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Review article

The common cold: a review of the literature

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Abstract

Respiratory viral infections, also known as the common cold, are the most common infections in humans. Despite their benign nature, they are a major cause of morbidity and mortality on a worldwide basis. Several viruses have been associated with such illness, of which rhinovirus is the most common. Symptom production is a combination of viral cytopathic effect and the activation of inflammatory pathways. Therefore, antiviral treatment alone may not be able to prevent these events. The optimal use of such agents also requires earlier initiation; therefore, it is important to develop accurate and rapid diagnostic techniques for respiratory viruses. Before any reliable and effective treatment is available, symptomatic therapies may remain the only possible choice of management.
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1. Introduction

The common cold is the most commonly encountered infectious syndrome of human beings. Most observers consider colds to include symptoms of rhinitis with variable degrees of pharyngitis, but the major associated symptoms include nasal stuffiness and discharge, sneezing, sore throat, cough and hoarse voice. Patients frequently report chills, but significant high temperature is unusual. Colds are usually self-limiting to previously healthy individuals, but there are also recognised complications such as secondary bacterial infections, exacerbations of asthma [1], chronic obstructive airways disease [2] and cystic fibrosis [3–5]. Despite the benign nature of the illness in the majority of cases, it is still a significant economic burden on society. It leads to an increase in consultations with clinicians, increased absence from school and work and subsequently causes loss of earnings.

Although the term ‘‘common cold’’ tends to imply that there is a single cause for the illness, it is, in fact, caused by anyone of a large number of antigenetically distinct viruses (Table 1).

Different respiratory viruses utilise different routes of transmission (Table 2). Rhinovirus and respiratory syncytial virus (RSV) are spread by direct hand contact with contaminated skin and environmental surfaces. This is followed by self-inoculation of virus into the nasal mucosa or conjunctiva [6]. Airborne transmission of rhinovirus is also possible, but this depends on the duration of exposure to infected individuals [7]. Transmission of parainfluenza virus (PIV) is by direct person-to-person contact or by large particle aerosol spread. The high rate of infection in childhood, coupled with the frequency of reinfection, suggests that they spread from person to person. There is evidence to suggest that the infectious dose of PIV is small, as two-thirds of volunteers developed flu-like symptoms following low-titre PIV intranasal challenge [8]. RSV is spread by infected respiratory secretions. The major route of transmission appears to be by large particle aerosol or direct contact with self-inoculation. Spread requires either close contact with the infected individual or contamination of the hands followed by introduction into conjunctiva. Influenza tends to spread by small-particle aerosols [9]. The relative efficacy of the various transmission routes under natural conditions for each virus is unknown.

Many respiratory viruses exhibit a seasonal variation in incidence (Table 2). The exact seasonal variation of each virus in the community is impossible to predict, but there are some generalisations that may be helpful to plan infection control strategies. For example, both RSV and influenza epidemics occur predominantly in the winter months, with a

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Table 1
Viruses associated with the common cold

Virus	Percentage of cases (%)
Rhinovirus	30–50
Coronavirus	10–15
Influenza virus	5–15
Respiratory syncytial virus	5
Parainfluenza virus	5
Adenovirus	<5
Metapneumovirus	±2
Undiscovered virus	20–30

peak prevalence in January to March in the northern hemisphere. Parainfluenza virus type 3 (PIV3) infections tend to peak in spring time, whereas parainfluenza virus type 1 (PIV1) and parainfluenza virus type 2 (PIV2) are more common in autumn and early winter. Both rhinovirus and adenovirus may be isolated throughout the year.

Since the discovery of rhinovirus in 1956 [10,11], more than 100 serotypes have been identified, the relative prevalence of which seems to vary between different geographical areas and also over the course of time [12]. These viruses are the most common cause of upper respiratory tract infections in all age groups. The reservoir for rhinovirus is schoolchildren, who transmit rhinovirus infections among their peers [13] and infect other family members at home [14].

Parainfluenza virus is the most common cause of croup (acute laryngotracheobronchitis) in young children and accounts for 5% of all causes of the common cold. The human parainfluenza viruses are categorised into types 1–4, on the basis of antigenic differences. They are transmitted from person to person by direct contact with infectious respiratory secretions or by large-particle aerosols. The incubation period is about 3–6 days. Bone marrow transplant recipients, children with bronchopulmonary dysplasia, prematurity, congenital heart disease or asthma are prone to develop lower respiratory infection and require additional oxygen supplementation [15,16]. One-third of children with lower respiratory infection due to parainfluenza are thought to develop secondary bacterial infections [17].

Coronavirus accounts for 7–26% of all upper respiratory tract infections in adults [18–20]. An important feature of coronavirus infection is the short-lived immunity, resulting in a high reinfection rate [21]. The mode of transmission of coronavirus is most likely due to aerosol inhalation. However, it does not grow well at all in cell culture, and therefore, its virology is not fully appreciated. Recently, a novel coronavirus, SARS-associated coronavirus (SARS-CoV), has been proposed as the cause for the outbreak of severe acute respiratory syndrome (SARS) [22]. The virus induces symptoms of atypical pneumonia, clinically indistinguishable from similar syndromes. The severity is such that a 15% mortality rate has been reported. No treatment has yet been identified as reliably successful. Transmission is by droplet spread, requiring close contact. Stringent infection control precautions in health care institutions, broad isolation measures in affected communities and international surveillance with barrier restrictions to travel have led to termination of the epidemic. As of July 11, 2003, 8437 people in 32 countries had been affected, with 813 deaths reported [23].

Influenza virus infection accounts for 5–15% of common colds. Small-particle aerosol spread has been implicated in several outbreaks [24], and it can retain its infectivity for prolonged periods after aerosolisation in conditions under low humidity [25]. There are two features that distinct influenza from other respiratory viruses. First, influenza viruses are able to produce new strains for which most of the population lack immunity, leading to worldwide outbreaks. The unique feature of antigenic variation is referred to as antigenic shift or drift. Second, a recent outbreak in humans of the lethal H5N1 influenza subtype suggested that direct transmission between humans and infected birds without an intermediate host is possible [26]. This avian influenza subtype caused high mortality, killing 70–100% of chicken and also 6 humans [27]. There was also a high proportion of amino acid changes in all gene products within H5N1 influenza virus except the surface genes [28]; this provides further support for antigenic drift.

Respiratory syncytial virus (RSV) is a highly successful human pathogen; by 2 years of age, 95% of all children will have been infected [29]. It spreads from person to person or through exposure to contaminated environment surfaces. However, transmission via aerosolised droplets is unlikely because the virus is inactivated in aerosols. Incubation is from a few days to a week. Natural immunity to RSV is incomplete, and reinfection is the rule.

