

## REVIEW

## Palivizumab for preterm infants. Is it worth it?

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Respiratory syncytial virus infection is an important cause of morbidity. Although palivizumab prophylaxis is widely used, it is uncertain whether the cost is justified. A systematic review was therefore performed of the safety, efficacy, and the likely cost effectiveness of prophylaxis for preterm infants in the United Kingdom using a standard search strategy. The only randomised controlled trial identified showed a reduction in hospital admission but no benefit on more serious outcomes. None of the United Kingdom cost studies showed economic benefit for palivizumab prophylaxis. New treatments are rarely cost effective, and, in the absence of a comprehensive economic assessment, continued use for high risk infants may appear justified.

Palivizumab is a recombinant, humanised, mouse monoclonal antibody to the RSV fusion or F protein which is given intramuscularly. It carries no risk of viral transmission, will not interfere with routine vaccination schedules, and shortages are theoretically avoidable.<sup>6</sup> It is currently licensed in the United Kingdom for the “prevention of serious lower respiratory-tract infection caused by RSV requiring hospitalisation in children born at 35 weeks gestation or less and who are less than 6 months old at the onset of RSV season, or in children less than 2 years old who have received treatment for bronchopulmonary dysplasia within the last 6 months”.<sup>7</sup> It has become widely used but is costly, and a number of studies have been performed in an attempt to identify which infants may benefit from palivizumab, and what this may cost. The aim of this article is to review the evidence base for the efficacy and safety of palivizumab in preterm infants and its cost effectiveness in a United Kingdom health setting.

Respiratory syncytial virus (RSV) infection is the most common cause of lower respiratory tract disease in infants and young children in the United Kingdom. Most infants develop an upper respiratory tract infection but in some (12–40% according to different studies), a lower respiratory tract infection takes place.<sup>1</sup> Most infants present with bronchiolitis, and in about 1–2% this leads to hospital admission because of poor feeding, oxygen requirement, or even apnoea in the very young. RSV accounts for about 70% of cases of bronchiolitis,<sup>2</sup> with other cases caused by other respiratory viruses such as adenovirus and parainfluenza virus. RSV related rates of hospital admission have tripled in the last 25 years,<sup>3</sup> but most of these infants follow a largely uncomplicated course. Infants who were born preterm or those with chronic lung disease (CLD) are at particular risk of requiring ventilatory support, and for all infants there is a very small risk of death.

Many treatments have been tried but few, if any, show any benefit, and we are left with supportive, yet effective treatments: oxygen, management of poor feeding, and good nursing care. Development of an effective vaccine has been fraught with difficulty, and there appears little prospect of a vaccine becoming available in the next decade.<sup>4</sup> Pooled hyperimmune RSV intravenous immunoglobulin reduces admission rates for RSV bronchiolitis in preterm infants.<sup>5</sup> However, this treatment requires monthly intravenous injections of a large volume, carries the risk of transmission of blood borne pathogens, may disrupt the routine vaccination schedule, and availability may be affected by donor shortage. It is not currently licensed in the United Kingdom.

## METHODS

We identified relevant articles by searching Medline, Embase, Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials), Cinahl, AMED, BNI, and DH-Data up to and including August 2004. We used the basic search terms “RSV”, “respiratory syncytial virus”, “bronchiolitis”, “palivizumab”, “Synagis” and “Medi-493”. Depending on which database was reviewed, these articles were then combined with the terms “costs”, “cost effectiveness”, “cost benefit analysis”, “health care costs”, “cost analysis”, “economic analyses”, “drug costs”, “cost of illness”, “cost minimisation analysis”, “hospital cost” and “efficacy”. Two investigators (NDE, CH) independently searched the databases, conducting an unlimited search initially and then by applying the limits “infants”, “randomised controlled trials”, “clinical trials”, “meta-analysis” and “practice guidelines”. Publications relevant to the review’s aim were identified by title and abstract and, if necessary, by the full text article. A common list of publications identified by the two independent searches were then independently assessed and selected for inclusion.

