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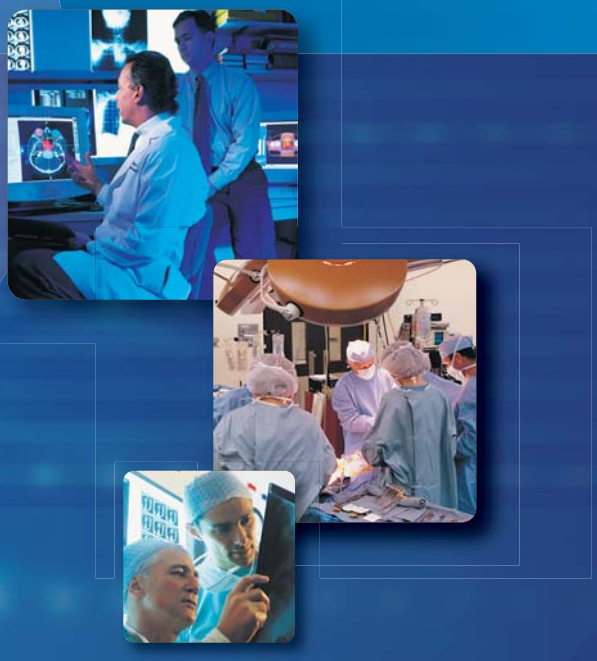
Palivizumab Prophylaxis against Respiratory Syncytial Virus



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Canadian Agency for Drugs and Technologies in Heath

Palivizumab Prophylaxis against Respiratory Syncytial Virus

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March 2007

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure they were addressed appropriately.

Reviewers

CADTH takes sole responsibility for the final form and content of this bulletin. The statements and conclusions in this bulletin are those of CADTH and not of the reviewers.

Reviewers who agreed to be acknowledged include:

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Conflict of Interest

Dr. Langley has received research funding from the manufacturer of MedImmune and has participated in the efficacy studies.

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ABBREVIATIONS

ARR	absolute risk reduction
BPD	bronchopulmonary dysplasia
CA	cost analysis
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CHD	congenital heart disease
CPS	Canadian Paediatric Society
CUA	cost-utility analysis
GA	gestational age
ICER	incremental cost-effectiveness ratio
NNT	number needed to treat
QALY	quality-adjusted life year
RSV	respiratory syncytial virus

Title: Palivizumab prophylaxis for respiratory syncytial virus

Date: November 17, 2006

1 CONTEXT AND POLICY ISSUES

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections in infants.[1,2] By the age of two years, most children have been infected with RSV, resulting in hospitalization of 1% to 2% of these children.[1-3] Premature infants (<35 weeks), infants with bronchopulmonary dysplasia (BPD), and infants with congenital heart disease (CHD) have an increased risk of morbidity and mortality due to RSV infection.[1] Children who are hospitalized with RSV infection have a mortality rate of about 1%; this is increased in children with cardiac or lung disease.[3]

Palivizumab is a humanized monoclonal antibody used for the prevention of serious lower respiratory tract infections caused by RSV.[1,3] It is produced by recombinant technology and targets the F-protein of RSV. In Canada, palivizumab is indicated for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease.[4] Treatment with palivizumab is funded through Canadian Blood Services for these patients.[5]

The Canadian Paediatric Society (CPS) recommends that priority for palivizumab prophylaxis be given to patients who are at the highest risk of developing severe RSV infection, i.e., children ≤24 months old with BPD who required oxygen treatment within the six months preceding the RSV season; and infants born at ≤32 weeks' gestation who are ≤6 months old (with or without BPD) at the start of the RSV season.[6] The CPS also recommends the use of palivizumab in children with hemodynamically significant CHD who are <2 years old.[7] British Columbia provincial guidelines from the 2005-2006 RSV season recommend that palivizumab be used for children with BPD who required medical treatment six months before the beginning of RSV season and who are <2 years old, and for children who are <6 months old at the beginning of RSV season who were born <29 weeks gestation; and that infants <6 months old at the beginning of RSV season who were born after 29 to 35 weeks gestation be evaluated for eligibility for palivizumab.[8]