Adenoviruses were the first important respiratory viruses to be discovered by the tissue culture method [30]. There are many different serotypes, 47 of which are associated with

Table 2
Characteristics of respiratory viruses

	Mode of transmission	Incubation period	Seasonality
Rhinovirus	airborne/by large particle aerosol	2–7 days	early autumn/late spring
Coronavirus	possibly airborne	2–4 days	winter/early spring
Influenza	airborne/by small-particle aerosol	1–4 days	winter/spring
RSV	large-particle aerosol/direct contact with self-inoculation	4–5 days	autumn to spring
PIV	large-particle aerosol/direct contact with self-inoculation	3–10 days	PIV1 and 2—autumn PIV3—throughout the year
Adenovirus	airborne/direct contact with self-inoculation	4–14 days	late autumn/late spring

human infections [31]. The incubation period is in the range of 4–7 days, but may be as long as 2 weeks [32]. It is thought to cause around 10% of all common colds in children [33], and it accounts for high mortality in neonates [32].

A new pneumovirus, human metapneumovirus (HMPV), has recently been isolated in the Netherlands [34]. It is closely related taxonomically to RSV [34]. This virus possibly accounts for about 10% of unexplained respiratory infections in children during the winter season. Seroprevalence studies show that the virus has been circulating in humans for at least 50 years, that 25% of children by age 1 year have antibodies to the virus and that by age 5 years virtually all are seropositive [34]. Analysis of the amplified sequences showed two clusters of HMPV [35]. The clinical manifestation of HMPV can vary from mild upper respiratory symptoms to severe infections requiring hospital admissions. This clinical picture is indistinguishable form that of other respiratory viruses. Coinfection of HMPV with other respiratory viruses is uncommon [36], and its role in human respiratory infections is still poorly understood. This new pathogen will certainly warrant long-term surveillance.

2. Pathogenesis

Respiratory viruses characteristically differ from bacteria in that viruses have the ability to evade the protection offered by the mucociliary escalator and the host's non-immunologic mechanisms. In addition, the pathogenesis of respiratory viruses is not fully understood. This may be due to different viruses adopting different manners of infection and infecting different sites to cause variable degrees of damage to the respiratory tract lining.

Rhinovirus, the most important cold virus, accounting for 80% of all upper respiratory illnesses during autumn [37], commonly invades the upper respiratory tract with minimal nasal epithelial damage [38], whereas influenza mainly causes extensive damage to the lower airways [9]. Due to the prevalence of rhinovirus, most of the studies of common colds are based on this virus. The initial deposition of rhinovirus in the eyes and nose leads to attachment of the virus to host cell intercellular adhesion molecule-1 (ICAM-1) receptors at the back of the throat. Once inside the nasal epithelial cell, there is no significant increase in the number of inflammatory cells [39], but increases in neutrophils have been detected in nasal mucosa and secretions [40]. This may reflect the release of a cascade of inflammatory cytokines such as kinins, leukotrienes, histamines, interleukin-1, interleukin-6 interleukin-8, tumour necrosis factor and RANTES (regulated by activation normal T-cell expressed and secreted) [41,42], which are partly responsible for the symptoms [43]. Levels of kinins, interleukin-1, interleukin-6 and interleukin-8 in nasal secretions have also been shown to correlate with the severity and duration of symptoms [42,44,45].

There are two distinct groups of coronaviruses that infect humans: HCoV-229E and HCoV-OC43. They are distinct from each other by the structural proteins as demonstrated by immunoelectrophoresis and enzyme-linked immunoabsorbant assay (ELISA), despite being similar in charges and molecular weights [46,47]. HCoV-229E utilises human aminopeptidase N (hAPN) as a receptor to gain entry into the respiratory epithelium. hAPN is a 150-kDa zinc-binding protein with endopeptidase activity. In experimental studies, when human cell cultures are pretreated with monoclonal antibodies against hAPN, viral infection appears blocked [48]. However, HCoV-OC43 gains entry into the respiratory epithelium by using the two surface glycoproteins, Haemagglutinin-esterase (HE) and Spike (S) glycoproteins [49]. Despite their differences in pathogenesis, they both cause similar clinical manifestations [50]. Reinfection of coronavirus is common, though the underlying reason is not clearly defined. It may be due to infection with closely related but different strains [51] or to a reduction in immunity over time [21]. Volunteers who are seropositive to coronavirus prior to intranasal challenge are not completely protected from symptom development [52].

Influenza virus replicates throughout the respiratory tract, and it is recoverable from the upper and lower airways. However, it tends to cause more significant damage in the lower respiratory tract [53,54]. Acute diffuse inflammation of the larynx, trachea and bronchi has been demonstrated during bronchoscopy of people with uncomplicated influenza infection [55]. Both the innate and cellular immune responses are heightened during infection. Proinflammatory cytokines such as interleukin-6 (IL-6) and interferon-α (IFN-α) are induced and are released from infected cells. They reach their peak levels 2 days following infection, which coincides with the most severe clinical symptom score, mucous production, fever and viral load [56]. Animals deficient in both CD4+ and CD8+ T lymphocytes succumb to severe influenza infection, indicating that an intact cellular immune system is necessary to restrict overwhelming infection [57].

RSV replicates primarily in the superficial layer of the respiratory epithelium [58], and it spreads from the upper to lower airways by aspiration of secretions via the respiratory epithelium. RSV infection causes significant damage to the epithelium and, more importantly, to the mucociliary escalator [59]. This inhibits the removal of mucous and cell debris, leading to occlusion of small bronchioles. Interferon plays a pivotal role in inhibiting viral replication, and RSV infection is notable for lack of local interferon production [60]. RSV induces the production of IL-5 and interferon-gamma. Their levels are especially depressed in infants compared to adults [61], and this may explain why 95% of children would have acquired RSV antibodies by the age of 2 [29].

Little is known about the pathophysiology of hMPV infection. However, similar to the related pneumovirus, human respiratory syncytial virus (RSV), hMPV appears

to have a tropism for the respiratory epithelium. Experts in the field of pneumovirus infections agree that the pathophysiology of hMPV infection likely parallels that of RSV infection, including the absence of viraemia. hMPV has proven to be difficult to identify using commonly used clinical virologic procedures. It replicates slowly in primary cynomolgus monkey kidney cells and poorly in Vero cells and A549 cells (a human respiratory epithelial cell line). Other cell lines commonly used in viral diagnostic laboratories do not appear to support the replication of hMPV. Commercial reagents to confirm the presence of hMPV are not yet available. Currently, hMPV is not included in the routine surveillance programme of respiratory infections; therefore, research provides the only means for its detection [62].

