Seminar

Respiratory syncytial virus infection

Eric A F Simoes

Respiratory syncytial virus (RSV), long recognised as the major viral pathogen of the lower respiratory tract of infants, has also been implicated in severe lung disease in adults, especially the elderly. This fact, and the demonstration that passive prophylaxis with either polyclonal or monoclonal antibody to RSV prevents severe lung disease in high-risk infants and children, has led to renewed interest in the immune mechanisms surrounding protection, and the development of vaccines

Since it was first identified as the agent that causes chimpanzee coryza in 1956,[1] and after its subsequent isolation from children with pulmonary disease in Baltimore, USA,[2] respiratory syncytial virus (RSV) has been described as the single most important virus causing acute respiratory-tract infections in children. The WHO estimates that of the 12·2 million annual deaths in children under 5 years, a third are due to acute infections of the lower respiratory tract.[3] *Streptococcus pneumoniae*, *Haemophilus influenzae*, and RSV are the predominant pathogens. Vaccination against RSV could reduce RSV-related morbidity. A formalin-inactivated RSV vaccine, tested in the 1960s,[4] was immunogenic, with high-rates of seroconversion. Despite this immunogenicity, vaccinated children were not protected from subsequent RSV infection. Furthermore, RSV-naïve infants who received formalin-inactivated RSV vaccine, and who were naturally infected with RSV later, developed more severe disease in the lower respiratory tract than a control group immunised with a trivalent parainfluenza vaccine. This experience has been one of the main reasons for the cautious approach to testing prophylactic measures in RSV-naïve babies. However, administration of antibodies against RSV can protect against RSV disease in infants and young children born prematurely.[5,6] This finding has rekindled interest in the prevention of RSV infection of the lower respiratory tract, and has encouraged the development of active prophylactic measures.

Epidemiology

RSV causes a substantial amount of illness in young infants and elderly people. It is a seasonal virus, with peak rates of infection occurring annually in the cold season in temperate climates, and in the rainy season, as temperatures fall, in tropical climates. It affects about 90% of infants and young children by the age of 2 years; peak rates occur in infants aged 6 weeks to 6 months, but particularly in those under 3 months of age. Infection rates in Houston, USA, were 68·8 per 100 child-years in infancy, and 82·6 per 100 child-years in the second year of life.[7] In Sweden, antibodies to RSV develop in 87% of children by age 18 months, and in virtually all children by age 3 years.[8] Repeated infections are common in all age-groups, and previous infection does not prevent subsequent infections, even in sequential years. RSV may be the cause of up to 2·4% of community-acquired lower-respiratory-tract infections in adults less than 60 years of age.[9] In elderly people, at least 10% of winter hospital admissions are caused by RSV, and the case-fatality rate is about 10%. These values are similar to those of influenza.[10]

In developed countries, there are well-defined high-risk groups, generally with chronic underlying disorders, in whom infection with RSV is more likely to progress into severe lower-respiratory-tract infections. Healthy infants younger than 3 months old are also susceptible to such infections. High-risk groups include infants with a history of premature birth; those with bronchopulmonary dysplasia, congenital heart disease (especially left-to-right shunts with pulmonary hypertension), or cystic fibrosis; immunosuppressed patients (including those undergoing chemotherapy, bone-marrow and solid-organ transplantation, and those with underlying disorders of cellular immunity); individuals living in institutions; and elderly people. There is no particular age-group that is not at risk for RSV infection, but certain risk factors have been implicated in more severe disease: low socioeconomic status, crowded living conditions, indoor smoke pollution, a family history of asthma or atopy, and perhaps infection with the A subgroup of RSV.

Data on acute respiratory-tract infections in children under 5 years of age from ten developing countries (Argentina, Colombia, Guatemala, Kenya, Nigeria, Pakistan, Papua New Guinea, the Philippines, Thailand, and Uruguay)[11] showed that the most frequent cause of lower-respiratory-tract infection was RSV, which accounted for up to 70% of all cases. In developing countries, risk factors are not defined, although crowding, indoor smoke pollution, and malnutrition may play a part in the development of more severe disease. Although the age distribution of RSV infection in children in developing countries is similar to that seen in developed countries, older children are more severely affected in developing countries, perhaps reflecting these risk factors.[12] A mortality rate of up to 7% has been reported in hospital inpatients in developing countries.[13] This rate is much higher than that seen in high-risk patients in developed countries (0·5–2·0%). To elucidate the extent of this problem, to identify risk factors, and to estimate mortality, the WHO has sponsored field studies in Indonesia, Ethiopia, Guinea Bissau, Mozambique, Nigeria, and South Africa. However, in addition to the results of these field studies, many more clinical and epidemiological data are required from developing countries.