Palivizumab was approved for use in Canada in 2002. It has been available since 1999 as part of Health Canada's Therapeutic Products Special Access Program.[3] Palivizumab is administered monthly during RSV season as an intramuscular injection, at a dose of 15 mg/kg of body weight.[3] The first dose is given before the start of RSV season, which in Canada typically occurs between November and January, and lasts about five months.[3] The cost in Canada of one dose of palivizumab is approximately $1,000; a season would cost an average of $5,000 per patient.[7,9] Canadian Blood Services and Hema Québec provide funding of palivizumab for the specified groups of patients.[6] Because of differences in the guidelines regarding who should receive palivizumab prophylaxis, it is uncertain in which patient populations drug funding is optimal.

2 RESEARCH QUESTIONS

What is the evidence for the cost and clinical effectiveness of palivizumab prophylaxis versus no prophylaxis against lower respiratory tract disease caused by RSV in pediatric patients who are at high risk for RSV? In particular:

- premature infants (29 to 32 weeks gestational age and 33 to 35 weeks gestational age)
- infants with BPD
- children with hemodynamically significant CHD.

3 METHODS

A literature search was conducted on key health technology assessment sources, including bibliographic databases such as BIOSIS Previews®, EMBASE®, MEDLINE®, which were searched through the Ovid interface. We searched PubMed and The Cochrane Library (Issue 3, 2006). Grey literature was obtained by searching

the web sites of international health technology agencies, including the University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, HEED, and NICE. Retrieval was limited by human population, and English or French language. No date restrictions were applied. Studies investigating the clinical effectiveness of palivizumab were limited to systematic reviews, health technology assessments, and randomized controlled trials (RCTs). Any type of cost analysis or economic evaluation, including cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis, was considered.

4 SUMMARY OF FINDINGS

4.1 Clinical effectiveness

The IMPact-RSV study group conducted a multi-centre RCT in 1998 with 1,502 children.[10] Children who were born at ≤35 weeks gestational age and were ≤6 months old at the beginning of RSV season, or children who were diagnosed with BPD and were ≤2 years old at the beginning of RSV season were included in the study. An interactive voice randomization system was used to randomize the children to receive 15 mg/kg palivizumab (1,002 children) or placebo (500 children) every 30 days during RSV season (five months for a total of five doses). The length to follow-up was 150 days from randomization.[10] The primary endpoint was hospitalization for respiratory illness and a positive test for RSV, or for children who were already hospitalized, a positive RSV test with a lower respiratory tract illness score of 3 (moderate).[10]

Palivizumab administration resulted in a 55% reduction in RSV-associated hospitalization (4.8% versus 10.6%, p=0.0004).[10] The absolute risk reduction (ARR) was 5.8%, and the number needed to treat (NNT) was 17.2. Palivizumab also resulted in a 78% reduction (p <0.001) in RSV-associated hospitalization in premature children with no BPD, whereas a 39% reduction (p=0.038) was seen in children with BPD. Infants born at <32 weeks gestational age who received palivizumab had a 47% reduction in RSV-associated hospitalization (p=0.003), whereas infants born between 32 and 35 weeks gestational age who received palivizumab had a reduction in RSV-associated hospitalization of 80% (p=0.002). There was a reduction in the number of days of RSV-associated hospitalization (36.4 days versus 62.6 days, p<0.001), days with oxygen use (30.3 days versus 50.6 days, p<0.001) and days with moderate or severe lower respiratory tract infection (29.6 days versus 47.4 days, p <0.001) in those who received palivizumab.[10] Adverse events related to the treatment were similar in the placebo and palivizumab groups (10% in the placebo group and 11% in the palivizumab group). Adverse events included injection site reactions, fever, and rash; and there were no statistically significant differences between the placebo and palivizumab groups for adverse events. Five deaths were reported in the placebo group (1%) and four deaths in the palivizumab group (0.4%), although no deaths were found to be related to palivizumab. Among participants, 99% completed the study, and 94% of the placebo group and 92% of the palivizumab group received all scheduled injections.[10] A follow-up study found that palivizumab was safe and well tolerated in premature children or children with BPD who received it for two seasons.[11]