The signal illness of PIV is croup (tracheobronchitis). It is manifested by fever, hoarseness and a barking cough in young children. Host immune response may play a role in its pathogenesis, as children who develop viral croup tend to produce a large amount of virus-specific IgE antibodies. This rise in IgE levels causes histamine release in the trachea and subglottic area, which, in turn, leads to swelling and obstruction of the upper airways [63].

The understanding of the pathogenesis of respiratory viruses has important implications for the development of therapies against common colds.

2.1. Diagnosis

The diagnosis of common colds is usually based on the patient's clinical presentation and the clinician's assessment of the disease. Sometimes, the diagnosis can be less straightforward for three reasons. First, clinical features of a common cold may overlap with those of pharyngitis and bronchitis, which are related syndromes of shared viral origins. To complicate matters, pharyngitis and sinusitis can also be caused by bacterial infections. Second, allergic diseases of the upper airway often have clinical features resembling those of common colds. Third, infants and young children are not able to express their symptoms, and clinicians have the challenge to distinguish between benign viral infections and severe invasive bacterial infections.

Some respiratory viruses have typical clinical presentations that may be helpful in assessing the aetiology of illness when considered in conjunction with epidemiological factors such as age and clinical presentation of the patient and seasonality. Sometimes, it is virtually impossible to ascertain a specific virus inducing the common cold in the individual patient on clinical grounds alone [9,20]. Determination of the aetiology of virus infections becomes increasingly essential with the introduction of new antivirals. The optional use of these new therapeutic options is problematic because all these drugs are virus specific. Some therapies are initiated on the basis of a presumptive diagnosis; a specific diagnosis may be important to confirm the initial impression and to determine the length of time for treatment. Conversely, viral detection is important to avoid unnecessary antibiotic prescriptions. The principal laboratory methods of respiratory virus diagnosis rely on their detection in respiratory secretions.

Another important factor in respiratory viral diagnosis is to submit an appropriate sample for testing. Inadequate or improper specimen collection and transport account for the largest source of error in the accuracy of viral detection results [64]. Nasal swabs, nasopharyngeal aspirates and nasal wash specimens are generally considered to be the specimens of choice for the detection of respiratory viruses [65–67]. Obtaining an aspirate is unpleasant and requires the use of a suction device by a trained individual, which makes it unattractive in widespread clinical application. In contrast, the collection of a nasal swab is simple, painless and quick, and it does not require special equipment and skilled personnel. A recent prospective study showed that the sensitivity of nasal swabs was comparable to nasopharyngeal aspirates for the detection of all major respiratory viruses by tissue culture with the exception of RSV [68].

2.2. Tissue culture

Isolation of viruses in tissue culture is the gold standard of virus detection. The processing of clinical specimens often starts with the addition of antibiotics and antifungals prior to inoculation into the appropriate cell lines. They are usually incubated at 33 °C and are observed daily for virus-induced effect (cytopathic effect, CPE). The three major tissue cell lines commonly used to isolate and identify respiratory viruses are primarily monkey kidney (sensitive to PIV and influenza), human fetal lung fibroblasts (sensitive to adenovirus and rhinovirus) and a continuous cell line, such as HEP-2 cells (sensitive to adenovirus and RSV) [69]. However, the slowness of tissue culture in viral detection makes it clinically impractical, especially when rapid diagnosis is required in order to initiate the appropriate therapy. Since there are more than 100 serotypes of rhinovirus [70], accurate diagnosis by such a method also becomes impossible and unreliable.

2.3. Antigen testing

The major advantage of antigen detection in respiratory secretions by immunofluorescence assay (IFA) or enzyme-linked immunoabsorbent assay (ELISA) is that they can be performed rapidly and can provide results within 24 h of receiving the specimen in the laboratory. IFA can be divided into direct and indirect methods. Direct immunofluorescence utilises a fluorochrome-labelled antibody that is specific to viral proteins or antigens. It involves fixing the specimens containing viral materials onto a slide so that virus-specific monoclonal antibody labelled with the fluorochrome can bind to the antigen. Following the addition of a substrate, a colour change with the fluoro-

chrome can be induced, which in turn can be detected by a fluorescence microscope. Indirect immunofluoroscence uses an unlabelled monoclonal antibody that binds to the viral antigen. It is then washed away, and any bound monoclonal antibody is detected with a labelled anti-mouse antibody. The use of multiple antibodies can, in theory, improve the sensitivity of the detection because multiple conjugate molecules can attach to virus-specific antibodies. ELISA is very similar to IFA; however, instead of using a fluorescent label, an enzyme label is used. This assay utilises a double antibody sandwich. A 'capture' antibody specific for the viral antigen being sought is bound to a reaction surface. When the specimen or viral antigen is added, it binds to the capture antibody. Bound antigen is detected by a second antiviral antibody, the 'detector' antibody. This detector antibody carries an enzyme label and, once bound, this enzyme produces a colour change. This colour change can be detected by photometry. The disadvantages of ELISA are that it is usually less sensitive and the reagents are only available for a limited number of viruses. In addition, adults tend to have lower viral titres in nasopharyngeal aspirates, making the sensitivity of this test understandably lower.

2.4. Serology (antibody detection)

Serological assays are one of the oldest techniques of diagnostic virology, with detection of antibodies in patient sera being indicative of recent (IgM) or past (IgG) infection. They are now even more important when it comes to determining the immune status of an individual or to evaluating the immune response to vaccination. Serum is the specimen of choice for serological diagnosis and paired serum specimens 4 weeks apart are required for the diagnosis of current or recent viral infections. Demonstration of a seroconversion from a negative to a positive IgG antibody response or detection of the presence of virus-specific IgM can be diagnostic of primary viral infection. A fourfold increase in IgG titres between acute and convalescent sera (usually 4 weeks apart) may indicate a recent infection due to reinfection or reactivation; yet, such testing is retrospective and has little impact on a patient's immediate care. In addition, the result of serological tests for viral-specific antibodies must be interpreted with care for a number of reasons. First, there may be a delay or lack of production of serum antibodies, especially in the immunocompromised. Second, in recurrent infections, a significant rise in antibodies may not be apparent. Third, antibody levels can remain elevated for a long period of time following infection. Therefore, the clinical status of the patient has to be taken into account.

2.5. Molecular techniques

Molecular techniques utilise viral nucleic acid and antigen detection systems, which are fundamentally different from serological assays since they only detect a component of the organism itself, rather than demonstrating the evidence of its past presence. Therefore, in the case of nucleic acid detection, the integrity of the specimen itself is not so important, whereas in the case of tissue culture, the whole virus is often required. Respiratory viruses possess either RNA or DNA, but not both. It is, therefore, essential to know the structure of each individual virus in order to develop molecular techniques identifying nucleic acid.

