Bronchiolitis is a distressing, potentially life-threatening respiratory condition that affects young babies. Around 2–3% of all infants younger than 1 year are admitted to hospital with bronchiolitis, usually during the seasonal epidemic. The majority of these infants are infected with respiratory syncytial virus and all have an intense inflammatory response in their airways. Although most infants recover, they have an increased risk of recurrent wheezing. Although bronchiolitis is common, little is known about what causes infants to be susceptible. Diagnostic interventions have little effect on clinical outcome, and apart from supportive measures, there is no specific treatment. Bronchiolitis therefore presents an intriguing clinical conundrum and a major challenge to researchers. High quality clinical studies are needed to clarify assessment of disease severity and criteria for hospital admission, particularly the use of pulse oximetry and chest radiography. Careful mapping of the inflammatory pathways in the pathogenesis of bronchiolitis should lead to development of new therapies to alleviate symptoms.

The word “bronchiolitis” is a pathological description, which has become used as a clinical diagnosis. In this Seminar, we will use “bronchiolitis” to describe an acute respiratory illness that affects infants and young children, with coryza and sometimes low-grade fever that progresses over a few days to cough, tachypnoea, hyperinflation, chest retraction, and widespread crackles, wheezes, or both. Most cases are caused by respiratory syncytial virus (RSV) (figures 1 and 2). The purpose of this Seminar is to provide an up-to-date clinical review of bronchiolitis, discussing international differences in epidemiology and clinical practice, highlighting new developments, and providing a balanced account of current controversies.

Epidemiology

Hospital admission rates in the USA and Europe for bronchiolitis are reported to be around 30 per 1000 for children younger than 1 year. High-risk groups for severe infections are infants younger than 6 weeks; premature infants; and those with chronic lung disease of prematurity, congenital heart disease, neurological disease, or immunodeficiency. The mechanisms that contribute to increased disease severity in infants in each of these risk groups are not fully understood, but are probably related to abnormalities in physiological and immunological responses to infection.

Bronchiolitis-associated deaths are fortunately very rare. Rates in the USA in the late 1990s were reported to be 2·0 per 100 000 livebirths. This rate has remained stable in the USA since 1979, whereas in the UK, the post-neonatal mortality rate due to bronchiolitis fell from 21·47 per 100 000 in 1979 to 1·82 per 100 000 in 2000.

Risk factors for death are low birthweight, increasing birth order, low Apgar score at 5 min, young maternal age, unmarried mother, and tobacco use during pregnancy. However, an epidemiological study in the UK, which compared excess deaths during RSV-active weeks with those during RSV-inactive weeks, suggested that RSV could have a greater influence on mortality than that estimated by direct ascertainment of respiratory certified deaths. For the babies aged 1–12 months, the RSV-attributed winter mortality rate per 100 000, averaged over 11 winters, was 2·9 for respiratory causes, compared with 8·4 for all causes.

In the USA, hispanic children are more likely to present to the emergency department and thereafter to be admitted to hospital than the general population. Native American and Alaskan infants likewise have slightly higher rates of hospital admission than the general population and this shows striking regional variation, which is especially high in Alaska and the southwest (70·9 and 48·2 per 1000 infants, respectively, compared with 27·4 hospital admissions per 1000 infants in the general population of the USA). Inuit infants living in Baffin Island, Nunavut, have the highest prevalence of bronchiolitis requiring hospital admission in the world (197 per 1000 infants). These findings are probably due to a combination of socioeconomic factors and reduced access to healthcare care in remote areas; these children could be more severely ill by the time they arrive at the hospital emergency department or might be more likely to be admitted than sent back home over long distances or difficult terrain.

There are few studies of the epidemiology or clinical course of bronchiolitis in resource-limited settings and where reports exist, differences in defining bronchiolitis can cause difficulties in comparing with data from resource-rich countries. For example, a study in Bangladesh that examined the clinical features of more than 400 children admitted to hospital with a diagnosis of bronchiolitis reported a mortality rate of 2%. The clinical...
features described were similar to bronchiolitis, but the definition of bronchiolitis as “first attack of wheeze in previously healthy children below two years of age” might have included some children with asthma,13 and so the reported mortality figure for bronchiolitis could be misleading.

