Respiratory syncytial virus (RSV) infection causes respiratory illness in all ages, and is the leading cause of hospitalizations of infants and children around the world. Those at increased risk for severe disease include infants with congenital heart disease, premature infants, children with neuromuscular disease, airway abnormalities, underlying immunodeficiencies and the elderly. Attempts to develop a safe and effective vaccine have been unsuccessful thus far. However, significant progress has been achieved in the field of passive immunoprophylaxis for protection against RSV. This review will concentrate on the past, present and future history of RSV immunoprophylaxis with an emphasis on the role of polyclonal and monoclonal antibodies.

Introduction

Human respiratory syncytial virus (RSV) is the major viral cause of serious lower respiratory tract illness requiring hospitalization in infants and children [1]. Almost all infants become infected with RSV during the first 2 years of life, and infants younger than 6 months are at highest threat to acquire severe illness. A recent meta-analysis estimated that in 2005 ≥33.8 million episodes of RSV-associated acute lower respiratory infections occurred worldwide in children <5 years [2]. Mainly a paediatric pathogen, RSV has been shown to cause life-threatening disease in elderly patients, immunocompromised hosts and those with cardiopulmonary disease [3]. The groups of patients at especially increased risk for severe RSV disease include premature infants (<35 weeks gestational age), those with underlying chronic lung disease (CLD) of infancy, infants with haemodynamically significant congenital heart disease (CHD), and individuals with T-cell immunodeficiency disorders or neuromuscular disorders [4]. Several studies also suggest that severe RSV infection during childhood is associated with an increased risk for the development of asthma and allergies in adulthood [5,6].

Since it was first discovered in 1956 from chimpanzees suffering colds, scientists have worked to understand the pathogenesis of RSV infections and immunity to this infectious virus. Since infection can occur in the presence of circulating antibodies, re-infection is common in all age groups [7]. Although RSV infections occur despite maternally acquired antibodies to the virus, and antibody to the virus is not completely protective, anti-RSV antibodies are associated with some degree of protection against lower respiratory tract infection (LRTI) [8].

The basis of therapy for RSV infection is supportive care, mainly supplemental oxygen, mechanical ventilation and fluid replacement therapy as needed. Currently, only two US Food and Drug Administration (FDA)-approved drugs are available either for the specific prevention or treatment of RSV LRTI. Palivizumab is a monoclonal antibody for RSV prevention in high-risk infants, mainly those with CLD, CHD, and those born prematurely [9,10]. Aerosolized ribavirin, a broad spectrum antiviral agent, has been used as treatment for severe RSV infections. However, there is limited evidence of therapeutic benefit, and the possibility for teratogenic effects in health care workers as well as the high cost limit its use [11,12].

Classification and structure

RSV is a member of the Paramyxoviridae family, and more specifically the subfamily of Pneumovirinae, which also includes the recently discovered pediatric respiratory pathogen human metapneumovirus. RSV is an enveloped RNA virus with a non-segmented
single-stranded negative-sense genome. The RNA is associated with viral proteins, consisting of a nucleocapsid core that is packaged within a lipid envelope. Two glycosylated surface proteins, the F (fusion) and G protein are the major antigenic determinants of the virus. The F protein mediates viral penetration and initiates viral spread to adjacent uninfected cells, thus resulting in syncytia formation. The G protein mediates attachment of the virus to the host cells and is a major determinant of the host inflammatory and immune response. There are two major groups of RSV strains, A and B, which are differentiated primarily by variations within the G protein [1,13]. While both F and G are important targets for antibody response, F is considered to contain the major epitopes that stimulate virus neutralizing antibodies. The F glycoprotein exists only on the surface membrane and is highly conserved across both major antigenic subtypes of RSV [14]. Epidemiological studies have shown that strains of both groups circulate simultaneously in the population, but the proportions that are A and B vary, as well as do the subtypes. The antigenic differences that occur among these viruses may contribute to the ability of RSV to establish reinfections throughout life [15].