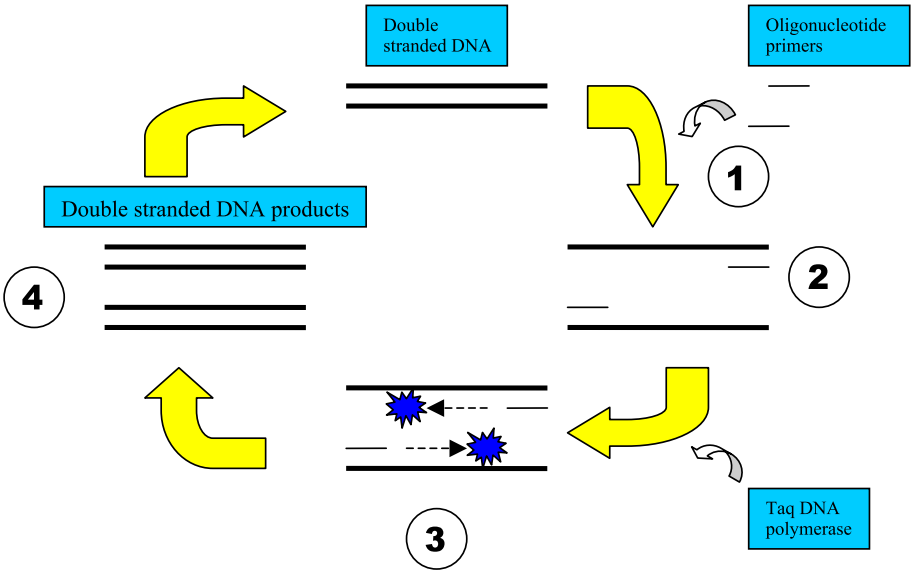

Fig. 1. Principles of PCR. (1) DNA melts at 94 °C. (2) As DNA reanneals at 68 °C; the primers bind to the template. (3) As the temperature is raised to 72 °C, the DNA undergoes polymerisation due to Taq polymerase. (4) The first cycle is complete. The two new DNA strands make up the template DNA for the next cycle, thus doubling the amount of DNA duplicated for each cycle.

Polymerase chain reaction (PCR) has dramatically altered the detection and characterisation of viral nucleic acids. It can identify target organisms from specimens with low concentrations of nuclear material in a matter of a few hours. For DNA viruses, PCR amplification is straightforward; the principle is demonstrated in Fig. 1. However, for RNA viruses, the genome is too unstable to be used in PCR, and RNA has to be converted to complementary DNA (cDNA) using reverse transcriptase, a retroviral enzyme that makes a precise copy of the mRNA. PCR is then performed in the normal manner to amplify genomic material. Once DNA has been amplified, it can be detected on the basis of size by gel electrophoresis or by Southern blotting, where the resolved nucleic acids are transferred to a membrane and react with nucleic acid probes specific for the desired PCR product.

Newer techniques in virus identification are nucleic acid sequence-based amplification (NASBA), as shown in Fig. 2. It is an isothermic nucleic acid amplification method that amplifies RNA in a manner analogous to the amplification of DNA by PCR [71,72]. The NASBA reaction mixture contains oligonucleotide primers and three enzymes: avian myelobastosis virus-reverse transcriptase (AMV-RT), RNase H and T7 RNA polymerase for target-specific amplification [73]. The process takes place at 41 °C and results in exponential amplification of products within 2 h, producing single-stranded RNA of opposite sense to the original target. Detection of NASBA products can be reported by using a probe-capture hybridisation and electrochemiluminescence (ECL) [71]. More recently, 'real-time' detection using molecular beacons has been described [74].

Molecular techniques have a number of advantages over 'conventional' methods currently utilised for respiratory viral detection. Traditional virus culture and serology analysis may require 1–2 weeks before results are available, and direct antigen detection can have variable sensitivity and specificity [75]. Molecular assays have particular advantages where the starting material available is acellular (swab) material or where surveillance samples that may have a low copy number of the target are to be analysed. Nucleic acid amplification has the potential to produce rapid turnover of results, allowing diagnostic virology to have an impact on patient management, avoiding the inappropriate prescription of antibiotics and allowing proper use of antivirals. A comparison between molecular techniques and 'conventional' methods in viral detection is shown in Table 3.

Table 3
A comparison of molecular probes with conventional methods for the detection of respiratory viruses

	Culture	Immunofluorescence	ELISA	Molecular techniques
Speed to produce result	+	+++	+++	+++
Sensitivity	+++	++	++	++++
Specificity	+++	++	++	++++
Quantifiability	++	++	++	+++
Ease of use	+	+	+++	+++

An advantage of the NASBA assay compared with PCR methods [76,77] is the continuous isothermic process that does not require a thermocycler. A constant temperature throughout the amplification reaction enables each step of the reaction to amplify the targeted RNA or DNA exponentially. Thus, the NASBA reaction is more efficient than PCR methods that are restricted to binary increases per cycle [76,77].

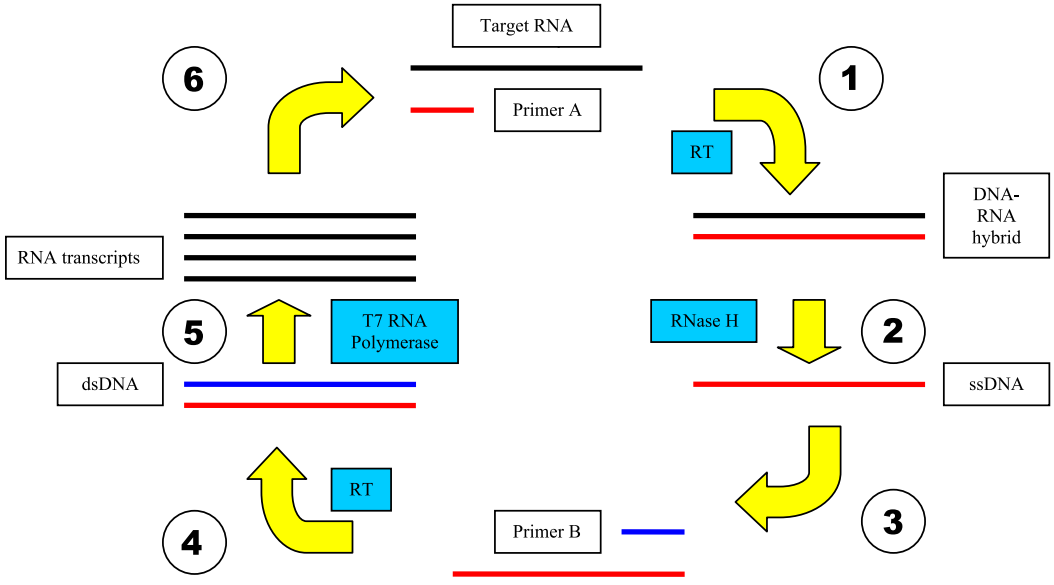

Fig. 2. Principles of NASBA. (1) Reverse transcriptase (RT) extends primer A along target RNA to form DNA–RNA hybrid. (2) RNase degrades the RNA portion of DNA–RNA molecule. (3) Primer B binds to single-stranded DNA (ssDNA). (4) RT extends primer B to form a double-stranded DNA (dsDNA). (5) dsDNA transcribed by T7 RNA polymerase to 50–1000 RNA transcripts. (6) Cycle to be repeated.

