from an infected person or indirectly from environmental surfaces; 2) small-particle aerosols lingering in the air for an extended time; or 3) direct hit by large-particle aerosols from an infected person. Although all these mechanisms are likely to be involved in the spread of any respiratory virus, the primary routes of transmission do differ between viruses. For instance, influenza viruses are thought to be spread mainly via small-particle aerosols,<sup>34</sup> whereas hand contact followed by self-inoculation with the virus into the nose or eye has been reported as the most efficient way of transmission for rhinoviruses.<sup>35</sup> However, aerosol transmission of rhinoviruses has also been clearly documented.<sup>36</sup>

## Pathogenesis

The pathogenesis of the common cold involves a complex interplay between replicating viruses and the host's inflammatory response. The detailed pathogenetic mechanisms of the various respiratory viruses can be very different from each other, as indicated by the fact that the primary site of replication of influenza viruses is in the tracheobronchial epithelium,<sup>34</sup> whereas rhinovirus replication starts predominantly in the nasopharynx.<sup>37</sup> The available evidence,<sup>38</sup> albeit scarce, does not lend support to the popular belief that colds are associated with chilling or exposure to a cold environment.

Much of our understanding of the pathogenetic events in the common cold is derived from studies of volunteers infected with rhinoviruses.<sup>35-37</sup> Rhinovirus infection begins with the deposition of viruses in the anterior nasal mucosa or in the eye, from where they get to the nose via the lacrimal duct. The viruses are then transported to the posterior nasopharynx by mucociliary action. In the adenoid area, the viruses gain entrance to epithelial cells by binding to specific receptors on the cells. About 90% of rhinovirus serotypes use intercellular adhesion molecule-1 (ICAM-1) as their receptor.<sup>39,40</sup> Once inside the epithelial cell, the virus starts to replicate rapidly. Progeny viruses can be detected within 8-10 h after intranasal inoculation of rhinoviruses.<sup>41</sup> The infectious dose of rhinovirus is small,<sup>42</sup> and up to 95% of individuals without antibodies against the specific viral serotype are infected after intranasal challenge.<sup>43</sup> However, for reasons still unknown, all infections do not lead to clinical illness; symptomatic colds develop in only 75% of infected persons.<sup>43</sup> The shedding of rhinoviruses peaks on the second day after intranasal inoculation and decreases rapidly thereafter, but small amounts of viruses can be discovered in nasal secretions for up to 3 weeks after infection.<sup>37,44</sup>

Viral infection of the nasal mucosa results in vasodilation and increased vascular permeability, which in turn cause nasal obstruction and rhinorrhoea, which are the main clinical symptoms of the common cold. Cholinergic stimulation leads to increased mucous gland secretion and sneezing. The detailed mechanisms by which viral infection causes such changes in the nasal mucosa are still incompletely understood. Distinct differences exist in the degree of epithelial destruction between various respiratory viruses. Whereas influenza viruses and adenoviruses cause extensive damage to the respiratory epithelium,<sup>45,46</sup> no histopathological changes are observed in nasal biopsy specimens from individuals infected with rhinoviruses.<sup>37</sup> The absence of epithelial destruction during rhinovirus infections has led to the idea that the clinical symptoms of the common cold might not be caused by a direct cytopathic effect of the viruses, but instead are primarily caused by the inflammatory response of the host. Extensive research into the role of inflammatory mediators in the pathogenesis of the common cold has produced evidence for increased concentrations of several mediators, such as kinins, leukotrienes, histamine, interleukins 1, 6, and 8, tumour necrosis factor, and RANTES (regulated by activation normal T cell expressed and secreted) in the nasal secretions of patients with colds.<sup>47-52</sup> The concentrations of interleukin 6 and interleukin 8 in nasal secretions correlate with the severity of the symptoms.<sup>53,54</sup> The host response mechanisms triggered by viral infection are, however, interrelated, extremely complex, and far from resolved. For example, in respiratory epithelial cells infected with RSV, interleukin 1 $\beta$  and tumour necrosis factor  $\alpha$  induce the synthesis of interleukin 8 at 24 h, but partly inhibit the synthesis of this cytokine at 48 h.<sup>55</sup>