Inclusion criteria for reviewing efficacy were randomised controlled trials and clinical trials in the first place, and then other literature such as post-marketing studies. We identified a number of studies and systematic reviews addressing costs, but we did not identify any high quality

**Abbreviations:** BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; RSV, respiratory syncytial virus

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cost-benefit analyses according to accepted criteria.<sup>8</sup> As the principal healthcare costs involved in treating RSV infection are due to hospital admission, and because this in turn is highly dependent on the healthcare system, we elected to restrict our systematic review of cost effectiveness to studies using United Kingdom hospital costs, admission rates, or incidence. As admission rates for bronchiolitis are likely to change over time, we restricted our review to studies in which data had been collected in the last 10 years. In a group meeting, a final list of publications for inclusion was agreed. All included literature was studied in full text. We did not include abstracts presented at scientific meetings or any other study where it had not been published in full. The reference lists of the included articles were then hand searched for additional relevant literature.

## EFFICACY OF PALIVIZUMAB

The IMpact RSV study<sup>9</sup> is the only randomised controlled trial of palivizumab in preterm infants<sup>10</sup> and provides the only data on which a grade A recommendation can be made. The only other controlled trial of palivizumab is in children with heart disease.<sup>11</sup> The IMpact RSV study was a multicentre, randomised, double blind, placebo controlled trial, and enrolled 1502 children who were born preterm  $\leq 35$  weeks, or had CLD and were  $\leq 24$  months of age. Participants received either five intramuscular injections of 15 mg/kg palivizumab or an equivalent volume of placebo every 30 days. This was a well conducted trial with a high completion rate (99%). The trial showed a highly significant 55% relative reduction in RSV associated hospital admission between the palivizumab (4.8%) and placebo (10.6%) groups ( $p = 0.00004$ ). Secondary outcomes showed that those in the palivizumab group spent significantly fewer days in hospital, fewer days with increased oxygen, and fewer days with a worse illness score. There was no significant difference between the groups with respect to days spent in intensive care or length of ventilation.

We identified a number of studies reviewing admission rates after the introduction of palivizumab in 1998, and present data from two large studies. During the first season in 1998–1999, a review of 1839 patients from nine centres in the United States showed an overall admission rate of 2.3% (4% for infants with CLD, 2.1% for premature infants without CLD).<sup>12</sup> These rates were similar to those of the IMpact study. A large 18 centre Canadian study during 1999–2000 enrolled 480 infants (preterm  $\leq 32$  weeks gestation and  $< 6$  months old or bronchopulmonary dysplasia (BPD)  $< 2$  years old), and planned to give five monthly injections of palivizumab.<sup>13</sup> Five or more injections were given to 193 subjects. The estimated rate of hospital admission overall was 2.4%: highest in those with BPD (6.0%), and lowest in infants with prematurity alone (1.6% overall, 2.2% in infants born at  $\leq 28$  weeks gestation, 1.3% in infants born at 29–32 weeks gestation).

## SAFETY

Preceding the IMpact RSV Study, palivizumab (then called MEDI-493) was assessed for its safety, tolerance, and pharmacokinetics by two stage I/II, multicentre, randomised, double blind, placebo controlled, dose escalation trials.<sup>14 15</sup> Sixty two<sup>14</sup> and sixty five<sup>15</sup> infants either born prematurely ( $\leq 35$  weeks) or having BPD  $\leq 24$  months of age were included. The design of the two studies differed mainly by route of administration (intravenous<sup>14</sup> or intramuscular<sup>15</sup>) and dose of MEDI-493 (3, 10, or 15 mg<sup>14</sup> and 5, 10, or 15 mg<sup>15</sup>). The incidence of reported adverse events in the intravenous study<sup>14</sup> was 15% and 33% in the placebo and treatment groups respectively, with fever, pneumonia, and infusion site infiltration as the most common. In the other

study,<sup>15</sup> only three patients experienced mild adverse effects attributed to the study drug.

The IMpact RSV study did not identify significant differences in rates of adverse events between the palivizumab and placebo groups.<sup>9</sup> Most were mild local reactions at the injection site, or rash and fever. Discontinuation for adverse effects of palivizumab was rare (0.3%).

A number of post-marketing studies have also examined the safety of palivizumab. The occurrence of antibodies to palivizumab was examined in infants receiving palivizumab for a first or second season. No first ( $n = 71$ ) or second ( $n = 63$ ) season subjects experienced a significant antibody response, and serious adverse events were mostly respiratory and considered unrelated to palivizumab.<sup>16</sup> Previous studies had also found immune reactions to be rare events.<sup>9 11 13</sup> A phase III and IV, multicentre, single arm, open label study on 565 infants in the northern hemisphere collected additional data on safety.<sup>17</sup> In 6.9% of infants, adverse events were reported that were attributed to the drug; most were mild.