3. Prevention

The existence of diverse viral serotypes in causing the common cold has made vaccine preparation very difficult. Frequent mutations of viral proteins of RNA viruses (for example, genetic drift and shift of influenza) have further hampered prevention of the illness.

Influenza vaccines are the only commercially available vaccines. They are virtually all split products or purified subunit vaccines being used around the world. The strains (either A or B) that are used in immunisation are selected yearly, based on the recommendation by the World Health Organisation in conjunction with national public health institutions. Recent vaccines contain antigens of two influenza A subtypes, strains of the currently circulating H3N2 and H1N1 subtypes and one influenza B virus. The waning of vaccine-induced immunity over time requires annual re-immunisation, even if the vaccine antigens are unchanged. The current recommendation for influenza vaccination in the UK is to offer it to those over the age of 65, those with chronic heart, respiratory or renal disease and those who are diabetic or immunosuppressed. The national policy also states that those living in long-stay residential and nursing homes should be prioritised for vaccination. Despite the wide availability of the vaccine against influenza A, it still causes 13,000–20,000 excess deaths per year in the UK [78].

Rhinovirus has more than 100 serotypes; it is unlikely that a unifying vaccine will be developed. However, the use of antivirals as chemoprophylaxis may have practical value. Topical application of interferon in the nose has been shown to be effective in reducing the incidence of colds in people who are exposed to others with a fresh cold [79]. This strategy reduced the overall risk of cold by 40% and almost eliminated proven rhinovirus colds in contacts.

The development of an RSV vaccine has been hampered by the experience with formalin-inactivated whole RSV vaccine in the 1960s, as it caused 80% of RSV vaccinees to become hospitalised compared with 5% of controls, as well as two fatalities [80]. Current major research has focused on a prophylaxis using a humanised mouse monoclonal antibody, Palizivumab, which has been shown to reduce the rate of RSV-associated hospitalisation in premature infants [81]. However, its use on a wider population will require further research.

There is currently no licensed Parainfluenza vaccine to date. The formalin-inactivated vaccine generated in the 1960s was not able to prevent PIV infection and was soon abandoned. At present, recombinant bovine PIV3 and human PIV3 attenuated vaccines are being evaluated in animal models as vectors for the delivery of other viral antigens such as RSV-G and RSV-F proteins. This bivalent vaccine combination provides a high level of resistance to challenge with PIV3 and RSV in animal models [82].

The conventional methods of vaccination are via the intramuscular and subcutaneous routes. Mucosal immunisation has recently been explored and represents an attractive manner of delivering vaccines. It is fast, simple and noninvasive, and it can be carried out by unskilled individuals. The use of mucosal vaccination seems logical in that most respiratory viral infections initially start at the mucosal sites. Therefore, inducing local immunity can help arrest the infection at an early phase before systemic complications arise.

Thus far, there has been inconclusive evidence to support the use of vitamin C and extracts of the plant Echinacea in common cold prevention. Daily supplementation with large doses of vitamin C does not seem to prevent common colds; however, there seems to be a modest (8–9%) reduction in the number of symptom days in individuals with established cold symptoms, with larger doses having a greater effect [83]. For Echinacea, currently available data from studies conducted in the adult population show positive findings both in the treatment and prevention of upper respiratory infection. However, variations in the design of the clinical trial and in Echinacea preparations have to be taken into account [84].

Zinc has been shown to possess antiviral properties in vitro, and different preparations of zinc have been proposed for the treatment of the common cold. Zinc lozenges appeared to have positive effects on adults, but negative effects on children in terms of duration and severity of common cold symptoms [85,86]. Zinc nasal spray appears to reduce the total symptom score but has no effect on the duration of the common cold [87]. Recent research shows that zinc nasal gel can reduce the median time to cold resolution compared to placebo (4.3 days vs. 6.0 days; $p = 0.02$) and decrease the median time to resolution of nasal congestion, nasal drainage, hoarseness and sore throat [88].

4. Treatment

There are, so far, no effective therapeutic options available to treat the common cold since so many viruses are involved in its aetiology. Recent studies have focused on three areas for treatment of the common cold: symptomatic management, pharmacological treatment and antiviral agents.

The most disturbing symptoms of the common cold are nasal discharge and stuffiness. Alpha agonists, either alone or in combination with a nonsteroidal anti-inflammatory drug, are effective in reducing nasal blockage and rhinorrhoea [89]. Nasal decongestants improve cold symptoms in adults and improve nasal patency in children; however, their side effects, such as rebound obstruction and nasal epithelial drying, have impeded their use [90]. First-generation antihistamines have shown favourable effects upon nasal symptoms in adult studies, probably because of their anticholinergic effects [91]. Topical application of ipratropium (an anticholinergic drug) at a moderate dose, which is minimally absorbed across biologic membranes, reduces rhinorrhoea and sneezing in colds [92]. The routine use of cough medications in healthy children and adults should

pose no potential problem, but they should be used with caution in patients with chronic obstructive airway disease. Nonsteroidal anti-inflammatory drugs have been shown to reduce symptoms in rhinovirus infections [93] by reducing fever, headache, sore throat and cough. This may be because prostaglandins are amongst the inflammatory mediators responsible in the pathogenesis of rhinovirus colds. Intranasal interferon alone is not a practical treatment option for the common cold; however, when it is used in combination with ipratropium and a nonsteroidal anti-inflammatory drug, it can significantly reduce symptoms in experimental colds [94].

Amantadine has been the conventional antiviral against of influenza. However, it is strain-specific as it is only effective against influenza A and has common side effects, such as insomnia, poor concentration and irritability; it is now being replaced by newer agents such as zanamivir and oseltamivir. They are licensed for the treatment of influenza A and B. Early initiation of these therapies, i.e., within 48 hours of the onset of symptoms, can reduce the duration of common cold symptoms by 1–2 days [95,96]. Zanamivir has a poor oral bioavailability, and intranasal application has been shown to be effective in treating experimental influenza infection with a reduction in symptoms caused, virus shedding and the development of otitis media [97].