Results of studies have shown that the effect of the common cold in the upper respiratory tract is not limited to the nasal cavity, but that paranasal sinuses are also frequently affected. CT scans and plain radiographs of sinuses obtained during the early course of illness in adults with colds show substantial abnormalities that usually resolve spontaneously without antibiotic treatment.<sup>56,57</sup> These findings imply that most sinus abnormalities observed during the common cold are not evidence of a bacterial complication, but are instead part of the normal course of illness. Findings of an experimental study<sup>58</sup> showed that blowing of the nose creates such a high intranasal pressure that it could propel fluid from the nasal cavity to the paranasal sinuses. Furthermore, rhinovirus RNA has been detected in sinus aspirates even in the absence of bacteria,<sup>59</sup> and results of a study<sup>60</sup> that used in-situ hybridisation provide evidence for the presence of rhinovirus in the epithelial cells of maxillary sinuses in patients with acute sinusitis.

In adults and children, viral infection of the upper respiratory tract often causes dysfunction of the Eustachian tube, which is considered the most important factor in the pathogenesis of acute otitis media.<sup>61</sup> Great middle ear negative pressures are recorded in most preschool and school-aged children with colds.<sup>62,63</sup> In adult volunteers challenged with rhinoviruses or influenza A viruses, normal Eustachian tube function deteriorated in 50–80% of individuals.<sup>64,65</sup>

Several respiratory viruses—eg, influenza viruses, RSV, and parainfluenza viruses—can also infect the lower respiratory tract, but the ability of rhinoviruses to replicate in the lower airways has been much debated. Although rhinoviruses have been detected in secretions obtained from the lower airways by bronchoscopy,<sup>66</sup> potential viral contamination from the upper respiratory tract was not ruled out until recently, when investigators of one study<sup>67</sup> of adult volunteers infected with rhinoviruses avoided potential contamination from the upper airways by use of in-situ hybridisation on bronchial biopsies. The findings of the study showed conclusively that rhinoviruses are able to replicate in the lower airways.

### Clinical manifestations

The symptoms of the common cold arise after an incubation period that can vary considerably between different viruses. In experimental rhinovirus infections, the onset of symptoms has been reported to occur as soon as 10–12 h after intranasal inoculation of the virus,<sup>41</sup> whereas the incubation period of influenza ranges from 1 to 7 days.<sup>34</sup> Generally, the severity of the symptoms increases rapidly, peaks within 2–3 days after infection, and decreases soon after. The mean duration of the common cold is 7–10 days, but in a proportion of patients some symptoms can still be present after 3 weeks.<sup>8,68,69</sup>

Rhinovirus infections typically start with a sore throat, which is soon accompanied by nasal stuffiness and discharge, sneezing, and cough. The soreness of the throat usually disappears quickly, whereas the initial watery rhinorrhoea turns thicker and more purulent.<sup>70</sup> The purulence of the nasal discharge is not associated with changes in the nasopharyngeal bacterial flora<sup>71</sup> and is not considered to indicate a simultaneous bacterial infection of the nasal mucosa. Fever is an infrequent finding during rhinovirus infections in adults, but it is fairly common in children with upper respiratory infections of any cause.<sup>72,73</sup> Other symptoms associated with the cold syndrome include hoarseness, headache, malaise, and lethargy. Myalgia is an occasional complaint in patients with colds, although it is a more typical feature of influenza infection.<sup>34</sup>

Although the common cold is usually a self-limited illness of short duration, the viral infection is sometimes accompanied by a bacterial complication. In children, the most common bacterial complication is acute otitis media, which occurs in about 20% of children with viral upper respiratory infections.<sup>74,75</sup> The seasonal incidence rates of otitis media closely parallel the general occurrence of viral respiratory infections,<sup>76,77</sup> and the complication is diagnosed most frequently on days 3 or 4 after the onset of upper respiratory symptoms.<sup>78,79</sup> Findings of studies indicate that respiratory viruses play a crucial part in the development of acute otitis media,<sup>61</sup> and the detection rates of different viruses in the middle-ear fluid suggest that at least some viruses actively invade the middle ear and contribute to the inflammatory process in the middle ear mucosa.<sup>80–83</sup>

Other common bacterial complications of viral upper respiratory infections include sinusitis and pneumonia. Sinusitis has been estimated to occur as a complication in 0.5–2% of colds,<sup>12</sup> but on the basis of recent evidence for the high incidence of sinus abnormalities during apparently uncomplicated colds it is difficult to ascertain whether changes in paranasal sinuses represent real bacterial complications or whether they are part of the natural history of the common cold.<sup>56,57</sup> Pneumonia associated with a viral upper respiratory infection is often a true bacterial complication of the predisposing viral illness, but it can also be a pure extension of the viral illness to the pulmonary level. Research into the microbial cause of pneumonia has suggested that mixed viral-bacterial infections are common, especially in children.<sup>84,85</sup>