Predictable seasonal epidemics in many parts of the world are the most notable features of RSV bronchiolitis.14 In the USA, the median time of onset of the epidemic is in late December, with a median epidemic peak in early February.15 However, there are distinct variations within the USA, with earlier seasons reported in the south and later ones in the midwest. In the UK and most of northern Europe the season is a little earlier, with the infection peak in December or January.1 In temperate climates, the RSV epidemic generally happens during the winter months, but in Hong Kong its peak season is in spring or summer16 and in other tropical and subtropical areas north of the equator the peak season occurs during the cool rainy season. In South America and South Africa, epidemics occur during the cool dry season.1 Human metapneumovirus (HMPV) infection is also thought to occur in seasonal epidemics that overlap with, or are slightly later than, RSV outbreaks around the world.14,16,17 The timings of other common respiratory virus epidemics, including those of adenovirus, parainfluenza virus, and influenza virus are somewhat different to both those of RSV and HMPV,14 which could explain why co-infection with HMPV and RSV is frequently reported,18 but co-infection with RSV and the other named respiratory viruses is not. However, longer-term surveillance is needed before the relations between the RSV and HMPV epidemics and their clinical consequences can be fully understood.

Clinical diagnosis

Although most clinicians would find bronchiolitis a straightforward diagnosis during the epidemic months, the lack of a standard definition of bronchiolitis presents challenges to clinicians and clinical researchers. Bordley and colleagues undertook a systematic review of diagnostic testing in acute bronchiolitis.19 Most of the 65 studies reviewed included tachypnoea and wheezing in the case definition, but many stated only that “infants with signs and symptoms consistent with bronchiolitis” were included. Mulholland and colleagues20 investigated 60 infants with acute bronchiolitis to show which clinical features were related to disease severity—determined by pulse oximetry and arterial blood gas analysis. They noted that crackles and cyanosis were closely linked to disease severity, but respiratory rate was not. Additionally, the validity of auscultatory findings within a definition of bronchiolitis is questionable. A study of 102 infants with acute respiratory disorders, most of whom had bronchiolitis, investigated the validity and reliability of stethoscope examination and computerised analysis in the detection of abnormal respiratory noises. Agreement between observers for the presence of crackles and wheeze was moderate and poor, respectively, for stethoscope examination.21

The words “bronchiolitis” and “pneumonia” are both used to describe the lower respiratory tract manifestations of viral respiratory infections, including RSV infections, and there are some international differences in meaning. For example, in the UK, “RSV pneumonia” is not a commonly recognised clinical entity, but in the USA22 and some other European countries’ pneumonia caused by RSV can be defined by the presence of localised crackles and consolidation on chest radiograph.
Clinical assessment

The decision to admit a baby to hospital is usually made in the emergency department. A routine part of this assessment is measurement of oxygen saturation by pulse oximetry. Detection of hypoxia in infants is thought to be responsible for an increase in admission rates since its increased use over the past two decades might have resulted in the hospitalisation of infants whose other symptoms were too mild to result in admission.23 Mallory and colleagues undertook a randomised controlled survey of emergency physicians to investigate their care preferences for infants presenting with moderately severe bronchiolitis.24 The doctors were randomly allocated to receive one of four case descriptions, which differed in only two respects: oxygen saturation values (94% or 92%) and respiratory rate (50 per min or 65 per min) as variables. Respondents who received a case description in which the oxygen saturation was 92% were almost twice as likely to admit the infant as those who received the case in which the oxygen saturation was 94%. There was no difference in recommendations for admission when the respiratory rate was the variable. These findings are quite striking, particularly as the two percentage points difference in oxygen saturation is likely to represent a very small difference in partial pressure of arterial oxygen and highlights how, in the absence of good clinical criteria for diagnosis and assessment of disease severity, much reliance might have to be placed on other measurements.

Although this study suggests that oxygen saturation measurements strongly influence clinicians’ decisions to admit infants with respiratory illness, the benefits of pulse oximetry for babies with bronchiolitis have not been proven in clinical studies.