Ribavarin, a synthetic guanosine nucleoside that has a broad spectrum of antiviral activity, has been approved for the treatment of RSV-related respiratory infection in children since 1986. It is the only approved therapy for lower respiratory tract disease caused by RSV [98]. Potential benefits of ribavarin therapy include the inhibition of RSV-specific IgE production in nasal secretions, which has been associated with the development of hypoxaemia and wheezing [99], and improved pulmonary function [100]. Controlled studies also show that the use of ribavarin is effective in reducing the clinical severity score, duration of mechanical ventilation, supplemental oxygen use and days of hospitalisation [101].

Although rhinovirus is the major cause of colds, its vast amount of serotypes has made development of antivirals against it problematic. Some 90% of rhinovirus serotypes gain entry into epithelial cells using ICAM-1 cellular receptors. Blockade of these receptors in experimental studies showed reduced infection severity [102], but further study is required before this treatment option becomes widely available.

Contrary to common belief, there is no evidence for the use of antibiotics in the treatment of colds. Inappropriate antibiotic use can induce significant side effects and increase colonisation with resistant organisms.

5. Conclusion

The recent discovery of human metapneumovirus and the development of molecular techniques in viral detection represent an exciting time in the study of the common cold. Further research into host inflammatory response and the use of combination therapies may provide a long-term treatment option for this debilitating disease. In the meantime, we as clinicians will have to concentrate on patient education regarding vaccination and avoid unnecessary antibiotic prescription.

References

[1] Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 1995;310(6989):1225–9.
[2] Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164(9):1618–23.
[3] Hiatt PW, Grace SC, Kozinetz CA, Raboudi SH, Treece DG, Taber LH, Piedra PA. Effects of viral lower respiratory tract infection on lung function in infants with cystic fibrosis. Pediatr 1999;103:619–26.
[4] Wang EE, Prober CG, Manson B, Corey M, Levison H. Associations of respiratory viral infections with pulmonary deterioration in patients with cystic fibrosis. N Eng J Med 1984;311:1653–8.
[5] Prober CG. The impact of respiratory viral infections in patients with cystic fibrosis. Clin Rev Allergy 1991;9:87–102.
[6] Gwaltney Jr JM, Moskalski PB, Hendley JO. Hand-to-hand transmission of rhinovirus colds. Ann Intern Med 1978;88(4):463–7.
[7] Meschievitz CK, Schultz SB, Dick EC. A model for obtaining predictable natural transmission of rhinoviruses in human volunteers. J Infect Dis 1984;150(2):195–201.
[8] Smith CB, Purcell RH, Bellanti JA, Chanock RM. Protective effect of antibody to parainfluenza type 1 virus. N Engl J Med 1966; 275(21): 1145–52.
[9] Nicholson K. Human influenza. In: Nicholson K.G.W.R., Hay AJ, editors. Textbook of influenza 275. Oxford: Blackwell; 1998. p. 219–64.
[10] Pelon W, Mogabgab W, Philips I, et al. A cytopathic agent isolated from nasal recruits and mild respiratory illness. Proc Soc Exp Biol Med 1957;94:262–7.
[11] Price W. The isolation of the new virus associated with respiratory clincal disease in humans. Proc Natl Acad Sci U S A 1956;42: 892–6.
[12] Monto AS, Bryan ER, Ohmit S. Rhinovirus infections in Tecumseh, Michigan: frequency of illness and number of serotypes. J Infect Dis 1987;156(1):43–9.
[13] Beem MO. Acute respiratory illness in nursery school children: a longitudinal study of the occurrence of illness and respiratory viruses. Am J Epidemiol 1969;90(1):30–44.
[14] Hendley JO, Gwaltney Jr JM, Jordan Jr WS. Rhinovirus infections in an industrial population: IV. Infections within families of employees during two fall peaks of respiratory illness. Am J Epidemiol 1969;89(2):184–96.
[15] Lewis VA, Champlin R, Englund J, et al. Respiratory disease due to parainfluenza virus in adult bone marrow transplant recipients. Clin Infect Dis 1996;23(5):1033–7.
[16] Heidemann SM. Clinical characteristics of parainfluenza virus infection in hospitalized children. Pediatr Pulmonol 1992;13(2):86–9.
[17] Korppi M, Leinonen M, Makela PH, Launiala K. Bacterial involvement in parainfluenza virus infection in children. Scand J Infect Dis 1990;22(3):307–12.
[18] Makela MJ, Puhakka T, Ruuskanen O, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol 1998;36(2):539–42.
[19] Larson HE, Reed SE, Tyrrell DA. Isolation of rhinoviruses and coronaviruses from 38 colds in adults. J Med Virol 1980;5(3): 221–9.