Findings of several studies indicate a clear association between viral respiratory infections and acute exacerbations of asthma in both adults and children. In a study<sup>86</sup> of adult patients with asthma, symptoms of the common cold were reported in 80% of episodes of wheezing or dyspnoea, and rhinoviruses accounted for about 60% of those asthma exacerbations for which the viral cause could be identified. The central role of rhinoviruses in triggering acute exacerbations of asthma has also been well documented in children.<sup>87</sup> In the elderly population, the overall morbidity due to respiratory viruses other than influenza is often under-rated, although results of surveillance studies<sup>13</sup> indicate that two thirds of elderly patients with colds can be expected to develop lower respiratory illness. Individuals with chronic obstructive pulmonary disease (COPD) form another important risk group for viral infections.<sup>88</sup> Although the frequencies of colds are similar in patients with and without COPD, the use of medical resources, including hospital admissions and visits to emergency clinics, during viral respiratory illnesses is substantially increased in patients with COPD.<sup>89</sup> In immunocompromised patients, RSV is usually the most common cause of severe viral respiratory illness, but rhinovirus infections have also been associated with severe and even fatal lower respiratory tract disease.<sup>90</sup>

### Diagnosis

In most instances, the clinical diagnosis of the common cold is simple and can be made reliably by adult patients themselves.<sup>8</sup> However, diagnosis is sometimes problematic in infants and young children who are not capable of expressing their symptoms. Diagnosis in infants is especially difficult in cases in which fever is the leading symptom during the early phase of the infection, and the doctor is challenged to distinguish benign viral infections from severe invasive bacterial infections. Allergic or vasomotor rhinitis can sometimes mimic the common cold, but usually these conditions can be differentiated



easily. The soreness of the throat caused by streptococcal pharyngitis often resembles the initial symptoms of the common cold. However, nasal stuffiness and discharge, which are the primary symptoms of the common cold, are untypical to streptococcal pharyngitis. Although most cases of exudative tonsillitis in children are caused by viruses, the clinical findings on inspection of the pharynx cannot reliably distinguish bacterial from viral tonsillitis.<sup>91</sup> In children, intranasal foreign bodies should be searched for in cases of persistent nasal discharge, particularly if the discharge is unilateral.

Although respiratory infections caused by different viruses tend to have some variations in their typical clinical presentations, the wide range of the clinical manifestations of each virus makes it virtually impossible to ascertain the specific virus causing the problem in an individual patient with the common cold on clinical grounds alone.<sup>14,34,92</sup> Even for influenza, which is often regarded as a distinct disease entity among respiratory viral infections, the positive predictive value of clinical signs and symptoms has ranged between 27% and 79%.<sup>93,94</sup>

Methods for identification of viruses include viral culture, antigen detection, and PCR. Isolation of viruses in cell cultures is considered the gold standard for detection, but has little value for clinical practice because of the slowness of the process. Immunoperoxidase staining of the cultures with monoclonal antibodies speeds up viral identification substantially, with results usually available within 48 h.<sup>95</sup> Various antigen detection tests are frequently used to identify influenza viruses, parainfluenza viruses, RSV, and adenoviruses,<sup>96,97</sup> but these techniques cannot be routinely used to detect rhinoviruses because of the huge number of different serotypes that exist. Recently developed rapid antigen detection kits for influenza and RSV can provide results within 15–30 min,<sup>98,99</sup> but there are concerns about the real-life sensitivity and specificity of these tests.<sup>100</sup> PCR has proved valuable in diagnosis of viral infections in general, and especially rhinovirus infections, for which other methods have been suboptimum.<sup>8,9,101,102</sup> However, PCR-based techniques are still too laborious for use in everyday clinical practice, and the extreme sensitivity of PCR can pose problems for the interpretation of results.<sup>19,20</sup>

Nasopharyngeal aspirates and nasal wash specimens are usually considered the specimens of choice for the detection of respiratory viruses, but nasal and throat swabs are also often used because of their greater feasibility.<sup>103–106</sup> Scarce data are available on the optimum sampling methods, and the best sites to collect specimens from for viral detection could differ between viruses.