Lancet 1999; **354:** 847–52

Department of Pediatrics, Section of Infectious Diseases, University of Colorado School of Medicine, and Children's Hospital, 1056 E 19th Ave, Denver, CO 80218, USA (E A F Simoes MD)

RSV and the immune response to infection

The RSV genome comprises a single strand of negative-sense RNA, 15 222 nucleotides in length,[14] which yields ten major proteins. The F (fusion) and G (attachment) glycoproteins are the major surface antigenic determinants. Other proteins are primarily structural: the small hydrophobic proteins, matrix proteins, and the 22 kDa protein are associated with the viral envelope, and the nucleoprotein, phosphoprotein, and large nucleoprotein are found in the nuclear capsule. The function and localisation of the two non-structural proteins are unclear at present.

RSV infects through the upper respiratory tract (particularly the nasopharynx) and the eyes, and has an incubation period of 3–5 days. Infection of the bronchiolar epithelial cells results in mucosal inflammation and oedema of the peribronchial region. Epithelial-cell necrosis and intraluminal plugs containing mucus and cellular debris cause a ball-valve type of airway obstruction leading to hyperinflation of distal airways and alveoli (bronchiolitis). Infections with RSV occur annually in the first few years of life, in many cases with the same strains of virus, and thus the protective immunological response is incomplete. The F and G surface glycoproteins are the only RSV proteins to induce protective neutralising antibodies in the host. Local secretory IgA is the primary humoral mediator of resistance in the upper respiratory tract; protection of the lower respiratory tract is mediated partly by serum IgG, concentrations of which are boosted with each reinfection.

Cellular immunity seems to play a prominent role in recovery from RSV infection. Thus, individuals with cellular immunodeficiency (inherited or acquired) have more severe and long-lasting RSV infections than normal individuals. After RSV infection, normal children show RSV-specific lymphocyte proliferation, which suggests T-cell stimulation,[15] and an RSV-specific cytotoxic T-lymphocyte response has been shown to decrease the severity of infection in adults, implicating cytotoxic T-lymphocyte function as integral to recovery from illness. Both CD4 and CD8 T-lymphocyte subsets are involved in terminating RSV replication during infection.[16] The same cytotoxic T-lymhocyte response may also exacerbate or augment the clinical disease associated with RSV infection. This hypothesis has been used to explain the more severe disease seen with the formalin-inactivated RSV vaccine.[17] The key to protection from lower-respiratory-tract infection may be the provision of viral neutralising (antibody and cellular) responses without an enhanced cytotoxic T-lymphocyte response.

Clinical manifestations and diagnosis

The most common infection caused by RSV is of the upper respiratory tract; such infections are characterised by rhinitis, cough, and sometimes fever. Acute otitis media occurs in up to a third of children with RSV illness; both RSV and bacterial pathogens have been isolated from the middle ears of children with RSV. Croup also occurs with RSV infection, but bronchiolitis and pneumonia are the commonest manifestations in children. Signs of upper-respiratory-tract involvement commonly precede those of the lower respiratory tract by a few days, and fever, when present, is usually low grade. Dyspnoea, lower chest-wall indrawing, and difficulty in feeding characterise lower-respiratory-tract infection. In bronchiolitis, wheeze may be audible with or without a stethoscope, and a prolonged expiratory phase and crackles are characteristic. Air trapping results in very fast breathing, a palpable liver and spleen, and a typical radiographic pattern of hyperinflation with diffuse interstitial markings and peribronchial thickening. Segmental atelectasis, which usually clears spontaneously, is often seen. Children with pneumonia, on the other hand, have fine crackles and a radiographic pattern of alveolar, segmental, or lobar consolidation. Although bacterial superinfection is rare in developed countries, it is more common in developing countries. This may partly explain the higher fatality rates seen in developing nations.