[20] Nicholson KG, Kent J, Hammersley V, Cancio E. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. BMJ 1997;315(7115):1060–4.
[21] Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect 1990;105(2):435–46.
[22] Zeng FY, Chan CW, Chan MN, et al. The complete genome sequence of severe acute respiratory syndrome coronavirus strain HKU-39849 (HK-39). Exp Biol Med 2003;228(7):866–73 [Maywood].
[23] Whitby N, Whitby M. SARS: a new infectious disease for a new century. Aust Fam Physician 2003;32(10):779–83.
[24] Moser MR, Bender TR, Margolis HS, Noble GR, Kendal AP, Ritter DG. An outbreak of influenza aboard a commercial airliner. Am J Epidemiol 1979;110(1):1–6.
[25] Loosli C, Lemon H, Oh R, et al. Experimental airborn influenza infection: I. Influenza of humidity on survival of virus in air. Proc Soc Exp Biol Med 1943;53:205–6.
[26] Suarez DL, Perdue ML, Cox N, et al. Comparisons of highly virulent H5N1 influenza A viruses isolated from humans and chickens from Hong Kong. J Virol 1998;72(8):6678–88.
[27] Claas EC, Osterhaus AD, vanBeek R, et al. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. Lancet 1998;351(9101):472–7.
[28] Zhou NN, Shortridge KF, Claas EC, Krauss SL, Webster RG. Rapid evolution of H5N1 influenza viruses in chickens in Hong Kong. J Virol 1999;73(4):3366–74.
[29] Parrott RH, Kim HW, Brandt CD, Chanock RM. Respiratory syncytial virus in infants and children. Prev Med 1974;3(4):473–80.
[30] Rave W, Heubner R, Gilmore L, et al. Isolation of cytpopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. Proc Soc Exp Biol Med 1953;84:570–3.
[31] Hierholzer JC, Wigand R, Anderson LJ, Adrian T, Gold JW. Adenoviruses from patients with AIDS: a plethora of serotypes and a description of five new serotypes of subgenus D (types 43–47). J Infect Dis 1988;158(4):804–13.
[32] Finn A, Anday E, Talbot GH. An epidemic of adenovirus 7a infection in a neonatal nursery: course, morbidity, and management. Infect Control Hosp Epidemiol 1988;9(9):398–404.
[33] Brandt CD, Kim HW, Vargosko AJ, et al. Infections in 18,000 infants and children in a controlled study of respiratory tract disease: I. Adenovirus pathogenicity in relation to serologic type and illness syndrome. Am J Epidemiol 1969;90(6):484–500.
[34] van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7(6):719–24.
[35] Peret TC, Boivin G, Li Y, et al. Characterization of human metapneumoviruses isolated from patients in North America. J Infect Dis 2002;185(11):1660–3.
[36] Nissen MD, Siebert DJ, Mackay IM, Sloots TP, Withers SJ. Evidence of human metapneumovirus in Australian children. Med J Aust 2002;176(4):188.
[37] Arruda E, Pitkaranta A, Witek Jr TJ, Doyle CA, Hayden FG. Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol 1997;35(11):2864–8.
[38] Winther B, Gwaltney Jr JM, Mygind N, Turner RB, Hendley JO. Sites of rhinovirus recovery after point inoculation of the upper airway. JAMA 1986;256(13):1763–7.
[39] Fraenkel DJ, Bardin PG, Sanderson G, Lampe F, Johnston SL, Holgate ST. Immunohistochemical analysis of nasal biopsies during rhinovirus experimental colds. Am J Respir Crit Care Med 1994; 150(4): 1130–6.
[40] Winther B. Effects on the nasal mucosa of upper respiratory viruses (common cold). Dan Med Bull 1994;41(2):193–204.
[41] Noah TL, Henderson FW, Wortman IA, et al. Nasal cytokine production in viral acute upper respiratory infection of childhood. J Infect Dis 1995;171(3):584–92.
[42] Fritz RS, Hayden FG, Calfee DP, et al. Nasal cytokine and chemokine responses in experimental influenza A virus infection: results of a placebo-controlled trial of intravenous zanamivir treatment. J Infect Dis 1999;180(3):586–93.
[43] Naclerio RM, Proud D, Lichtenstein LM, et al. Kinins are generated during experimental rhinovirus colds. J Infect Dis 1988;157(1): 133–42.
[44] Turner RB, Weingand KW, Yeh CH, Leedy DW. Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds. Clin Infect Dis 1998;26(4):840–6.
[45] Zhu Z, Tang W, Ray A, et al. Rhinovirus stimulation of interleukin-6 in vivo and in vitro. Evidence for nuclear factor kappa B-dependent transcriptional activation. J Clin Invest 1996;97(2):421–30.
[46] Schmidt OW. Antigenic characterization of human coronaviruses 229E and OC43 by enzyme-linked immunosorbent assay. J Clin Microbiol 1984;20(2):175–80.
[47] Schmidt OW, Kenny GE. Immunogenicity and antigenicity of human coronaviruses 229E and OC43. Infect Immun 1981;32(3): 1000–6.
[48] Yeager CL, Ashmun RA, Williams RK, et al. Human aminopeptidase N is a receptor for human coronavirus 229E. Nature 1992; 357(6377): 420–2.
[49] Kunkel F, Herrler G. Structural and functional analysis of the S proteins of two human coronavirus OC43 strains adapted to growth in different cells. Arch Virol 1996;141(6):1123–31.
[50] Tyrrell DA, Cohen S, Schlarb JE. Signs and symptoms in common colds. Epidemiol Infect 1993;111(1):143–56.
[51] Reed SE. The behaviour of recent isolates of human respiratory coronavirus in vitro and in volunteers: evidence of heterogeneity among 229E-related strains. J Med Virol 1984;13(2):179–92.
[52] Bradburne AF, Bynoe ML, Tyrrell DA. Effects of a ‘‘new’’ human respiratory virus in volunteers. Br Med J 1967;3(568):767–9.
[53] Hers JF. Disturbances of the ciliated epithelium due to influenza virus. Am Rev Respir Dis 1966;93(3 Suppl):162–77.
[54] Hers JF, Mulder J. Broad aspects of the pathology and pathogenesis of human influenza. Am Rev Respir Dis 1961;83(2 Pt 2):84–97.
[55] Walsh JJ, Dietlein LF, Low FN, Burch GE, Mogabgab WJ. Bronchotracheal response in human influenza. Type A, Asian strain, as studied by light and electron microscopic examination of bronchoscopic biopsies. Arch Intern Med 1961;108:376–88.
[56] Hayden FG, Fritz R, Lobo MC, Alvord W, Strober W, Straus SE. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. J Clin Invest 1998;101(3):643–9.
[57] Eichelberger MC, Wang ML, Allan W, Webster RG, Doherty PC. Influenza virus RNA in the lung and lymphoid tissue of immunologically intact and CD4-depleted mice. J Gen Virol 1991;72(Pt 7): 1695–8.
[58] Neilson KA, Yunis EJ. Demonstration of respiratory syncytial virus in an autopsy series. Pediatr Pathol 1990;10(4):491–502.
[59] Tristram DA, Hicks Jr W, Hard R. Respiratory syncytial virus and human bronchial epithelium. Arch Otolaryngol Head Neck Surg 1998;124(7):777–83.
[60] Hall CB, Douglas Jr RG, Simons RL. Interferon production in adults with respiratory syncytial viral infection. Ann Intern Med 1981; 94(1): 53–5.
[61] Lilic D, Cant AJ, Abinun M, Calvert JE, Spickett GP. Cytokine production differs in children and adults. Pediatr Res 1997;42(2): 237–40.
[62] Stockton J, Stephenson I, Fleming D, Zambon M. Human metapneumovirus as a cause of community-acquired respiratory illness. Emerg Infect Dis 2002;8(9):897–901.
[63] Welliver RC, Wong DT , Middleton E Jr., Sun M, McCarthy N, Ogra PL. Role of parainfluenza virus-specific IgE in pathogenesis of croup and wheezing subsequent to infection. J Pediatr 1982; 101(6): 889–96.