## Treatment

Since the common cold is caused by a multitude of different virus types with varying pathogenetic mechanisms, that an effective universal treatment for this disorder has not been developed is understandable. The symptomatic treatment of colds has been aimed at relieving the most disturbing symptoms of the illness, and hundreds of different over-the-counter preparations are available.<sup>107,108</sup> Although antibiotics are not effective against viruses, they are widely used in the treatment of uncomplicated viral upper respiratory infections.<sup>2,109</sup>

Most patients find nasal stuffiness and discharge the most bothersome symptoms of the common cold.<sup>8</sup> Nasal blockage can be effectively reduced with intranasally or orally administered decongestants.<sup>110</sup> First-generation (but not second-generation) antihistamines reduce sneezing and rhinorrhoea, probably because of their anticholinergic rather than antihistamine effects.<sup>111</sup> Results of several

studies have also shown the efficacy of local ipratropium in reducing rhinorrhoea.<sup>112</sup> Theoretically, corticosteroids as potent anti-inflammatory agents could be thought to effectively reduce nasal symptoms, but results of clinical studies of either intranasal or oral steroids have shown no clinical benefit.<sup>44,69,113</sup> The use of intranasal steroids in children during rhinovirus infection could even increase the risk of acute otitis media.<sup>114</sup> Cough medications, both



antitussives and mucolytic agents, are frequently used, although their efficacy has been poorly shown.<sup>115</sup> Non-steroidal anti-inflammatory drugs reduce fever and soreness of the throat, and might also have some beneficial effect on cough.<sup>116</sup> Data on the efficacy of zinc in reducing the severity and duration of colds are still inconclusive.<sup>117</sup>

At present, specific antiviral treatments for respiratory viruses are commercially available only for influenza viruses. The usability of amantadine and rimantadine is limited by their side-effects, their inefficacy against influenza B viruses, and the rapid development of resistant viral strains during treatment.<sup>118</sup> The new influenza-specific antivirals, zanamivir and oseltamivir, have fewer side-effects and are effective against both influenza A and B viruses. When treatment is initiated within 48 h of the onset of symptoms, the duration of the clinical illness is reduced by 1–2 days with either of these drugs.<sup>119,120</sup> Scarce evidence exists for the efficacy of these drugs in the prevention of bacterial complications, especially in high-risk patients,<sup>121</sup> but early treatment of influenza with oseltamivir does reduce the development of acute otitis media in children by more than 40%.<sup>122</sup>

Because of the leading role of rhinoviruses in the common cold, effective antivirals against rhinoviruses could be expected to have the greatest effect in the treatment of this disease. In the 1980s, much hope was laid on the use of interferon, but disappointingly it provided no benefit in the treatment of naturally occurring colds or experimental rhinovirus infections.<sup>123,124</sup> The discovery of

ICAM-1 as the main cellular receptor for rhinoviruses led to attempts to block the attachment of the virus to the receptor, using a recombinant soluble decoy ICAM-1. Findings of clinical trials showed that this approach could reduce the severity of experimental rhinovirus infections, but the effect was modest.<sup>125</sup>

Recent advances in antirhinoviral drugs include the development of pleconaril, a novel viral capsid binder, and rupintrivir, a human rhinovirus 3C protease inhibitor.<sup>126–128</sup> Pleconaril is administered orally and is active against a wide range of rhinoviruses and enteroviruses. Findings of early clinical trials have indicated that when pleconaril treatment is instituted within 24–36 h of the onset of symptoms, the duration of illness is reduced by 1–1.5 days.<sup>129</sup>

Increasing knowledge about the central role of the host inflammatory response in producing the symptoms of the common cold has led to attempts to treat colds with combinations of antiviral and anti-inflammatory agents.<sup>130</sup> In a recent trial<sup>131</sup> in adults challenged with rhinoviruses, the combination of intranasal interferon with oral chlorphenamine and ibuprofen showed effect in reducing not only nasal but also several other symptoms of the illness.