Panel 1: **Management of bronchiolitis**

Admission criteria

Severe disease (absolute indications)
- Poor/non-responsiveness
- Inability to feed
- Hypoxia unresponsive to low-flow (≤1 L/min) oxygen
- Apnoea

Moderate disease (observation/admission)
- Poor feeding, with signs of dehydration
- Oxygen requirement that cannot be managed at home

Lower threshold for admission
- Underlying cardiopulmonary disease
  - Bronchopulmonary dysplasia
  - Prematurity
  - Congenital heart disease with increased pulmonary blood flow/pulmonary hypertension
  - Other pre-existing disorders causing relative respiratory compromise—eg, hypoplastic lung, lobar emphysema, cystic fibrosis
- Immune compromise, including congenital disorders such as severe combined immunodeficiency syndrome, and severe immunosuppression associated with bone-marrow or solid-organ transplantation
- Suspected sepsis
- Age <6 weeks
- Malnutrition
- Uncertain home care

Discharge criteria

Adequate oral intake
Improved work of breathing
Maintenance of >90% oxygen saturation on room air or low-flow oxygen via nasal cannula
Advice on smoke avoidance given

Severe bronchiolitis may lead to acute respiratory failure associated with severe bronchospasm, moderate to severe hypoxia, and carbon dioxide retention. With lung-function tests,[18] two patterns of severe disease are seen: in about two-thirds of cases there is obstructive small airways disease (bronchiolitis), and in the remainder there is a restrictive pattern (pneumonia). Most of the latter cases meet the criteria for acute respiratory distress syndrome. They tend to be younger, have more predisposing underlying disease, and are ventilated for longer. In severely ill children, complications include pulmonary hypertension and cardiovascular compromise requiring inotropic support.[19]

Apnoea tends to occur in infants under 2 months of age with atelectasis on chest radiography,[20] and is common in those born prematurely. In cases of severe apnoea, mechanical ventilation may be necessary, despite the absence of respiratory failure. The pathophysiology of this manifestation is unknown, but postulated

mechanisms include the immaturity of the respiratory centre in the brain-stems of premature infants, and RSV-associated hypersensitivity of the laryngeal chemoreceptors.

The geographical variability in disease presentation in children remains largely unexplained, although a combination of genetic susceptibility and viral, environmental, and socioeconomic factors can be invoked. For example, the ratio of children with a primary presentation of bronchiolitis to those with a primary presentation of pneumonia is about three/one in Rochester, NY, USA,[21] and continental Europe,[22] but the exact opposite (one/three) in The Gambia.[23] These differences may be attributed to socioeconomic, nutritional, and environmental factors, but viral factors may also be important. In Rochester, more severe RSV lower-respiratory-tract infection was associated with the A subgroup,[21] whereas the B strain caused longer hospital stays in Gambian children.[23] Even in developed countries there are differences in severity. A comparison of children admitted to hospital in Rotterdam, the Netherlands, and Geneva, Switzerland,[24] showed significant differences in disease presentation (mean respiratory rate 51 *vs* 59/min; proportion with wheezing, 29 *vs* 66%; proportion with severe apnoea, 24 *vs* 2%; and rate of admission to the intensive-care unit, 28 *vs* 4% for the two sites, respectively). The cause of these differences may be genetic or environmental.

In adults, RSV can cause exacerbation of chronic obstructive lung disease, pneumonia, and bronchitis, and can result in death in elderly people. The development of these disorders may be related to lower concentrations of antibody in the serum; however, the pathophysiology has not been studied extensively.[25] RSV lower-respiratory-tract infection in adults presents as a wheezing illness in up to 90% of cases, with crackles and a pneumonic radiographic appearance in 40%. Wheezing is not merely a manifestation of infantile disease, but is almost a hallmark of infection of the lower respiratory tract.

Nasopharyngeal aspirates or washes are used routinely for diagnostic purposes. Such samples are tested for RSV antigens by immunofluorescence or ELISA, or for live RSV by means of a shell vial system or routine culture. The immunofluorescence assay is more sensitive than the ELISA, but requires trained personnel and a fluorescence microscope. ELISA takes 20 min, it can be done with little training, and it requires only a refrigerator for storage of reagents. In most situations, during the RSV season, children with bronchiolitis can be cohorted (grouped together and isolated from children without RSV infection) and managed without the need for a definitive diagnosis, since management is not RSV-specific. On the rare occasions when a definitive diagnosis is required (eg, when the use of ribavirin is being considered), a cost-effective strategy would be to carry out ELISAs, followed by cultures on ELISA-negative samples. In elderly patients, the duration of shedding of RSV is shorter than in younger patients, and mucosal surfaces are drier. Also, elderly patients dislike nasopharyngeal washes. Samples are therefore difficult to obtain in the elderly. Diagnosis by antigen detection is only 50% sensitive compared to that of seroconversion in this population.[10] Hence making a definitive diagnosis is difficult. Use of nasopharyngeal brushes, and detection of RSV genome using reverse transcription and PCR are alternative experimental options in the elderly.