Respiratory syncytial virus immunoprophylaxis

History of antibody development

Despite decades of research, a vaccine for RSV is still not available. The importance of the immune system in RSV pathogenesis has been exemplified by the immune response to the Lot 100 formalin-inactivated RSV vaccine (conducted in 1966–1967) in children 2 months to 9 years of age [16,17]. RSV-naive RSV vaccine recipients who were exposed to RSV during the subsequent winter season experienced a significant increase in the frequency and severity of RSV LRTI, as well as increased hospitalization, and catastrophically, two vaccinated children died of severe RSV disease. At autopsy there was a severe pulmonary inflammatory infiltrate suggesting an immunopathologic disease [18,19]. Probable theories for mechanisms responsible for vaccine-enhanced disease include development of poorly neutralizing antibodies [20], immune complex mediated disease [21,22], biased/amplified T helper 2 response resulting in exaggerated pulmonary eosinophilic response [23] and a lack of cytotoxic CD8+ T helper 1 response [24,25].

In the 1980s, studies performed in cotton rats suggested that passive immunoprophylaxis might provide protection against RSV infection without resulting in enhanced disease [26]. Antibodies might play several roles in antiviral immunity (interference with pathogen binding, opsonization, neutralization and elimination), thus making them appealing therapeutic agents [27]. Polyclonal antibodies contain a mixed population of antibodies that target multiple viral epitopes, thus potentially overcoming the problem of antigenic escape [14].

Prince et al. [26] evaluated the quantitative aspects of passive immunity to RSV in the cotton rat model to determine the level of serum neutralizing antibodies needed to confer resistance. Infant cotton rats were inoculated with set dilutions of a single pool of convalescent sera from RSV-infected animals and then inoculated intranasally after 24 h with RSV. A serum neutralizing antibody titre of 1:100 or greater was associated with suppression of viral replication in the lower respiratory tract with almost complete resistance in the lungs at a serum neutralizing antibody titre of >1:380 [26]. Based on these observations, a subsequent clinical trial was designed to assess whether infants at risk for severe RSV disease might be protected by monthly infusions of standard intravenous immunoglobulin (IG-IV; 2 mg/kg) prior to RSV infection [28]. However, monthly IG-IV infusions (doses 500–750 mg/kg) administered to high-risk infants prior to and during the RSV season in two studies had no effect on RSV-related hospitalizations. Around the same time, Siber et al. [29] at the Massachusetts Public Health Laboratories (Boston, MA, USA) gauged the outcomes of low-dose and high-dose RSV-enriched immunoglobulin and standard immunoglobulin with regards to their antibody concentrations to RSV and protective activity against RSV challenge in cotton rats. In this animal model the serum neutralizing antibody titres needed to lower RSV concentration in the lungs by 99% was shown to be 1:390, whereas the titre to have a comparable effect in the nose was 1:3,500. Mean serum neutralizing titres after high-dose RSV IG-IV were approximately 10-fold higher than those after standard IG-IV.

Thus, standard immunoglobulin preparations had proven to be inadequate for protecting the lower respiratory tract against infection with RSV, mainly because the anti-RSV titres were too low [30]. Studies in animals as well as clinical observation of infants infected with RSV showed that RSV antibody titres between 1:200 and 1:400 are required to prevent LRTI [31,32]. Due to the large volume of fluid needed to obtain adequate neutralizing antibody titres from standard immunoglobulin, research shifted to developing an enriched hyperimmune RSV globulin with much higher RSV neutralizing ability.

Respiratory syncytial virus intravenous immunoglobulin

RSV immunoglobulin contains a sixfold higher concentration of RSV neutralizing antibodies than do standard immunoglobulin preparations [33]. In 1993, the National
Institute of Allergy and Infectious Disease (NIAID) funded a randomized controlled trial of two doses of RSV IG-IV (150 and 750 mg/kg) given monthly compared to no treatment to 249 high-risk children (CLD, CHD and/or prematurity) <2 years of age [31,34]. A statistically significant reduction in the incidence of RSV-related LRTI was seen in the high-dose RSV IG-IV groups (P=0.01), but not in the low-dose RSV IG-IV group. Although the total number of RSV infections (upper respiratory tract infections and LRTI) was not affected significantly, the severity of infections was reduced in the high-dose RSV IG-IV group [35].