A multi-centre RCT by Feltes *et al*., investigating palivizumab in children with hemodynamically significant CHD, was published in the US.[12] Children (n=1,287) ≤24 months of age were randomized by an interactive voice response system to receive palivizumab (639 children) or placebo (648 children) once a month for five months. The length to follow-up was 150 days from randomization.[12] A 45% reduction in RSV-associated hospitalization in the palivizumab group was observed (9.7% placebo, 5.3% palivizumab, p=0.003). The ARR was 4.4%, and the NNT was 22.7. A significant reduction in the number of days of RSV-associated hospitalization (129 days per 100 children versus 57.4 days per 100 children, p=0.003) and days with oxygen use (101.5 days per 100 children versus 27.9 days per 100 children, p=0.014) was found with palivizumab prophylaxis.[12] Adverse events were similar in both groups, and included injection site reactions, fever, conjunctivitis, arrhythmia, and cyanosis. There were two deaths in the palivizumab group and four deaths in the placebo

group due to RSV. All injections were received by 93% of the palivizumab group and by 91.8% of the placebo group; and 95% of both groups completed the study.[12]

The two RCTs had differences in study population characteristics that are expected, because one study focused on premature children. The gender ratios were similar in both trials, but gestational age and weight at study entry were less in the IMPact trial. More children in the Feltes study were in daycare (10.6% to 11.9% compared with 6.7% to 6.8%).

Systematic reviews have assessed the clinical effectiveness of palivizumab. A systematic review conducted by Simpson and Burls in the UK used data from the IMPact RSV study.[1] Their conclusions were that palivizumab is effective in preventing RSV-caused lower respiratory tract infections and hospitalization in infants at high risk.[1] A US systematic review and one from the UK reached similar conclusions, stating that palivizumab is effective for the prevention of RSV infection in infants and children who are at high risk. These studies also used data from the IMPact RSV study.[13,14]

4.2 Cost studies and economic evaluations of palivizumab

A systematic review conducted in 2002 reviewed economic analyses (Table 1).[15] The results of the studies included in the systematic review are variable. The cost data sources used and the economic outcome measure may be the reasons why the results are varied. Cost-effectiveness ratios are affected by the differences in rates and costs of RSV hospitalizations. Some studies used the efficacies from the subgroups, whereas others used overall efficacies. The authors found that palivizumab was not cost-effective when used in all infants for whom it is recommended, and suggest that only infants with a very high risk of RSV should be administered palivizumab because of the high costs, although the authors did not define their qualifications for very high-risk infants.[15]

Data sources for the studies in Table 1 included literature on the RSV infection incidence,[16] the IMPact trial,[16-18] and other studies on RSV prophylaxis.[17,18] The Lofland *et al*. study used a range of costs of palivizumab, a range of RSV infection rates, and variable costs for hospitalization. Therefore, the results reported in Table 1 reflect these ranges. Limitations to the Lofland *et al.* study include the fact that data from the IMPact trial were used, and the resources used may be different in a non-study population. The costs of adverse events were not considered in this study, and cost data were taken from urban academic medical centres and may not be representative.[16] The children with BPD could not be identified in the Joffe *et al*. study, and therefore, the cost-effectiveness for these children could not be determined. The subgroups of infants would have differences in RSV hospitalizations and efficacy of palivizumab, which would affect the accuracy of the results.[17]

A sensitivity analysis that was done in the Lofland *et al.* study found that the number of health care visits (emergency department, physician's office, home health care) did not affect the model. Hospitalization was the major factor that affected costs.[16] Joffe *et al*. conducted a sensitivity analysis on various factors. The efficacy of palivizumab at preventing hospitalization affected the model, the acquisition cost, and the assumptions about hospitalization likelihood.[17] Costs were affected by size and demographic characteristics of the population in the Marchetti study.[18] Sensitivity analysis was not done for the Stevens, Thomas, or Numa studies.[19-21]