Panel 2: **Treatment of bronchiolitis in inpatients**

Indicated
Oxygen (external delivery) for responsive hypoxia
Mechanical ventilation for:
  Respiratory failure (PaO_2 <7·3–5·3 kPa [<55–40 mm Hg] causing changes in mental status)
  Respiratory acidosis ($PaCO_2$ >6·0–6·7 kPa [>45–50 mm Hg], arterial pH ⩽7.32)
  Shock with impending arrest
  Recurrent apnoea
Upper-airway suctioning

Conditional
Nebulised salbutamol 0·5 mL
Racemic epinephrine 2·25% solution, 0·1 mL/kg (maximum 0·5 mL)
  Give if no response to salbutamol
  If responsive, repeat doses may be considered
Ribavirin in immunocompromised children or for impending respiratory failure in children with cardiopulmonary disease

Not indicated
Chest physiotherapy
Steroids
Antitussive agents
Antibiotics

Management

Infection of the lower respiratory tract with RSV is a self-limited condition in most cases. In normal infants with RSV lower-respiratory-tract infection, the inflammatory response has a greater effect on severity than does viral replication, and there is no unequivocal evidence to suggest that any antiviral or anti-inflammatory agents (alone or in combination) can reduce the length of RSV-related hospital stays in normal infants and young children. There is, therefore, much variation in the management of children with bronchiolitis. In multicentre or multinational studies, the only consistent finding is the variability in hospital practice.[22,26] With the advent of successful prophylactic measures, this variation is not merely of academic importance, but may have a substantial effect on the design and execution of studies involving many countries and continents. In most of Europe, infants admitted to hospital are discharged only when they have recovered completely. The median duration of stay is therefore 8–9 days.[22] By contrast, in North America, Australia, the UK, and Finland, the median duration is 4 days, and children may be sent home earlier on oxygen and other ancillary therapy.

There are no definitive guidelines or criteria on when to admit or discharge infants and children with bronchiolitis. The criteria used at the Denver Children's Hospital, CO, USA, are presented in panel 1. Since the measurement and definition of hypoxia varies according to altitude, instrument used, and physician's judgment, I have purposely not defined hypoxia. Likewise, the decision on whether to give oxygen and the definition of poor feeding will vary, but the guidelines should be applicable in many situations.

Panel 2 shows current guidelines for treatment of bronchiolitis. Hypoxia can be treated with oxygen via a nasal cannula (which is preferred to a nasal catheter, because it is associated with fewer complications, and to a head box, because it uses less oxygen). In developing countries, oxygen concentrations are cheap alternatives and could be considered when other sources are not available. Mechanical ventilation for children with respiratory failure, shock, or recurrent apnoea can lower mortality. In developed countries, about 2% of infants

	NIAID trial[5]			PREVENT trial[49]			Cardiac trial[50]			IMpact-RSV trial[6]		
	RSV Ig (n=81)	Control (n=89)	p	RSV Ig (n=250)	Control (n=260)	p	RSV Ig (n=202)	Control (n=214)	p	Palivizumab (n=1002)	Control (n=500)	p
RSV admissions	6	18	0·02	20	35	0·047	21	32	0·16	48	53	<0·001
Days in hospital	43	128	0·02	150	335	0·045	145	229	0·15	365	313	<0·001
RSV admissions <6 months of age	. .	. .	. .	13/184	16/185	0·17	10/96	20/82	0·01	. .	. .	. .
All LRI admissions	. .	. .	. .	41	69	0·005	34	57	0·02	220	80	0·008
Episodes of acute otitis media	5/33	19/41	0·03	68	112	0·01	. .	. .	. .	400	210	0·505

RSV Ig=RSV immune globulin. NIAID=National Institute of Allergy and Infectious Diseases

Prevention of RSV—results of efficacy trials

and children admitted to hospital with RSV require assisted ventilation.[22]

Inhaled salbutamol has been studied in many controlled trials, the results of which vary. A meta-analysis[27] showed that salbutamol induced a moderate short-term improvement in mild or moderate bronchiolitis, but that it had no effect on the risk of admission to hospital. Inhaled salbutamol seems to work in a small subgroup of patients (about a third) who respond to bronchodilators. Racemic epinephrine was shown to be superior to salbutamol in improving airway resistance and clinical scores,[28] and in decreasing the need for hospital admission in babies with bronchiolitis.[29] In patients admitted to hospital, salbutamol could be tried initially, and continued in those who respond; a trial of epinephrine might be justified in those who do not respond. Despite the lack of effect on absolute measures of outcome, bronchodilators provide symptomatic relief to a subset of hypoxic, uncomfortable, and distressed babies in whom its use is justified.