## Prevention

The diversity of the viral cause of the common cold has hampered prevention as well as treatment initiatives. In the absence of a suitable common antigen across the wide range of rhinovirus serotypes, the prospects for development of a vaccine against rhinoviruses seem poor. Influenza is the only respiratory infection for which a vaccine is commercially available. In addition to the present inactivated influenza vaccine, which is administered intramuscularly, new types of influenza vaccines for intranasal administration have been developed.<sup>132–134</sup> Several types of vaccines against RSV and parainfluenza viruses are also being developed and are in early clinical trials.<sup>135–137</sup>

The antiviral drug approach to prevention of respiratory infections is currently to influenza, for which the efficacy of the specific antivirals has been shown for both seasonal prophylaxis and post-exposure prophylaxis within families.<sup>138–142</sup> Contrary to the lack of effect in the treatment of rhinovirus infections, the prophylactic efficacy of intranasally administered interferon has been well demonstrated, but the unacceptably high rate of nasal adverse events during extended administration has decreased enthusiasm about its use for prevention of colds.<sup>143</sup> In a proof of concept study,<sup>144</sup> intranasally administered immunoglobulin reduced episodes of rhinitis in children, but no further investigations of passive immunisation of the nasal mucosa have been published.

Despite the widespread use of vitamin C and extracts of the plant *Echinacea* for the prevention of the common cold, conclusive evidence for such an effect is still lacking.<sup>145,146</sup> In view of the available data, it seems obvious that complete prevention of colds would only be possible by total long-term isolation from the community.<sup>147</sup> While waiting for the next ship bound for Antarctica, however, many people might find solace in a report<sup>148</sup> that suggests that intake of wine, especially red wine, may have a protective effect against the common cold.

## Future considerations

Together with the substantial proportion of colds without a proven microbial cause, the recent discovery of human metapneumovirus suggests that other important respiratory viruses might still remain undetected, and the

use of highly sophisticated molecular techniques could lead to new discoveries. Further research into the host inflammatory response and viral-bacterial interaction during the common cold might reveal pathways that could serve as targets for intervention to better alleviate the symptoms and to prevent the development of complications. Optimum use of the newly available and forthcoming antiviral agents is likely to increase the need for simple, rapid, inexpensive, and accurate point-of-care tests to identify the specific virus causing the infection on an individual level. In this era of ever-increasing antimicrobial resistance of bacteria, efforts aimed at the education of people about the ineffectiveness of antibiotics in the treatment of uncomplicated colds should be intensified.

## Conflict of interest statement

T Heikkinen has received support for research on the epidemiology of respiratory viral infections from Wyeth and GlaxoSmithKline; has participated as one of the local investigators in Finland in international multicentre studies of zanamivir sponsored by GlaxoSmithKline; and has received honoraria for lectures in the area of respiratory infections at academic meetings organised by various pharmaceutical companies. None of these sources have contributed to the content of this Seminar. A Järvinen has no conflict of interest with respect to this Seminar.

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## Uses of error

### Mistakes are lessons of the past

H S Bawaskar

A 16-year-old boy was bitten on his finger by a krait at 0300 h when sleeping on the floor of his hut. He reported to my clinic at 0500 h. He walked into my examination room, but he had bilateral ptosis, bulbar palsy, and was unable to talk. I gave him antivenom and intravenous atropine and neostigmine. As soon as I removed the intravenous needle, he vomited, aspirated, and died. A patient paralysed from an elapid snake bite should be treated in a semi-prone position and intubated.

A 6-year-old boy was stung by a scorpion and admitted to a rural hospital. I was called to examine the child. He had signs suggestive of an autonomic storm. I advised oral prazosin, and the staff nurse handed over the prazosin tablet to the mother for administration. The child refused to take the tablet, and the mother did not insist, as she was happy that the nurse gave him tetanus toxoid and scorpion antivenin injections. The child developed pulmonary oedema, and the medical officer transferred him to a cottage hospital without calling me. The child died on the way.

Prazosin is an antidote to venom and should be administered by a doctor or nurse. One should confirm that it has started acting by observing lowering blood pressure, improvement in peripheral circulation, a reduction in the heart rate and reappearance of local pain at the site of sting which was mild or absent due to vasoconstriction.

A 62-year-old retired man came alone from Mumbai to visit his village. He developed chest pain and bystanders brought him to my clinic. His electrocardiogram showed an extensive acute anterior myocardial infarction. I sedated him and gave him aspirin. I wanted to give him streptokinase but the bystanders would not pay, as they were not relatives. He was packed back to Mumbai, where he was admitted in cardiogenic shock and died within 12 h of admission. We have since kept 1.5 million units of streptokinase in the treatment room and given it to patients with acute myocardial infarct, without prepayment. We have treated 74 patients like this with good results.

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