Viral diagnosis

The initiating event in RSV disease is infection of the epithelial cells in the respiratory tract (figure 4). In the USA, most children admitted to hospital with bronchiolitis have specific diagnostic tests to identify RSV infection and this has been associated with a decreased likelihood of antibiotic treatment.27 In one study, compared with nasopharyngeal swabs, nasal swabs were negative in about a third of RSV-positive cases,30 which is perhaps because RSV grows better at 37°C than 33°C. Most clinical studies have used rapid antigen detection tests (eg, direct immunofluorescence and enzyme immunoassays), which have an overall sensitivity of 80–90%, although some studies have included viral culture, polymerase chain reaction (PCR), and acute and convalescent antibody titres.19

RSV is identified in about 70% of patients with bronchiolitis,7 and in some infants, more than one virus is identified. In a prospective study of 772 infants
admitted to a paediatric hospital in Vienna, Austria, with lower respiratory tract illness, PCR detected single viral agents in 443 (57%), and two viral agents in 153 (20%), mostly RSV and either rhinovirus or adenovirus. Other viruses that are commonly implicated in bronchiolitis include HMPV, influenza, parainfluenza, rhinoviruses, and adenoviruses.2,14,17,32

Since HMPV was discovered in 2001, its role in causing acute respiratory tract infections in childhood has been investigated intensively.33 Studies have shown HMPV infection to be associated with 3–12% of acute lower respiratory tract infections in young children; the proportion varies according to the ages of the children, their case definition, and the clinical setting.14,16,17,34,35 Compared with other respiratory viruses, the clinical pattern of illness seen with HMPV infection is very similar to RSV,14 but induces less striking changes in inflammatory markers in the nasopharynx.36 HMPV can cause fever, but otherwise has little effect outside the respiratory tract.14 Like with RSV, most HMPV-infected children have signs of bronchiolitis during first infections, and there is a strong association with exacerbations of asthma.14,16,34 Children in whom HMPV is detected are generally older than those infected with RSV.14,17,34 There is controversy about whether co-infection with RSV and HMPV causes more severe disease than either virus alone.18 Large prospective epidemiological studies are needed to investigate co-infection rates and their effects and outcomes, and to identify the most pathogenic RSV genotypes.17,38

Rhinovirus infection is known to cause acute exacerbations of asthma, but its role in bronchiolitis has not been widely investigated, largely because of difficulties in detection.39 Studies of children with bronchiolitis to distinguish the clinical patterns of illness caused by rhinovirus and RSV have shown that children with bronchiolitis who are infected with rhinovirus alone are more likely to be older and have evidence of atopic disease than those infected with RSV.32,40 These studies could have captured infants with asthma, which could account for the differences between the two groups. The role of rhinovirus infection in bronchiolitis is, as yet, unclear.

There is debate over whether RSV-testing of infants with bronchiolitis changes clinical management or outcome.41 Many hospitals require routine testing to allow RSV-infected infants to be cohorted together to reduce the risk of infecting other patients, although there is no good evidence for how effective this approach is. Such a policy can be justified as it could prevent transmission to other paediatric patients who would be at greater risk of severe disease and death as a result of RSV. However, cohorted on the basis of RSV status cannot prevent transmission of other viruses and a better understanding is needed of the role of such viruses in the development of severe bronchiolitis, to guide policymakers.

Acute complications
Bronchiolitis is associated with acute inflammation of the respiratory tract, including the Eustachian tubes and middle ear. The reported prevalence of otitis media among children with bronchiolitis varies from 16% to more than 50%.1,17,41 We suspect that this complication is frequently undiagnosed, in view of the difficulties in examining the middle ear of a small baby with acute respiratory distress.

In the USA there is controversy over whether infants with clinical bronchiolitis should undergo full investigations for the presence of bacterial infection.3 This is especially important for office-based paediatricians who may not have access to rapid detection tests for RSV. Prospective studies have shown that febrile infants with RSV infection are at significantly lower risk of serious bacterial infection (other than urinary tract infections) than those without RSV infection.42–44 In a prospective study of infants aged under 2 months, serious bacterial infection (mostly urinary tract infections) was detected in 7.0% of infants who tested positive for RSV, compared with 12.5% of RSV-negative infants. However, reports of such studies differ in their recommendations. One suggested that febrile infants younger than 29 days with RSV infection should have full investigations for the presence of systemic sepsis.42 Another advocated that
routine sepsis and meningitis tests were not necessary in infants with RSV infections who showed no toxic symptoms,48 which accords with clinical practice in the UK.