Since steroids alleviate wheezing in asthma, they might be expected to act similarly in bronchiolitis. However, several studies have shown that steroids have no beneficial effect on the first episode of wheezing associated with bronchiolitis, and that steroid therapy does not affect the clinical course of infants and children admitted to hospital with bronchiolitis.[30,31] Thus corticosteroids, alone or in combination with bronchodilators, have no place in the management of bronchiolitis in otherwise healthy unventilated patients. In infants and children with underlying cardiopulmonary diseases such as bronchopulmonary dysplasia and asthma, steroids are useful, perhaps because of the underlying reactive airway disease.

Ribavirin, a guanosine analogue, has been used for infants and children with RSV bronchiolitis since the mid 1980s,[32] but many studies have shown conflicting results. A meta-analysis of these studies in infants with RSV lower-respiratory-tract infection showed that there was no evidence of a significant benefit, and that studies lacked the power to detect reductions in mortality.[33] Four investigations attempted to assess the efficacy of ribavirin. In a study of 28 ventilated infants, the durations of ventilation, oxygenation, and hospital stay were significantly lower in the recipients of ribavirin than in the infants that received a water placebo.[34] By contrast, another study showed that in 22 patients who received it, the effect of ribavirin was no different from that seen in 19 patients who received a saline placebo.[35] A third study from 38 paediatric critical-care centres from the USA and Canada assessed mechanically ventilated children with RSV infection. Hospital stay was longer among infants in the ribavirin group (n=91) than among 132 infants who did not receive ribavirin ($p<0·01$); ribavirin did not lower mortality.[36] The choice of placebo, and the vehicle for administration of ribavirin in these studies has raised concerns that both water and saline cause bronchoconstriction. Controlled trials with a no-drug group are required to resolve this issue. In a cohort study of 750 non-ventilated children with RSV lower-respiratory-tract infection, the median length of RSV-attributable hospital stay was 2–3 days longer and the duration of hypoxia and the length of time spent in the intensive-care unit were significantly greater for ribavirin recipients.[37] These three studies raised further doubts about the clinical effectiveness of ribavirin in infants and children at risk of severe disease, or in ventilated children. In most centres, its use is now restricted to immunocompromised patients and to those who are severely ill. There have been no placebo-controlled trials of ribavirin in elderly people. However, a combination of ribavirin and intravenous immunoglobulin, given to nine adult bone-marrow-transplant recipients infected with RSV, resulted in the survival of seven of them (88%), compared with none of seven untreated patients (who all died of RSV infection).[38]

The severity of RSV bronchiolitis has been associated with low serum retinol concentrations, but trials in children in hospital with RSV bronchiolitis have shown that vitamin A supplementation has no beneficial effect.[39] Therapeutic trials of 1500 mg/kg RSV intravenous immune globulin[40] or 100 mg/kg inhaled immune globulin[41] for RSV lower-respiratory-tract infection have also shown no substantial beneficial effects.

In developed countries, the treatment of RSV lower-respiratory-tract infection is limited to symptomatic therapy in most patients; antiviral therapy is seemingly limited to life-threatening situations owing to its high cost and to the lack of consensus on its efficacy. In developing countries, oxygen is the main therapy (when available), and the only way to lower mortality is through prevention. In developing countries, bacterial superinfection may be difficult to rule out on clinical grounds, and antibiotics are commonly used in bronchiolitis.

Prevention

A vaccine for RSV is needed, and a protective live, attenuated vaccine administered at or around birth would be ideal. However, problems such as insufficient attenuation of the vaccine strain of RSV,[42] its thermolability, and the need to include A and B strains in each vaccine have hindered trials in infants under 3 months of age. Furthermore, since repeated infections with RSV occur in children, any vaccine will need to be more immunogenic than wild-type RSV itself. Several vaccine strains[42–44] are in early clinical trials or planned clinical trials. Current developments in attenuated vaccines have been reviewed by Dudas and Karron.[45]