A UK systematic review conducted in 2001 discussed the cost-effectiveness of palivizumab, and concluded that it is not cost-effective when used in all infants for which it is indicated.[1] If it is used only in infants who are at the highest risk (infants with BPD requiring oxygen therapy at home are reported to be the group at highest risk), then it may be cost-effective; this approach is the current practice in the UK.[1] Another more recent systematic review concluded that it has not been shown whether palivizumab is cost-effective for any of the risk groups in the UK.[14] A US systematic review suggested that the cost-effectiveness of palivizumab has not been demonstrated because of the variation in results

from the cost-effectiveness analyses.[13] The studies considered in the US systematic review are variable. The cost per hospitalization varies, the cost of palivizumab varies, and different perspectives are used (society, payer, and provider) to estimate costs. The authors suggest that better estimates are required for the costs of hospitalization and costs of administration to determine the cost-effectiveness of palivizumab.[13]

Table 2 summarizes the data from palivizumab economic evaluations in a US setting that were conducted after the systematic review discussed in Table 1 was published. A 2006 US study used a hypothetical cohort of infants born at 26 to 32 weeks, without BPD, and performed a cost-benefit and a cost-utility analysis using data from the IMPact trial.[22] In the cost-benefit analysis, the costs of palivizumab prophylaxis were found to be higher than the cost of no prophylaxis for all gestational ages. The incremental cost-effectiveness ratios (ICERs) for all gestational ages were found to be higher than $200,000 per quality-adjusted life year (QALY) in the cost-effectiveness analysis, with a maximum of $1,855,000 for a gestational age of 32 weeks. Sensitivity analyses found that the model was sensitive to alterations in the quality of life with asthma and to changes in the cost of palivizumab. A limitation to this study is that equal costs for hospitalization and length of hospitalization were assumed for the different gestational ages.[22]

A hypothetical cohort of pediatric patients with CHD was used to compare the cost savings and cost utility of palivizumab to no prophylaxis.[23] This study reported the costs of palivizumab to per life-year gained was found to be $100,338, be $6,160 per patient per RSV season. The cost and the cost per QALY was $114,337.[23] A sensitivity analysis was conducted in this study, and a profound effect on costs per QALY was found when the hospital mortality rate was altered.[23] A cost-effectiveness study found the cost per life year saved for palivizumab was $66,200 from a societal perspective and $66,400 from a payer perspective.[24]

A retrospective cohort study determined the costs and benefits of RSV prophylaxis in infants at high risk and found a cost-benefit ratio of 1:1.15, indicating the benefits of prophylaxis with palivizumab exceeded the costs.[25] The drug costs were found to be $3,461, whereas the hospitalization costs were $3,985. The hospitalization costs were determined by a 23.4% lower chance of hospitalization (average cost of RSV hospitalization=$17,031; 23.4% of $17,031=$3,985). A limitation of this study is that it compared two RSV seasons; the control group was taken from the 1994-1995 RSV season, whereas the palivizumab group was taken from the 1998-1999 RSV season. A sensitivity analysis revealed a change to the cost benefit with an altered success rate of palivizumab (1:0.85 to 1:0.99) and with altered hospitalization rates (1:1.43). The costs of hospitalization were derived from the 1994-1995 season and adjusted to reflect the costs in 1999. This study found that the cost of palivizumab is $12,000 per hospitalization averted.[25] Another cost-benefit analysis found drug costs to be $4,687. This study used subjects from the 1999-2000 RSV season.[26] RSV treatment caused hospitalization costs to be reduced by $703, resulting in a cost-benefit ratio of 6.67:1 ($4,687/$703) indicating that the costs of palivizumab treatment exceeded the benefits.[26] It is unclear why these two cost-benefit analyses have such different results, and it is unknown how the cost savings of $703 was calculated in the latter study.