Apnoea is frequently reported in infants with bronchiolitis, with one study reporting this in 8% of those admitted to hospital49 and 20% of those admitted to a paediatric intensive care unit,50 although a history of apnoea can influence the decision to admit. Apnoea does not seem to indicate CNS spread of virus48 and does not relate specifically to RSV infection. Other neurological complications have been reported, including encephalopathy, which is also more prevalent in infants admitted to intensive care.45-47 Electrolyte disturbances, particularly hyponatraemia, are common in infants admitted to intensive care and can be associated with seizures.50-51 Antidiuretic hormone is elevated during the acute phase of bronchiolitis and if infants are rehydrated with hypotonic intravenous fluid, hyponatraemia is a probable consequence.52

**Special features of bronchiolitis and the immunobiology of RSV**

As has already been described, RSV seems to have several features that distinguish it from other respiratory viruses (panel). Viral infections typically induce T-helper-1 (Th-1) cell responses, characterised by high levels of interferon-gamma production; by contrast, asthma and atopy are typically characterised by T-helper-2 (Th-2) cells producing interleukin 4 and interleukin 5. These responses are easily demonstrated in animal models, but have not been thoroughly examined in human infants. It is possible that infants with severe infections might sequester RSV-specific immune components in affected tissues, so that relevant cells are depleted from the peripheral blood and are therefore undetectable.51 In some studies, analysis of nasal lavage and peripheral blood samples from RSV infected children show elevated interleukin 4: interferon-gamma ratios in infants during the first week of acute bronchiolitis compared with infants with upper respiratory tract signs alone.51 These data are consistent with excessive Th-2 and deficient Th-1 immune responses in RSV bronchiolitis.52 RSV infection has also been reported to be associated with lower interferon-gamma production by γδ T cells, than rotavirus infection.53

Aberle and colleagues54 showed that infections with two respiratory viruses, neither of which were RSV, induced interferon-gamma responses in peripheral blood mononuclear cells that mimicked those of single infections, whereas co-infection with RSV and another respiratory virus was associated with reduced interferon-gamma responses in peripheral blood mononuclear cells and increased severity of illness. RSV infection has been reported to upregulate Toll-like receptor 4 (TLR4) expression on bronchial epithelial cells,55 thereby promoting sensitivity to bacterial endotoxins and other TLR4 ligands. This effect could be of substantial pathogenic importance, since TLR4 expression is also increased on peripheral blood cells during bronchiolitis,54,55 and common TLR4 polymorphisms have been linked to RSV bronchiolitis.56

Bont and colleagues57 noted depressed peripheral lymphocyte function, associated with raised plasma CCL8 (interleukin 8) concentrations in children with severe bronchiolitis. CCL8 is a CXC-chemokine that promotes neutrophil chemotaxis and survival, and neutrophils are the predominant cell type present in the bronchial secretions of children with severe bronchiolitis.18 Studies in Liverpool, UK, have shown that the amount of CCL8 mRNA in the nasal aspirates of infants with bronchiolitis correlates with severity of disease.19 The lower airways of infants with severe RSV bronchiolitis likewise contain large quantities of CXC-chemokines, which included CCL8, and CXCL10 (IP-10).48

CCL5 (RANTES) is produced in response to stimuli such as interferon-gamma, interleukin 1α, interleukin 1β, and tumour necrosis factor (TNF) by many cell types including fibroblasts, smooth muscle, and epithelial cells; in later stages of infection it is made by infiltrating cells including γδ T cells. CCL5 selectively recruits monocytes, memory T cells, and eosinophils, and (at high concentrations) activates T cells. Treatment of HEp-2 cells with recombinant human CCL5 inhibits infection with RSV in vitro, an effect not seen with other chemokines. Increases in CCL5 concentrations after RSV infection of mice correlate with severity of disease, and anti-CCL5 antibody administration decreases airway hyper-reactivity and increases interleukin 12 production. Additionally, CCL5 production seems to be regulated by interleukin 13 which is also important in RSV-induced airway hyper-reactivity49 and affected by genetic polymorphisms.50 CCL5 could also be important in human beings since genetic studies show that polymorphisms of CCR5 affect disease severity.51 CCL5 concentrations in nasal secretions during acute RSV bronchiolitis (although not correlated with disease severity) could be predictive of later development of recurrent wheeze.52

A little studied cytokine, interleukin 9, has been found in high concentrations in the airways of infants with severe bronchiolitis53 and it seems to be produced by neutrophils. Interleukin 9 is known to induce mucus

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**Panel: Features of RSV infection**

- Worldwide distribution, annual epidemics
- Infects almost all children by 2 years of age
- Responsible for about 70% of cases of bronchiolitis
- Causes coughs and colds in older children and adults
- Causes re-infection despite the presence of serum antibody
- The same serotype re-infects children and adults
- Associated with recurrent wheeze for many years after bronchiolitis
production by bronchial epithelial cells, cause goblet cell hyperplasia, and induce chemokine secretion by respiratory epithelial cells and neutrophils, suggesting that it could have an important role in the inflammatory cascade in the airways during acute bronchiolitis.