Adverse events during the 580 infusions were generally mild and included fluid overload (n=5 children), oxygen desaturation (n=8), and fever (n=6). Six children died: three in the high-dose group, three in the low-dose group and none in the control group (P=0.15), but no death was attributed to the use of immune globulin or to illness caused by RSV. However, since five of the six deaths were in children with CHD, questions arose with respect to the safety of RSV IG-IV for use in children with CHD. Hence, with the FDA guidance, two further studies with RSV IG-IV were conducted in children with prematurity and CHD. The PREVENT trial was the critical trial that led to the licensure of RSV IG-IV and explicitly studied the effect of immunoprophylaxis on RSV hospitalizations in premature infants [36]. This study used a dose of RSV IG-IV (750 mg/kg) to 510 premature children (with or without CLD). The frequency of RSV hospitalizations versus placebo was reduced by 41% (8% versus 13.5%) and the number of total days of RSV hospitalization by 53% (P=0.005). In 1996, the Massachusetts Public Health Laboratories RSV IG-IV (RespiGAM™), marketed by Medimmune, comprised of high concentrations of purified, polyclonal, anti RSV immunoglobulin G (IgG) antibodies became the first FDA-approved drug for RSV disease prevention in premature infants with and without CLD. The frequency of RSV hospitalizations versus placebo was reduced by 41% (8% versus 13.5%) and the number of total days of RSV hospitalization by 53% (P=0.005). In 1996, the Massachusetts Public Health Laboratories RSV IG-IV (RespiGAM™), marketed by Medimmune, comprised of high concentrations of purified, polyclonal, anti RSV immunoglobulin G (IgG) antibodies became the first FDA-approved drug for RSV disease prevention in premature infants with and without CLD. Simões et al. [37] in 1998 conducted the Cardiac Trial which was a prospective, randomized controlled trial of monthly RSV-IG-IV compared to no treatment for prevention of hospitalization in children <48 months of age with CHD. This was conducted in 17 centres in the US over three RSV seasons. While there was no significant reduction in the number of RSV respiratory tract illnesses in children with CHD (25% versus 31% reduction in control [P=0.25]), 11 cases (10%) of unexpected cyanosis occurred among 111 children with right to left shunts or complex cardiac defects who were given RSV IG-IV, compared to one event in 83 children in the control group (P=0.03). This was ascribed to hynerviscosity caused by the high doses of monthly IG-IV that were administered. Taken together with the NIAID trial, the safety issues raised by both these studies suggested a causal role of high doses of IG-IV in those with cyanotic heart disease, and resulted in a contraindication for its use in these patients.

Three other benefits of the polyclonal antibody preparation were found in the NIAID trial. First, a reduction in incidence of acute otitis media was demonstrated in 109 children with CLD, CHD or prematurity receiving monthly high dose RSV IG-IV (750 mg/kg) compared with control subjects during the RSV season [38]. These outcomes seen with RSV IG-IV were ascribed to the polyclonal nature of the preparation and the presence of antibodies against other viral and bacterial pathogens [29]. Second, in addition to reducing RSV-specific LRTI and hospitalizations, reductions in all cause LRTI were seen in the NIAID and Cardiac trials [31,37]. Third, a follow-up study of the patients enrolled in the NIAID trial suggested a positive effect on long-term wheezing. This study evaluated pulmonary function and atopy in 13 children at high risk for respiratory disease 7 to 10 years after they had received immunoprophylaxis with RSV immune globulin [39]. When compared with 26 high-risk controls matched for age and gestational age, children who had received RSV immunoprophylaxis had better lung function and less atopy than the control group. This small study suggested that preventing or blunting RSV infections might decrease the risk for asthma later in life, but larger prospective studies of children at high risk for asthma are warranted to confirm this association. Besides the specific effect of reducing RSV LRTI, a non-specific effect of high-dose IG-IV on decreasing cytokine production and down-regulation of T-cell responses, may have contributed to the effect seen in this study.