Because of enhanced disease seen in naïve infants vaccinated with formalin-inactivated RSV vaccine in the 1960s, progress in the use of subunit RSV vaccines had been cautious. The F protein of RSV is immunogenic in seropositive healthy children,[46] those with bronchopulmonary dysplasia,[47] and those with cystic fibrosis.[48] Neutralising antibody is produced in vaccinated children, but most RSV disease occurs within the first 3 months of age, so the subunit vaccine may not be useful in this age-group. However, if used as a maternal immunogen during pregnancy, it might help to prevent disease in young infants born at term, though not in those born prematurely. High-risk children can be protected against severe disease by means of monthly administration of either a hyperimmune-globulin against RSV[5,49,50] or a humanised monoclonal antibody[6] during the RSV season. The first multicentre trial of RSV immune globulin[5] studied children with bronchopulmonary dysplasia, congenital heart disease, or prematurity (table). There were significantly fewer RSV hospital admissions (p=0·02) and fewer RSV hospital days (p=0·02) in the high-dose group than in the controls. Two other trials were done in children with bronchopulmonary dysplasia or prematurity[49] or with congenital heart disease.[50] In the first, there were 41% fewer cases of RSV lower-respiratory-tract infection (p=0·047) in the RSV-infused group than in controls, whereas in the second trial there were 31% fewer cases; this finding was not significant overall, but it was significant in those under 6 months of age (56% fewer cases; p=0·01). RSV immune globulin is also associated with fewer cases of otitis media, fewer episodes of otitis media per child,[49,51] and significant reductions in admissions for any lower-respiratory-tract infections. However, children with cyanotic heart disease were more likely to experience adverse events associated with cardiac surgery (p=0·01) if they received RSV immune globulin; this product should definitely not be used in children with cyanotic congenital heart disease.

Although monthly infusions with RSV immune globulin are effective, they are cumbersome to administer, and need to be repeated every season. A randomised trial of a humanised monoclonal antibody (palivizumab) was carried out at 139 centres in North America and the UK.[52] Palivizumab (15 mg/kg), given intramuscularly to children every month during the RSV season, resulted in significantly fewer (55%, p≤0·001) RSV-related hospital admissions than in the control group. In children with bronchopulmonary dysplasia, the rate of admission was 39% lower in the treated than in the control group (7·9 *vs* 12·8%); this difference was especially pronounced in the subgroup born preterm (reduction 79%; rates 1·8 *vs* 8·1%). Palivizumab was not effective in decreasing the incidence of acute otitis media or non-RSV respiratory admissions. The monoclonal antibody was safe and well tolerated: less than 3% of infants had a reaction at the site of injection.[6] Palivizumab was licensed in the USA in June, 1998, and has been available in Australia and most Latin American countries since April 1999. It is scheduled to become available in Europe from autumn 1999, and is currently under regulatory review in Canada, South Africa, and other countries (Laurence Welford, Abbott Laboratories, IL, USA; personal communication, July 14, 1999).

Two products are now available for use in prevention of severe RSV disease in children; however, the ease of use, and the slightly lower cost (in the USA) make the monoclonal product the first choice. Children with severe bronchopulmonary dysplasia requiring oxygen, and with an intravenous line in place, may benefit from RSV immune globulin because of the effect on non-RSV lower-respiratory-tract infection and otitis media. However, the length of infusions (4–6 h), and the need for a skilled nurse to start them add to the cost of the infusion and make palivizumab the choice in most other circumstances. The monoclonal antibody is as effective in children born at 32–35 weeks of gestation as in those born at less than 32 weeks;[6] however, since infants born at 32–35 weeks of gestation are a large subset, those with the strongest risk factors (smokers in the family, twins or higher-order multiples, crowding, and daycare attendance) would benefit more than those without risk factors. Until such time as vaccines become available for universal use (and are effective in normal infants under 3 months of age), passive prophylaxis is available, but its use will be restricted to children in developed countries at high risk of developing severe disease.

Acknowledgments

I thank James Todd, Robin Deterding, and Joan Bothner at the Children's Hospital and the University of Colorado Health Sciences Center for helpful discussions. Supported by grant number M01 RR0069, General Clinical Research Centers Program, National Centers for Research Resources, and grant number AI-37271, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA.

References

1 Morris JA Jr, Blunt RE, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. *Proc Soc Exp Biol Med* 1956; **92:** 544–50.

2 Chanock RM, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent: I, isolation, properties and characterization. *Am J Hyg* 1957; **66:** 281–90.

3 Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. *World Health Stat Q* 1992; **45:** 180–91.