**Biological effects of RSV proteins on host cells**

Like many viruses, RSV is not just a passive target for the host's immune response, but is well adapted to control and manipulate the host. The RSV glycoprotein G has been shown to have structural homology with the CX3C chemokine, CX3CL1 (fractalkine). RSV glycoprotein G binds the human CX3CR1 receptor and mediates chemotaxis of cells that respond to CX3CL1. This interaction could facilitate RSV binding to CX3CR1-bearing cells, including mast cells and neuronal cells. The RSV fusion protein binds TLR4, upregulates surface expression of TLR4, and sensitises airway epithelial cells to endotoxin.

Once RSV has infected a cell, it rapidly and abundantly synthesises non-structural proteins (NS1 and NS2). These proteins cause species-specific resistance to type I interferons via interferon regulatory factor 3 (IRF3). Recombinant viruses lacking NS1 or NS2 tend to induce a weaker inflammatory response and are under development as vaccine candidates.

**Delayed respiratory sequelae**

Bronchiolitis obliterans is increasingly recognised as a serious sequel to severe respiratory infection in early childhood frequently resulting from adenovirus infection. It has been suggested that RSV might cause bronchiolitis obliterans, but, the only reports have been of infants in whom adenovirus has also been detected.

The relation between RSV bronchiolitis and subsequent wheezing illnesses in childhood has been consistently shown in clinical studies but it seems that not all colds are equally associated with wheeze, since uncomplicated common colds (without wheeze) and other common viral infections in early childhood (e.g., herpetic stomatitis, chickenpox, or exanthema subitum) seem to protect against wheeze. The risk of asthma diagnosis by 7 years of age is reduced by about 50% in children who have had two or more common colds by the age of 1 year. There is evidence that RSV-associated wheeze could even be associated with lung function abnormalities in adulthood. Although these findings tend to support the belief that RSV has unique activity that leads to persistent pulmonary abnormalities, other viruses of similar severity and tropism could possibly lead to delayed symptoms if they infect during a critical window of postnatal development.

Studies of the association between bronchiolitis in infancy and allergic sensitisation or atopic illness have not produced clear answers. Sigurs and colleagues followed up a cohort of 47 children, who had been admitted to hospital with severe RSV bronchiolitis in infancy, until the age of 13 years and noted that not only was the occurrence of asthma symptoms and wheezing more frequent in these children than the controls, but that allergic rhinoconjunctivitis and allergic sensitisation were more common. By contrast, Stein and colleagues studied children who had documented RSV infection with lower respiratory tract symptoms as infants, but who did not require hospital admission. RSV infection was shown to be an independent risk factor for wheeze up the age of 11 years, but did not influence the development of atopy. Additionally, a birth cohort study has investigated a group of 150 children (1-1% of the cohort) who were admitted to hospital with bronchiolitis within their first year and identified that, although these children did have a higher prevalence of asthma and wheezing in early childhood (cumulative prevalence of asthma was 38.4% in the RSV group compared with 20.1% in controls at age 7-5 years), there was no difference in rates of atopic disease at 7 years of age.

Different study cohorts vary, depending on the severity of RSV disease, genetic background, predominant environmental allergens, and geographical location. The varying results of these studies shows the importance of comparing “like for like” infections in diverse circumstances, and the difficulties in interpreting results from children with different disease severities.

**Pathogenesis of delayed effects of RSV bronchiolitis**

There is no clear explanation for the association between RSV bronchiolitis and recurrent wheeze in later life. The association could be causal (i.e., RSV bronchiolitis could lead to long-term changes in the lungs), or bronchiolitis could act as a marker for genetic predisposition or impaired respiratory reserve, which will later manifest as allergy or recurrent wheeze. Lower than normal lung function prior to RSV infection is a risk factor for the development of bronchiolitis.