RSV IG-IV was studied as a potential treatment option for young children at high risk for severe RSV LRTI [40] and in normal healthy children [41]. In these studies, infants and young children <2 years with CLD, CHD or prematurity who were hospitalized with LRTI [40] or children with no underlying conditions aged ≤2 years were enrolled in two separate double-blind trials. Patients were randomized in both trials to receive either 1,500 mg/kg RSV IG-IV or placebo in equal volumes. In the high risk group, 157 high-risk children were randomized, 54 in the RSV IG-IV group and 53 in the placebo group. In the healthy cohort, 101 patients were enrolled, 47 in the RSV IG-IV group and 54 in the placebo group. No significant differences were noted between treatment groups for any of the end points studied (duration of hospitalization, length of intensive care unit stay or time required on ventilator), in either study. However, in both studies, RSV IG-IV did achieve high neutralizing antibody titres and had significant reduction in the titre of RSV in the nasopharynx of RSV IG-IV treated patients. After these results, further RSV IG-IV treatment trials have not been performed.
Although RSV IG-IV offered marked advantages over standard IG-IV, it was found to have several shortcomings, including adverse effects in children with CHD, fluid overload, decreases in oxygen saturation or cyanosis, fever and need for intravenous access. Additionally, its administration delayed the vaccination schedule [14,31,36,37]. As RSV IG-IV could impede with the immune response to live virus vaccines, it was required to delay immunization with the measles/mumps/rubella vaccine until 9 months following the last dose of RSV IG-IV. RSV IG-IV was withdrawn by the manufacturers in March 2004 for reasons not related to safety concerns [42].

Currently, a new intravenous high-titre RSV immune globulin that has been isolated from healthy adults with high RSV titres, RI-001 (ADMA Biologicals) is being evaluated in Phase II clinical trials. This drug is being tested in the prevention of RSV from symptomatic upper respiratory tract infection to LRTI in immunocompromised patients [43].

Monoclonal antibodies
The finding that RSV IG-IV could protect the lower respiratory tract, without worsening disease once infected with wild-type virus, as had been seen with the formalin-inactivated vaccine, prompted development of monoclonal antibodies against RSV. Monoclonal anti-RSV antibodies target a single viral epitope. Advantages to monoclonal antibodies include virtually no risk of blood-borne pathogens, high titres of neutralizing antibody, and no risk of fluid overload. Almost simultaneously, three monoclonal antibodies were tested in humans – two administered systemically, including SB209763 developed by GlaxoSmithKline and palivizumab by Medimmune, and HNK20, an immunoglobulin A given daily intranasally from Oravax [44]. HNK20 was not developed further due to failure to produce favourable results [45].

Early studies of a monoclonal IgG antibody included several large, placebo-controlled trials involving two humanized monoclonal IgG antibodies (SB209763 and palivizumab) [9,45]. Both trials assessed monthly intramuscular injections of these monoclonal IgG antibody directed against F protein of RSV. With recombinant DNA technology, murine-derived sequences complementary to the A antigenic site of the RSV F protein were grafted into a human IgG frame; the result is an immunogenic and has broad reactivity towards both subtypes of RSV [46,47]. Both antibodies prevent RSV from fusing with the respiratory epithelial cell membrane, thereby preventing entry and replication [48]. The first study investigated the monoclonal antibody SB209763 and included 791 patients from 93 centres. Results did not show any difference between study subjects and controls with regards to hospitalizations [45]. This failure was attributed to lack of potency and insufficient dose. The dose that was studied in late-phase human trials included 15 mg/kg for palivizumab and 10 mg/kg for SB209673. These trials clearly showed a better clinical outcome with palivizumab [49].