4 Fulginiti VA, Eller JJ, Sieber OF, et al. Respiratory virus immunization: I, a field trial of two inactivated respiratory virus vaccines: an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. *Am J Epidemiol* 1969; **89:** 435–48.

5 Groothuis JR, Simoes EAF, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high risk infants and young children. *N Engl J Med* 1993; **329:** 1524–30.

6 The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998; **102:** 531–37.

7 Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child* 1986; **140:** 543–46.

8 Ukkonen P, Hovi T, Von Bonsdorff CH, et al. Age specific prevalence of complement fixing antibodies to sixteen viral antigens: a computer analysis of 58 500 patients covering a period of 8 years. *J Med Virol* 1984; **13:** 131–48.

9 Dowell SF, Anderson LJ, Gary HE Jr, et al. Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. *J Infect Dis* 1996; **174:** 456–62.

10 Falsey AR, Cunningham CK, Barker WH, et al. Respiratory syncytial virus and influenza A infections in the hospitalized elderly. *J Infect Dis* 1995; **172:** 389–94.

11 Selwyn BJ, on behalf of the Coordinated Data Group of BOSTID researchers. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. *Rev Infect Dis* 1990; **12** (suppl 8): S870–88.

12 Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. *Trop Med Int Health* 1998; **3:** 268–80.

13 Cherian T, Simoes EA, Steinhoff MC, et al. Bronchiolitis in tropical south India. *Am J Dis Child* 1990; **144:** 1026–30.