Genetic associations have been recorded between RSV bronchiolitis and polymorphisms of the genes encoding interleukin 4 and the interleukin 4 receptor, supporting the possibility that Th-2 cells are associated with RSV disease. Studies of frequencies of transmission of cytokine polymorphisms from parents to infants and case-control approaches have shown a significant association between RSV bronchiolitis and the interleukin 10-592C allele (odds ratio, 1-61, 95% CI 1-10–2-35), but did not show significant associations with TNF and interleukin 9 polymorphisms. Interleukin 10 is a key immunomodulatory cytokine associated with regulatory T cells, implying that bronchiolitis might partly be a consequence of a failure of host immune regulation.

Both immunological and virological mechanisms could cause the delayed wheezing effect. A sustained increase in interleukin 2 receptors in serum has been reported after RSV infection, and RSV infection has been seen to...
cause sustained increases in dendritic cell numbers in the lungs of mice\(^9\) and in nasal samples from children recovering from severe RSV infections.\(^8\) This finding suggests that inflammation might continue after the symptoms of acute disease have resolved. Sequential nasal biopsies of children recovering from viral bronchiolitis showed that gross ciliary and epithelial abnormalities persisted for 13–17 weeks.\(^4\) However, it has not been possible to obtain direct confirmation of persistent pulmonary inflammation in infants who have recovered from bronchiolitis.

Other possible immune mechanisms include “imprinting” or programming of the immune system as a result of exposure to viral infection at a stage of postnatal development when the immune system is relatively immature, a concept supported by animal studies.\(^5\) However, RSV also shows a tendency to cause persistent infection,\(^7,9\) and might be able to infect neuronal cells and gain access to nerves that serve the lung by binding to the CX3CR1 receptor.\(^6\) Nasal persistence can occur in some individuals,\(^8,9\) but is not commonly seen in adults.\(^8\) Occult persistence in the lungs could also provide a reservoir for future RSV outbreaks in infants.

In our view, there is a high probability that RSV bronchiolitis is a marker for a predisposition to airway disease, although it is also possible that RSV bronchiolitis leads directly to long-term pulmonary sequelae (figure 5). One of the best ways to test the relative importance of these mechanisms is in interventional studies for RSV prevention, by giving anti-RSV immune globulin in infancy. Studies with palivizumab are yet to be published, and large multicentre studies of a derivative antibody with even higher avidity (Numax, MedImmune Inc, USA), are underway. Administration of a polyclonal anti-RSV antibody in one small study in children at high risk of respiratory disease seemed to improve asthma scores and reduced atopy compared with a placebo group.\(^7\)

**Prevention of RSV infection with passive antibody in high-risk groups**

The introduction of palivizumab to prevent RSV bronchiolitis has been hailed as a major advance in RSV disease control. Palivizumab is the first humanised monoclonal to be used to prevent infection in humans, and it seems to be highly effective. However, the cost is about US$5000–6000 per patient per season and use of prophylactic therapy varies greatly from one country to another.

The authors of a systematic review of all published economic analyses of RSV immunoprophylaxis in high-risk infants were unable to make a clear judgment about the economic benefits of therapy.\(^9\) One of the studies reviewed, by Joffe and colleagues,\(^9\) reported that palivizumab was most cost effective for infants whose gestational age at birth was less than or equal to 32 weeks, who required long-term oxygen administration, and who were discharged between September and November. In such infants, palivizumab treatment costs about $12000 per hospital admission averted (after taking into account savings from prevention of RSV admissions) or $33 000 per life-year saved. The number of infants treated to avoid one hospital admission is estimated at 7·4.\(^9\) A relevant finding from the systematic review\(^9\) was that the economic analyses with some funding from a manufacturer were more likely to report the possibility of cost-effectiveness or cost-savings of prophylaxis in the entire high-risk infant population, than analyses without corporate funding.

Although palivizumab reduces hospital admissions for serious RSV disease, the direct cost-benefit balance for infants born at more than 32 weeks’ gestation is not proven. In a study of the North Carolina Medicaid Program, comparisons were made between 185 infants who received and 182 infants who did not receive palivizumab. The primary outcomes were actual 7-month seasonal costs and standardised seasonal costs. The average per-child total cost of RSV care and prophylaxis was $5117 for the prophylaxis group and $371 for the non-prophylaxis group, with five and 12 hospital admissions, respectively (odds ratio: 0·27). There were no RSV deaths in either group. Palivizumab treatment in infants born at 32–35 weeks therefore considerably adds to the direct costs of patient care.\(^9\)