Palivizumab: MEDI-493
Simultaneously with the SB209763 trial, a second more potent, humanized monoclonal antibody-palivizumab was evaluated. It is 50–100× more potent than RSV IG-IV in cotton rats. The IMpact-RSV study (1996–1997), a multicentre Phase III randomized double-blind placebo-controlled trial, demonstrated its safety and efficacy in children at high risk of serious RSV-associated LRTI [9]. Approximately 1,500 children with prematurity (35 weeks gestation or less) or bronchopulmonary dysplasia were randomized to receive either five injections of palivizumab (15 mg/kg) or placebo intramuscularly monthly during the 1996–1997 RSV season. There was a 55% relative reduction in RSV hospitalization in the palivizumab group (4.8% versus 10.6%). Children receiving palivizumab had fewer RSV hospital days, fewer days with increased supplemental oxygen and fewer days with severe lower respiratory tract illness (all P<0.001) and no differences in adverse events [9]. Trends towards decreased intensive care, mechanical ventilation, and length of stay were seen in the palivizumab group; however these results were not statistically significant. No effect was seen on mortality, however given the low case fatality rate of RSV LRTI in industrialized countries, it is unreasonable to expect to have seen one either in this trial or in subsequent observational studies. Most common reported adverse effects of palivizumab include local erythema, pain at the injection site, fever and rash (1–3% of patients). Subsequently, the US FDA approved palivizumab (Synagis™) for prevention of severe RSV disease in high-risk premature infants in 1998 and the European Commission for Proprietary Medicinal Products in August 1999. Currently, it is licensed in over 60 countries. The IMpact-RSV study also served as the basis for the usage guidelines of the American Academy of Pediatrics (Table 1) and the European consensus guidelines.

A subsequent randomized double-blind placebo-controlled trial examined the safety and efficacy of palivizumab in infants and children with significant CHD [10]. Children (n=1,287) received five monthly doses of palivizumab or placebo. In palivizumab recipients there were relative reductions of 45% (P=0.003) in RSV hospitalization rates, and 56% in total days of RSV hospitalization (P=0.03). Adverse events were similar between the two treatment groups. In both studies there was no significant decrease in the risk
of mechanical ventilation or mortality with the use of antibody prophylaxis.

Currently palivizumab is recommended to be given intramuscularly at a dose of 15 mg/kg once every 30 days in a series of 3–5 monthly intramuscular injections to infants and children during the RSV season. In the Northern Hemisphere and mainly the US, RSV circulates predominantly between November and March, followed by a peak in the Southern Hemisphere [50]. In equatorial countries, RSV tends to cause disease throughout the year, with increased activity associated with rainfall, and a decrease in temperature [51]. The half-life for palivizumab is between 18–21 days, therefore monthly dosing is sufficient to maintain its serum concentration at a protective level; although what that level is has not been definitively established in people [48]. Five monthly doses of palivizumab resulted in serum concentrations ≥30 μg/ml for >20 weeks in almost all patients in the IMPact-RSV trial [9]. A serum palivizumab concentration ≥30 μg/ml is the proposed serological correlate of protection, derived from the cotton rat model, in which this concentration results in a decrease in pulmonary RSV replication by >100-fold in the animal model [48].

Due to the high cost, guidelines limit its use to the highest risk groups of infants and children with the strongest evidence for value. The American Academy of Pediatrics has developed evidence-based guidelines for RSV immunoprophylaxis with palivizumab. Recently revised in 2009 (Table 1), it is currently recommended for infants and children born at <32 weeks gestation, and infants born <35 weeks gestation who are <6 months at the beginning of RSV season with one of two risk factors [childcare attendance and siblings <5 years of age] [32]. Palivizumab is also recommended for children ≤24 months with haemodynamically significant cyanotic, acyanotic, CHD or CLD necessitating medical therapy (supplemental oxygen, bronchodilator or diuretics or steroid therapy) within the last 6 months before start of the RSV season.

### Predictors of paediatric respiratory syncytial virus hospitalization

Given the high cost of RSV prophylaxis, identifying infants at high risk for RSV hospitalization would support the evidence base for recommendations for prophylaxis in this group. Two groups in Europe and Canada have developed models. The European model for predicting which premature infants 33 to 35 weeks gestational age were at highest risk for RSV hospitalization, used data from Spain and Germany [53] to develop the model then validated the scoring system using studies from France [54], Italy [55] and Denmark [56]. Using discriminant analysis, the model assigns individual weights to the seven most predictive factors: birth ±10 weeks from the start of the RSV season, birth weight, breast fed 2 or fewer months, number of siblings aged 2 years or older, number of family members with atopy, number of family members with wheezing and sex. The summary diagnostics of the initial model derived from the FLIP 2 study as well as the validations from Munich, France, Italy and Denmark are presented in Table 2.