14 Collins PL, Hill MG, Camargo E, et al. Production of infectious human respiratory syncytial virus from cloned cDNA confirms an essential role for the transcription elongation factor from the 5' proximal open reading frame of the M2 mRNA in gene expression and provides a capability for vaccine development. *Proc Natl Acad Sci USA* 1995; **92:** 11563–67.
15 Cranage MP, Gardner PS. Systemic cell-mediated and antibody responses in infants with respiratory syncytial virus infections. *J Med Virol* 1980; **5:** 161–70.
16 Graham BS, Bunton LA, Wright PF, Karzon DT. Role of T-lymphocyte subsets in the pathogenesis of primary infection and rechallenge with respiratory syncytial virus in mice. *J Clin Invest* 1991; **88:** 1026–33.
17 Graham BS. Pathogenesis of respiratory syncytial virus vaccine-augmented pathology. *Am J Respir Crit Care Med* 1995; **152:** S63–66.
18 Hammer J, Numa A, Newth CJ. Acute respiratory distress syndrome caused by respiratory syncytial virus. *Pediatr Pulmonol* 1997; **23:** 176–83.
19 Kim KK, Frankel LR. The need for inotropic support in a subgroup of infants with severe life-threatening respiratory syncytial virus infection. *J Invest Med* 1997; **45:** 469–73.
20 Kneyber MC, Brandenburg AH, de Groot R, et al. Risk factors for respiratory syncytial virus associated apnoea. *Eur J Pediatr* 1998; **157:** 331–35.
21 Walsh EE, McConnochie KM, Long CE, Hall CB. Severity of respiratory syncytial virus infection is related to virus strain. *J Infect Dis* 1997; **175:** 814–20.
22 Behrendt CE, Decker MD, Burch DJ, Watson PH. International variation in the management of infants hospitalized with respiratory syncytial virus. International RSV Study Group. *Eur J Pediatr* 1998; **157:** 215–20.
23 Weber MW, Dackour R, Usen S, et al. The clinical spectrum of respiratory syncytial virus disease in The Gambia. *Pediatr Infect Dis J* 1998; **17:** 224–30.
24 Brandenburg AH, Jeannet PY, Steensel-Moll HA, et al. Local variability in respiratory syncytial virus disease severity. *Arch Dis Child* 1997; **77:** 410–14.
25 Falsey AR, Walsh EE. Relationship of serum antibody to risk of respiratory syncytial virus infection in elderly adults. *J Infect Dis* 1998; **177:** 463–66.
26 Wang EE, Law BJ, Boucher FD, et al. Pediatric Investigation Collaborative Network on Infections in Canada (PICNIC) study of admission and management variation in patients hospitalized with respiratory syncytial virus lower respiratory tract infection. *J Pediatr* 1996; **129:** 390–95.
27 Kellner JD, Ohlsson A, Gadomski AM, Wang EL. Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis. *Arch Pediatr Adolesc Med* 1996; **150:** 1166–72.
28 Sanchez I, De Koster J, Powell RE, et al. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. *J Pediatr* 1993; **122:** 145–51.
29 Menon K, Sutcliffe T, Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–07.
30 Roosevelt G, Sheehan K, Grupp-Phelan J, et al. Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet* 1996; **348:** 292–95.
31 De Boeck K, Van der Aa N, Van Lierde S, et al. Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone efficacy study. *J Pediatr* 1997; **131:** 919–21.
32 Hall CB, McBride JT, Walsh EE, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial virus infection. *N Engl J Med* 1983; **308:** 1443–47.
33 Randolph AG, Wang EEL. Ribavirin for respiratory syncytial virus lower respiratory tract infection. *Arch Pediatr Adolesc Med* 1996; **150:** 942–47.
34 Smith DW, Frankel LR, Mathers LH, et al. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med* 1991; **325:** 24–29.
35 Meert KL, Sarnaik AP, Gelmini MJ, Lich-Lai MW. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double blind, randomized clinical trial. *Crit Care Med* 1994; **22:** 566–72.
36 Moler FW, Steinhart CM, Ohmit SE, Stidham GL, for the Pediatric Critical Care Study Group. Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. *J Pediatr* 1996; **128:** 422–28.
37 Law B, Wang EEL, MacDonald N, et al. Does ribavirin impact on the hospital course of children with respiratory syncytial virus infection? An analysis using the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) RSV database. *Pediatrics* 1997; **99:** E7.
38 Whimbey E, Champlin RE, Englund JA, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. *Bone Marrow Transpl* 1995; **16:** 393–99.
39 Breese JS, Fischer M, Dowell SF, et al. Vitamin A therapy for children with respiratory syncytial virus infection: a multicenter trial in the United States. *Pediatr Infect Dis J* 1996; **15:** 777–82.
40 Rodriguez WJ, Gruber W, Groothuis JR, et al. Respiratory syncytial virus immune globulin treatment of RSV lower respiratory tract infection in previously healthy children. *Pediatrics* 1997; **100:** 937–42.
41 Rimensberger PC, Burek-Kozlowska A, Morell A, et al. Aerosolized immunoglobulin treatment of respiratory syncytial virus infection in infants. *Pediatr Infect Dis J* 1996; **15:** 209–16.
42 Karron RA, Wright PF, Crowe JE Jr, et al. Evaluation of two live, cold-passaged, temperature-sensitive respiratory syncytial virus vaccines in chimpanzees and in human adults, infants, and children. *J Infect Dis* 1997; **176:** 1428–36.
43 Crowe JE Jr, Bui PT, Firestone CY, et al. Live subgroup B respiratory syncytial virus vaccines that are attenuated, genetically stable, and immunogenic in rodents and nonhuman primates. *J Infect Dis* 1996; **173:** 829–39.
44 Pringle CR, Filipiuk AH, Robinson BS, et al. Immunogenicity and pathogenicity of a triple temperature sensitive modified respiratory syncytial virus in adult volunteers. *Vaccine* 1993; **11:** 473–78.
45 Dudas RA, Karron RA. Respiratory syncytial virus vaccines. *Clin Microbiol Rev* 1998; **11:** 430–39.
46 Tristram DA, Welliver RC, Mohar CK, et al. Immunogenicity and safety of respiratory syncytial virus subunit vaccine in seropositive children 18–36 months old. *J Infect Dis* 1993; **167:** 191–95.
47 Groothuis JR, King SJ, Hogerman DA, et al. Safety and immunogenicity of a purified F protein respiratory syncytial virus (PFP-2) vaccine in seropositive children with bronchopulmonary dysplasia. *J Infect Dis* 1998; **177:** 467–69.
48 Piedra PA, Grace S, Jewell A, et al. Sequential annual administration of purified fusion protein vaccine against respiratory syncytial virus in children with cystic fibrosis. *Pediatr Infect Dis J* 1998; **17:** 217–24.
49 The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics* 1997; **99:** 93–99.
50 Simoes EAF, Sondheimer HM, Top FH Jr, et al. Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. *J Pediatr* 1998; **133:** 492–99.
51 Simoes EAF, Groothuis JR, Tristam DA, et al. Respiratory syncytial virus immune globulin prevents acute otitis media in high-risk children. *J Pediatr* 1996; **129:** 214–19.
52 Johnson S, Oliver C, Prince G, et al. Development of a humanized monoclonal antibody (MED-493) with potent in vitro and in vivo activity against respiratory syncytial virus (RSV). *J Infect Dis* 1997; **176:** 1215–24.

Further references are listed on *The Lancet* website (http://www.thelancet.com)