[64] Nutting PA, Main DS, Fischer PM, et al. Toward optimal laboratory use. Problems in laboratory testing in primary care. JAMA 1996; 275(8): 635–9.
[65] Covalciuc KA, Webb KH, Carlson CA. Comparison of four clinical specimen types for detection of influenza A and B viruses by optical immunoassay (FLU OIA test) and cell culture methods. J Clin Microbiol 1999;37(12):3971–4.
[66] Hall CB, Douglas Jr RG. Clinically useful method for the isolation of respiratory syncytial virus. J Infect Dis 1975;131(1):1–5.
[67] Schmid ML, Kudesia G, Wake S, Read RC. Prospective comparative study of culture specimens and methods in diagnosing influenza in adults. BMJ 1998;316(7127):275.
[68] Heikkinen T, Marttila J, Salmi AA, Ruuskanen O. Nasal swab versus nasopharyngeal aspirate for isolation of respiratory viruses. J Clin Microbiol 2002;40(11):4337–9.
[69] Corne JM, Green S, Sanderson G, Caul EO, Johnston SL. A multiplex RT-PCR for the detection of parainfluenza viruses 1–3 in clinical samples. J Virol Methods 1999;82(1):9–18.
[70] Hamparian VV, Colonno RJ, Cooney MK, et al. A collaborative report: rhinoviruses-extension of the numbering system from 89 to 100. Virology 1987;159(1):191–2.
[71] Compton J. Nucleic acid sequence-based amplification. Nature 1991;350(6313):91–2.
[72] Kievits T, van Gemen B, van Strijp D, et al. NASBA isothermal enzymatic in vitro nucleic acid amplification optimized for the diagnosis of HIV-1 infection. J Virol Methods 1991;35(3):273–86.
[73] Guatelli JC, Whitfield KM, Kwoh DY, Barringer KJ, Richman DD, Gingeras TR. Isothermal, in vitro amplification of nucleic acids by a multienzyme reaction modeled after retroviral replication. Proc Natl Acad Sci U S A 1990;87(19):7797.
[74] Leone G, van Schijndel H, van Gemen B, Kramer FR, Schoen CD. Molecular beacon probes combined with amplification by NASBA enable homogeneous, real-time detection of RNA. Nucleic Acids Res 1998;26(9):2150–5.
[75] Swierkosz EM, Erdman DD, Bonnot T, Schneiderheinze C, Waner JL. Isolation and characterization of a naturally occurring parainfluenza 3 virus variant. J Clin Microbiol 1995;33(7):1839–41.
[76] Fan J, Henrickson KJ, Savatski LL. Rapid simultaneous diagnosis of infections with respiratory syncytial viruses A and B, influenza viruses A and B, and human parainfluenza virus types 1, 2, and 3 by multiplex quantitative reverse transcription-polymerase chain reaction-enzyme hybridization assay (Hexaplex). Clin Infect Dis 1998;26(6):1397–402.
[77] Kehl SC, Henrickson KJ, Hua W, Fan J. Evaluation of the Hexaplex assay for detection of respiratory viruses in children. J Clin Microbiol 2001;39(5):1696–701.
[78] Fleming DM. The impact of three influenza epidemics on primary care in England and Wales. Pharmacoeconomics 1996;9(Suppl 3):38–45 [discussion 50–53].
[79] Douglas RM, Moore BW, Miles HB, et al. Prophylactic efficacy of intranasal alpha 2-interferon against rhinovirus infections in the family setting. N Engl J Med 1986;314(2):65–70.
[80] Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969;89(4):422–34.
[81] Group. TIRS. Palivizumab, a humanised respiratory syncytial virus monoclonal antibody reduces hospitalisation from respiratory syncytial virus infection in high risk infants. Paediatrics 1998;102:531–7.
[82] Schmidt AC, McAuliffe JM, Murphy BR, Collins PL. Recombinant bovine/human parainfluenza virus type 3 (B/HPIV3) expressing the respiratory syncytial virus (RSV) G and F proteins can be used to achieve simultaneous mucosal immunization against RSV and HPIV3. J Virol 2001;75(10):4594–603.
[83] Douglas RM, Chalker EB, Treacy B. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2000;(2) [CD000980].
[84] Giles JT , Palat CT III, Chien SH, Chang ZG, Kennedy DT. Evaluation of echinacea for treatment of the common cold. Pharmacotherapy 2000;20(6):690–7.
[85] Marshall I. Zinc for the common cold. Cochrane Database Syst, Rev 2000;20(2):690 [CD001364].
[86] Macknin ML, Piedmonte M, Calendine C, Janosky J, Wald E. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. JAMA 1998;279(24):1962–7.
[87] Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. Am J Med 2001;111(2):103–8.
[88] Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. QJM 2003;96(1):35–43.
[89] Sperber SJ, Sorrentino JV, Riker DK, Hayden FG. Evaluation of an alpha agonist alone and in combination with a nonsteroidal antiinflammatory agent in the treatment of experimental rhinovirus colds. Bull N Y Acad Med 1989;65(1):145–60.
[90] Taverner D, Bickford L, Draper M. Nasal decongestants for the common cold. Cochrane Database Syst Rev 2000;65(2):145 [CD001953].
[91] Gwaltney Jr JM, Druce HM. Efficacy of brompheniramine maleate for the treatment of rhinovirus colds. Clin Infect Dis 1997;25(5): 1188–94.
[92] Diamond L, Dockhorn RJ, Grossman J, et al. A dose–response study of the efficacy and safety of ipratropium bromide nasal spray in the treatment of the common cold. J Allergy Clin Immunol 1995;95(5 Pt 2):1139–46.
[93] Sperber SJ, Hendley JO, Hayden FG, Riker DK, Sorrentino JV, Gwaltney Jr JM. Effects of naproxen on experimental rhinovirus colds. A randomized, double-blind, controlled trial. Ann Intern Med 1992;117(1):37–41.
[94] Gwaltney Jr JM. Combined antiviral and antimediator treatment of rhinovirus colds. J Infect Dis 1992;166(4):776–82.
[95] Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet 2000;355(9218):1845–50.
[96] Group. TMS. Randomised trial of efficacy and safety of inhaled Zanamivir in the treatment of influenza A and B virus infections. Lancet 1998;352:1845–50.
[97] Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. JAMA 1996;275(4):295–9.
[98] Diseases CoI EK. Use of ribavarin in the treatment of respiratory syncytial virus infection. Pediatrics 1993;92:501–4.
[99] Rosner IK, Welliver RC, Edelson PJ, Geraci-Ciardullo K, Sun M. Effect of ribavirin therapy on respiratory syncytial virus-specific IgE and IgA responses after infection. J Infect Dis 1987;155(5):1043–7.
[100] Hiatt PT, Laber DL. Pulmonary function (PF) following treatment with ribavarin in infants hospitalised with RSV bronchiolitis. Am Rev Respir Dis 1990;141:A624.
[101] Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 1991;325(1):24–9.
[102] Turner RB, Wecker MT, Pohl G, et al. Efficacy of tremacamra, a soluble intercellular adhesion molecule 1, for experimental rhinovirus infection: a randomized clinical trial. JAMA 1999;281(19): 1797–804.