Simultaneously, Sampalis et al. [57] also developed a scoring system, based on a logistic regression model using Canadian data. The risk score also included seven risk factors with a sensitivity of 68% and specificity of 72% for predicting RSV hospitalization. In a single centre study using this scoring tool, 346 infants in the low-risk group received no prophylaxis, while 78 of 84 moderate to high risk infants received prophylaxis [58]. None of the latter group was hospitalized, but 5/346 low-risk group infants were hospitalized. The overall rate of hospitalization was 5/430 (1.2%) compared to the rate of 66/1,758 (3.7%) in the previous multicentre study of non-prophylaxed Canadian infants, which formed the basis for the model [59]. Validation of the European Risk Factor Scoring Tool is being undertaken in Holland and other European countries.

Since earlier studies suggested that RSV hospitalization in infants with bronchopulmonary dysplasia can

### Table 1. 2009 Committee on Infectious Disease of the American Academy of Pediatrics Guidelines for Palivizumab

<table>
<thead>
<tr>
<th>Classification</th>
<th>2009 Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease</td>
<td>Consider as ≤24 months of age; five doses starting at the first month of RSV season (needing medical therapy within 6 months of start of RSV season)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Consider as ≤24 months of age; five doses (on medication for congestive heart failure, moderate-severe pulmonary hypertension, cyanotic heart disease)</td>
</tr>
<tr>
<td>≤28 Weeks gestational age</td>
<td>During first RSV season administer five doses (≤12 months age)</td>
</tr>
<tr>
<td>29–32 Weeks gestational age</td>
<td>29 Weeks 0 days through to 31 weeks 6 days; &lt;6 months of age at onset of RSV season; monthly dosing starting at first month of RSV season for total five doses</td>
</tr>
<tr>
<td>32–35 Weeks gestational age</td>
<td>32 Weeks 0 days through to 34 weeks 6 days; &lt;3 months of age at start of RSV season; three doses maximum (stop dosing at ≥90 days of age); one of two risk factors (childcare attendance and siblings &lt;5 years of age)</td>
</tr>
</tbody>
</table>
be prevented with RSV IG-IV, investigators in Europe and Canada conducted a prospective controlled double cohort observational study of the effects of RSV prophylaxis with palivizumab on the development of subsequent recurrent wheezing. In that study, of 32–35-week gestation infants, those who received palivizumab prophylaxis had 50% less subsequent wheezing episodes over several years than infants who did not receive prophylaxis [60]. In addition, subjects previously treated with palivizumab had considerably longer time to onset of recurrent wheezing and physician-diagnosed recurrent wheezing. The palivizumab-treated cohort did not have any patients who were hospitalized secondary to RSV. In this study, RSV prophylaxis with palivizumab in non-atopic premature children was shown to decrease by 80% the relative risk of recurrent wheezing, but did not show any effect in infants with an atopic family history [61]. This suggested that RSV predisposes to recurrent wheezing in an atopy-independent mechanism. Additionally, the results of this study suggest that palivizumab, by preventing LRTI with RSV, may play a role in protecting against recurrent wheezing in premature infants without CLD. However, these observations need to be studied further in a randomized controlled trial before palivizumab prophylaxis can be recommended for long-term benefit, in premature children. Such a trial is being conducted in the Netherlands.

Palivizumab has not been studied in randomized trials in immunocompromised patients, although children with severe immunodeficiencies may benefit from prophylaxis. Presently, both RSV IG-IV and palivizumab have not been shown to be effective treatment against RSV [52,62]. There have been two placebo-controlled randomized treatment trials with palivizumab. The first was performed in children <24 months of age who needed mechanical ventilation for RSV. A trial of single-dose palivizumab given intravenously showed a significant decrease in RSV titres in nasal secretions, but no effect on course of illness [63]. The difference in mortality rate was not significant. The second trial was conducted in previously healthy children <24 months of age admitted with RSV LRTI and given escalated doses of palivizumab (5–15 mg/kg). There was no statistical difference in mortality, days of hospitalization, need for mechanical ventilation or need for intensive care [64].