Many infants are born with significant congenital heart disease (CHD) (>6000 patients per year in the USA), and palivizumab reduces RSV-related hospital admissions by about 45% in such children.\(^9\) The American Academy of Pediatrics recommends that infants with significant CHD be considered for palivizumab treatment. However, analysis of cost-benefit data applied to a hypothetical cohort of 10 000 CHD patients, shows that giving palivizumab to 5000 of these children would cost...
bronchiolitis in North America and Europe. The decision to discharge is not always clear, and there are concerns that its use in outpatients might cause harm. There is some evidence that epinephrine use in inpatients with bronchiolitis is beneficial, especially in the emergency department. A Cochrane review of eight randomised trials in mild to moderate bronchiolitis (total of 394 children) showed that bronchodilator treatment was associated with a significant improvement in clinical scores. However, this comparison could have been biased towards showing a difference, because studies included patients with recurrent wheezing. The improvement in clinical scores was not regarded as clinically significant and there was no improvement in oxygenation or rates of hospital admission.

Nebulised epinephrine is used to treat bronchiolitis, especially in the emergency department. A Cochrane review of this treatment showed that, compared with placebo, epinephrine led to short-term improvements in clinical scores, but no change in admission rates. When compared with salbutamol, again there was some benefit of epinephrine on short-term outcomes, but no effect on admission rates. There is thus no evidence to support epinephrine use in inpatients with bronchiolitis. There are concerns that its use in outpatients might cause transient clinical benefits, which could lead to a premature decision to discharge. The use of epinephrine is not generally recommended.

A systematic review of 13 trials (1198 patients) showed no benefit in clinical outcomes for the use of systemic corticosteroids in bronchiolitis. A randomised controlled trial of dexamethasone in infants with RSV lower respiratory tract infection who were mechanically ventilated showed no overall difference in outcomes. Although a post-hoc subgroup analysis showed benefit in the group with milder gas-exchange abnormalities, further clinical studies are required to confirm this finding. Ribavirin is a broad-spectrum antiviral agent that has been widely used but little tested in children with bronchiolitis. There is no conclusive evidence of benefit from ribavirin use for RSV bronchiolitis in children and there are important practical issues in its use, including safety concerns and high costs. Three trials of chest physiotherapy have shown no benefit. Treatments studied in the critical care setting including surfactant treatment, immunoglobulin, heliox (helium and oxygen), vitamin A, interferon, and erythropoietin have also shown inconclusive results.

In the absence of specific, proven therapies to treat infant bronchiolitis, the clinical treatment of these very sick small babies is limited to supportive care, including giving appropriate fluid replacement and oxygen. Neither oxygen therapy, nor fluid replacement strategies have been validated in large randomised controlled trials, although the dangers of hyponatraemic fluid overload are recognised. These treatment options should be addressed in randomised controlled trials.

Potential for novel antiviral treatments and vaccines
The value of antiviral agents in acute, transient infections seems limited. To be effective, they have to be given early, ideally within 1 or 2 days of disease onset. This stage could be before many infected children reach medical attention and moreover, precedes the peak of disease severity, which is caused by the inflammatory immune response and occurs when viral load is already declining. Despite these problems, there are several novel antiviral drugs under development. An exciting area for future exploration is the field of siRNA targeted against the RSV NS1, P, N, or L genes. Such treatment has shown considerable potential in animal models.

Live attenuated vaccines have the advantages of inducing local immune responses and of being deliverable without needles, but conventionally attenuated viruses continue to show a tendency to revert to pathogenicity and to cause disease in young infants. Fears of adverse effects would probably limit the use of these vaccines. Genetic modification to alter key elements of the RSV genome (eg, deletion of NS1) could produce even better candidates in the future. However, the introduction of new vaccines has slowed, partly because of public fears, a challenging regulatory environment, and commercial considerations.

Conflict of interest statement
In the past 3 years Rosalind Smyth has received travel expenses to attend scientific conferences from GlaxoSmithKline, Abbott Laboratories, and Chiron Pharmaceuticals. Peter Openshaw has received travel expenses and speaker’s fees from Abbott Laboratories, and honoraria or consulting fees from Arrow Therapeutics Ltd (UK) and Symphogen A/S (Denmark).

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$20·4 million. If a survival benefit of treatment is assumed, the cost per life-year saved is estimated at $100·338 and the cost per quality-adjusted life-year saved is $134·337. Clearly, the routine use of palivizumab in CHD would add considerably to costs of health care.