4.3 Additional studies

Additional economic evaluations in non-US settings and cost analyses have been identified. A cost-effectiveness study from Australia found that palivizumab is not cost-effective for the prevention of RSV infection.[27] The cost to prevent one hospital admission was A$88,549 for infants born at <2,500 g (NNT=14), A$73,294 for indigenous infants born at <2,500 g (NNT=13), A$69,861 for infants born <2,500 g with siblings (NNT=11), and A$98,818 for infants born at <33 weeks gestational age (NNT=16).[27] A New Zealand study investigated the costs per hospitalization averted with palivizumab prophylaxis in infants born at <32 weeks gestational age.[28] This study found that the mean cost per hospitalization avoided was NZ$60,000 and ranged from NZ$29,000 for infants born at <28 weeks on oxygen at home to NZ$166,700 for infants born at 29 to 31 weeks gestational age with BPD.[28]

Table 1: Characteristics of studies included in systematic review evaluating cost-effectiveness of palivizumab in high-risk infants and children[14]

Authors	Country	Study Design	Funding Source	Population	Model	Perspective	Main Study Results and Conclusions
Lofland *et al*.[16]	US	CEA	MedImmune Inc, Gaithersburg MD	Infants GA <32 weeks, infants between 32 and 35 week GA	decision-analytic model	provider	incremental cost per RSV infection avoided: $2,702 to $79,706 (for range of RSV infection rates from 5% to 38%); authors conclude that data can be used by physicians to decide whether palivizumab is cost-effective
Stevens *et al*.[19]	US	CEA	not specified	GA ≤26 weeks, GA 27 to 29 weeks, GA 29 to 30 weeks, GA 31 to 32 weeks	not specified	provider	incremental cost per hospitalization prevented by GA at ≤26 weeks: $18,183; 27 to 28 weeks: $24,113; >28 to 30 weeks: $36,878; >30 to 32 weeks: $72,712; authors conclude that net cost of care for study population would be increased by palivizumab
Thomas *et al*.[21]	UK	CA	not specified	children with BPD (using oxygen or stopped oxygen in previous 6 months; GA <29 weeks and <1 year; GA 29 to 32 weeks and <6 months of age	not specified	provider	incremental costs: £3,816 (children with BPD on oxygen), £117,672 (children with BPD no longer on oxygen), £29,652 (infants <29 weeks GA), £173,204 (infants 29 to 32 weeks GA)
Numa *et al*.[20]	Australia	CBA	not specified	children <2 years	not specified	provider	cost per hospital day saved: A$27,786 to A$55,572
Joffe *et al*.[17]	US	CEA	not specified	premature infants	decision-analytic model	societal	$12,000 per hospitalization avoided, $33,000 per life-year saved; authors conclude that RSV prophylaxis should be limited to infants with BPD or premature infants with other multiple risk factors
Marchetti *et al*.[18]	US	CA	MedImmune Inc, Gaithersburg MD	all infants at risk for lower respiratory tract infection	decision-analytic model	payer	incremental charges of ≤$3,459 per infant to savings of $39,107 per infant

CEA=cost-effectiveness analysis; CBA=cost-benefit analysis; CA= cost analysis; GA=gestational age; BPD=bronchopulmonary dysplasia; RSV= respiratory syncytial virus.