Most of the current economic analyses fail to show overall savings in health care spending because of the high cost if all high-risk children were to receive prophylaxis [62]. Many studies have examined short-term benefits such as reducing hospitalizations and associated costs, while fewer studies have examined long-term benefits such as quality-adjusted life years or life-years gained. In the IMpact-RSV trial, the number needed to treat with palivizumab to prevent one hospitalization among infants 32–35 weeks gestation without CLD was 15.9. Therefore, the cost of prophylaxis to prevent one RSV hospitalization in this age group was estimated to be approximately USD95,000 (USD6,000 cost of prophylaxis per infant per season ×15.9 [9,65]). These studies suggested that, irrespective of gestational age at birth, the added cost of prophylaxis with palivizumab was greater than savings from reduced hospitalizations. Direct cost analysis of palivizumab prophylaxis in the 32–35 week gestation age group in North Carolina’s Medicaid programme showed a huge cost increase for those infants treated with palivizumab compared with no prophylaxis [66]. Cost effectiveness of RSV prophylaxis are apt to be more favourable in populations with specific risk factors, including premature infants ≤32 weeks gestational age, and infants or children aged <2 years with CLD or CHD [67,68].

Motavizumab: MEDI-524

Given the lack of effective treatment, the large population of infants and children at risk for RSV, but who are not meeting guidelines for prophylaxis, as well as the lack of complete protection with palivizumab in certain patients, other monoclonal antibodies have been developed.

Motavizumab is a second generation recombinant humanized monoclonal IgG1 antibody, developed from palivizumab and directed to an epitope in the A antigenic site of the RSV F protein. It differs from palivizumab by

<table>
<thead>
<tr>
<th>Model</th>
<th>Participants, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
<th>Diagnostic accuracy, %</th>
<th>Reference</th>
</tr>
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<td>550</td>
<td>0.71</td>
<td>0.72</td>
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<td>83</td>
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<td>FLIP Final 8-variable model</td>
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<td>0.72</td>
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<td>84</td>
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<td>[53]</td>
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<tr>
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<td>0.72</td>
<td>13</td>
<td>99</td>
<td>73</td>
<td>[53]</td>
</tr>
<tr>
<td>French 7-variable model</td>
<td>231</td>
<td>0.51</td>
<td>0.68</td>
<td>44</td>
<td>73</td>
<td>63</td>
<td>[54]</td>
</tr>
<tr>
<td>Italian 6-variable model</td>
<td>56</td>
<td>0.83</td>
<td>0.70</td>
<td>75</td>
<td>79</td>
<td>77</td>
<td>[55]</td>
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<tr>
<td>Danish 7-variable model</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>66</td>
<td>[56]</td>
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*Missing data not available in reference.*
only 13 amino acids residues and has approximately 70-fold higher affinity for the RSV F glycoprotein and 20-fold greater neutralizing capacity [69]. In the cotton rat model, it was found to reduce nasal and lung RSV titres 25-and 100-fold, respectively [69]. In addition, motavizumab inhibits RSV replication in the upper respiratory tract of cotton rats, whereas palivizumab does not [69]. Finally, motavizumab is fully humanized, whereas the palivizumab antibody frame still contains a few murine-derived sequences [47].

After an initial Phase II trial of motavizumab involving >200 infants [70], a large Phase III non-inferiority study comparing motavizumab to palivizumab in preventing RSV in high risk children was carried out. In this randomized double-blind active control study, an estimated 6,600 preterm infants with CLD were given either 15 mg/kg monthly intramuscular motavizumab or palivizumab injections and followed for 5 months over the RSV season (2004–2006) at 347 sites in 24 countries. Motavizumab was shown to be non-inferior to palivizumab in reducing RSV hospitalizations, the primary end point. However motavizumab was superior to palivizumab in reducing the secondary end point of RSV-specific outpatient LRTI visits (50% relative reduction; \( P=0.005 \)) [71]. In addition, there was a significant increase in cutaneous reactions with motavizumab (7.2% versus 5.1% with palivizumab; \( P<0.001 \)), that correlated with the development of anti-motavizumab antibodies. These included reports of rash as well as events that were consistent with cutaneous hypersensitivity reactions.

A Phase III randomized double-blind placebo-controlled trial, which evaluated the safety, efficacy and tolerability of motavizumab in healthy Native American Indian infants in the southwestern region of the United States [72] demonstrated an 83% reduction in RSV hospitalizations compared to placebo (8.3 versus 1.4%) and a 71% reduction in outpatient acute LRT infections (9.5 versus 2.8%) [72,73].

In a third randomized multinational double-blind study by Feltes et al. [74], motavizumab and palivizumab were shown to have similar safety profiles in children with haemodynamically significant CHD, with the exception of skin events, which were increased in motavizumab recipients. A statistically significant higher incidence of skin events considered to be related to study medication was experienced by motavizumab recipients compared with palivizumab recipients (motavizumab 10 [1.6%] versus palivizumab 2 [0.3%]; \( P=0.038 \)). There were no differences in the rates of RSV hospitalizations and RSV LRTI between treatment groups (\( P>0.05 \)).

In June 2010, the Advisory Committee to the US FDA voted not to recommend approval of motavizumab secondary to questionable evidence of additional benefit in comparison to palivizumab and rare, but significant increase in adverse skin events from the previous studies [47]. The FDA has requested additional safety and efficacy data on motavizumab before considering it for approval [75], but Medimmune is not pursuing further these indications for its use.

A Phase I treatment trial studied the safety, tolerability, serum and nasal concentrations of motavizumab in healthy children hospitalized with RSV. Patients were randomized to receive a single dose-escalated intravenous infusion of motavizumab (3, 15 and 30 mg/kg) or placebo [76]. There was no improvement in lower respiratory disease scores between motavizumab and placebo recipients. However, by study day 7, the percentage of patients with detectable viral RNA from nasal secretions was significantly lower in motavizumab recipients compared with placebo (57% versus 93%; \( P<0.05 \)) [76].

See Table 3 for a description of the efficacy of the different immunoprophylaxis agents studied thus far.

**MEDI-557**

MEDI-557 is a third-generation humanized monoclonal antibody developed from motavizumab by introducing amino acid substitutions in the IgG1 Fc fragment [77]. Both palivizumab and motavizumab have a half-life of about 3 weeks, and need to be given via monthly intramuscular injections throughout the RSV season. Studies have shown that the neonatal Fc receptor plays an important part in prolonging and maintaining the serum IgG level [78]. Studies in cynomolgus monkeys regarding pharmacokinetics of this molecule showed a fourfold increase in serum half-life and bioavailability compared to motavizumab [79]. Currently a Phase I randomized double-blind dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of this drug has just been completed in healthy adults [80]. If successful, MEDI-557 could represent an advance in the prevention of RSV by improving efficacy and compliance, as well as opportunity for less frequent dosing, less costs and potential application to adult populations [81].

**Future prospects**

Given the prevalence of RSV and the constraints of currently available treatment, prevention is critical in diminishing the global burden observed with this disease. Monoclonal antibody prophylaxis might be beneficial in children apart from the high risk groups (including children with CLD, neuromuscular disease, immunocompromised states, and even healthy children with risk factors). However the high expense of these drugs excludes its use in these populations.
Dedicated and intense research has generated several promising therapeutic agents and vaccines that are currently in various stages of development and clinical trials. Emerging approaches to RSV treatment include small interfering RNA particles that interfere with viral protein synthesis, anti-RSV agents with greater potency than ribavirin and development of focal immunomodulatory agents that may target aspects of the inflammatory response seen in RSV disease [75]. However, RSV infection may be difficult to control by a single drug or monoclonal antibody. While we await a vaccine, combined therapy may be needed for better efficacy.

**Disclosure statement**

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References