Table 2: Characteristics of economic evaluations of palivizumab in infants and children at high risk							
Authors	**Country**	**Study Design**	**Funding Source**	**Population**	**Model**	**Perspective**	**Main Study Results and Conclusions**
ElHassan *et al*.[22]	US	CBA CUA	not specified	hypothetical cohort of infants born at 26 to 32 weeks gestation	decision-analytic model	societal	incremental cost per QALY>$200,000 (675,780 to 1,855,000 for different gestational ages); authors suggest stricter guidelines be used for palivizumab
Yount *et al*.[23]	US	CUA	not specified	hypothetical cohort of 10,000 CHD pediatric patients	decision-analytic model	societal	Incremental cost per QALY=$114,337; relative to benefits, costs of palivizumab are high; use of palivizumab should be evaluated further
Strutton *et al*.[24]	US	CEA	MedImmune Inc.	infants 32 to ≤28 weeks GA, ≤12 months at beginning of RSV season; infants born between 29 and 32 weeks GA who are ≤6 months at beginning of RSV season; infants born between 32 and 35 weeks GA with additional risk factors	not specified	societal and payer	cost per life-year gained: $66,200 (societal), $66,400 (payer)
Shireman *et al*.[26]	US	CBA	Kansas Department of Social and Rehabilitation services, and University of Kansas School of Pharmacy	premature children or children with chronic lung disease; <10 months old at beginning of RSV season	not specified	payer	cost-benefit ratio 6.67:1 (drug costs $4,687, hospitalization costs decreased by $703)
Schrand *et al*.[25]	US	CBA	not specified	infants <2 years old, at high risk for RSV infection	decision-analytic model	UIHC pharmacy and therapeutics committee	cost-benefit ratio 1:1.15 indicating benefit of prophylaxis (drug cost $3,461; hospitalization costs decreased by $3,985)

CBA=cost-benefit analysis; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; CA=cost analysis; QALY=quality-adjusted life year; GA=gestational age; ICER=incremental cost-effectiveness ratio; UIHC=University of Iowa Hospitals and Clinics.

A Canadian study analyzed the costs associated with palivizumab use and hospitalization for the 1998-1999 RSV season.[29] It was estimated that palivizumab would have cost $753,300 for the 159 infants in the study, if they had received the drug ($1,012.50 per dose, calculated for various number of doses for the 159 patients). Twenty-one of these infants were hospitalized costing $168,888. If palivizumab was used in these infants, it is estimated that $121,147 of the

hospitalization costs could have been averted, and therefore the net cost of palivizumab prophylaxis would have been $632,153.[29] A US study assessed the costs due to palivizumab treatment.[30] The cost of palivizumab to prevent one hospitalization was found to be $102,073.

The palivizumab prophylaxis group costs were $5,117 per person, and the control group costs were $371 per person.[30]

5 LIMITATIONS

Only two RCTs were found that examined the efficacy of palivizumab prophylaxis, and RSV-associated hospitalization was the primary outcome measured in these trials. Although the IMPact trial tried to group the infants by gestational age, the <32 week gestational age group was not separated to identify the reduction in hospitalization of infants born from 29 to 32 weeks versus infants born at <29 weeks gestational age. Neither RCT reported criteria for standardization of hospitalization. The economic evaluations are from the US, the UK and Australia; no Canadian evaluations (i.e., those that examine costs and consequences) were identified. It is difficult to determine whether the economic results can be translated to a Canadian setting because of differences in the health care systems. Furthermore, the number of economic analyses was limited, and the results were inconsistent, making it difficult to ascertain the true cost-effectiveness of palivizumab.

6 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Palivizumab has been shown toreduce RSV-associated hospitalization compared with placebo, as determined by one RCT of premature children (<32 weeks gestational age, and 32 to 35 weeks gestational age), some of whom had bronchopulmonary dysplasia. A second RCT demonstrated reductions in RSV-associated hospitalization in children with hemodynamically significant congenital heart disease. These are the only RCTs examining the efficacy of palivizumab in these groups of children.

No Canadian economic evaluations of palivizumab were found, although the costs of palivizumab were reported in a Canadian study. A recent review states that the cost-effectiveness of palivizumab is difficult to assess because of the lack of high quality cost-benefit analyses.[31] Societal costs such as the loss of parent's wages were not always considered in economic analyses, and therefore, a true determination of cost-effectiveness is challenging.[32]

The CPS recommends that palivizumab be considered for children at the highest risk, such as children with BPD, and children born at ≤32 weeks gestation.[6] Children born between 32 weeks and 35 weeks gestational age may not be at high risk for RSV hospitalization, and considering the costs of palivizumab, these infants should be assessed for other risk factors because palivizumab may be unnecessary.[6] Palivizumab is an expensive option, but it has been shown to be effective for certain groups of infants and children.

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