## COST EFFECTIVENESS

We did not identify any studies examining longer term respiratory outcome in infants receiving palivizumab. There is some evidence that RSV infection is a risk factor for future physician diagnosed asthma,<sup>18</sup> although others have suggested that infants who are predisposed to develop allergy are at increased risk of developing bronchiolitis.<sup>19</sup> There are therefore no data that allow us to examine the true individual or societal costs associated with RSV, and it is not therefore possible to model the true impact of palivizumab. Costs associated with palivizumab prophylaxis are orders of magnitude higher than for existing vaccine prophylaxis, but it is very difficult to compare cost effectiveness in this way.<sup>20</sup> Mortality from RSV is low even in high risk groups, so analysis of the benefits from the perspective of quality adjusted life years is unhelpful, and placing a cost value on the pain and suffering of affected infants and the loss of earnings and psychological stress to parents is virtually impossible.<sup>20</sup>

The IMpact study<sup>9</sup> is the only prospective controlled trial that provides data from which cost effectiveness can be assessed, but no short or long term economic or cost-benefit analyses have been published from this cohort. We identified seven studies that examined costs associated with RSV in a United Kingdom healthcare setting and reviewed them according to accepted criteria.<sup>8</sup> Five of these were studies that included an examination of costs from hospital admission in retrospective cohorts and calculated the likely cost effectiveness of palivizumab,<sup>3 21–24</sup> although one of these<sup>3</sup> was primarily designed to address a broader question on RSV infection in infancy. One study was a systematic review that also calculated cost effectiveness using United Kingdom incidence data,<sup>6</sup> and one was a study that compared use of healthcare resources and costs among infants either admitted or not admitted with RSV.<sup>25</sup>

All studies clearly stated the study question, and the six studies determining cost effectiveness all used data from the IMpact study. There was reasonable population homogeneity, although two studies restricted the inclusion criteria to  $< 32$  weeks.<sup>23 25</sup> Three were based in a single tertiary care setting,<sup>22–24</sup> one was based on data from four tertiary units,<sup>25</sup> and the remaining three were population (health authority) based. None of the studies were comprehensive economic analyses, and all noted that the true societal costs could not be addressed. One study included the costs of hospital admission, drugs, general practitioner and outpatient consultation, and domiciliary visits in an attempt to provide a more comprehensive assessment of costs associated with RSV, but this was the only study that did not perform an analysis to determine the potential cost effectiveness of palivizumab.<sup>25</sup>

The conclusions of the cost effectiveness studies were all similar. They showed that the costs of prophylaxis were far in excess of any likely savings achieved by decreasing hospital admission rates, but most felt that the broader costs associated with RSV infection (burden to the family and society, potential long term impact, etc) justified prophylaxis in high risk groups—for example, those with CLD. Only the systematic review attempted to perform a true sensitivity analysis: they calculated the incremental cost effectiveness ratio from the health provider (NHS) perspective to be £43 000 per hospital admission prevented, and £96 000 per life year gained when used for all children who met the licensed indication.<sup>6</sup> However, the assumptions on which mortality reduction is based have been previously questioned and it is possible there is no life-years saving.<sup>26</sup> Sensitivity analysis determined that the probability of hospital admission would have to be  $\geq 31\%$  for it to be a cost effective alternative to no prophylaxis.

## DISCUSSION

This review shows that palivizumab prophylaxis is safe and efficacious, but cost effectiveness has yet to be demonstrated in a United Kingdom healthcare setting. In the only United Kingdom study performing a sensitivity analysis, the probability of hospital admission was determined to be  $\geq 31\%$  for it to be a cost effective alternative to no prophylaxis.<sup>6</sup> There are likely to be few populations with such high admission rates.

There is only one high quality randomised controlled trial addressing the issue in preterm infants. Data from the recently published study in children with haemodynamically significant congenital heart disease shows a similar relative reduction in hospital admission, but no significant benefit in reduction of admission to intensive care or ventilation, and does not further clarify the role of palivizumab in preterm infants with or without CLD.<sup>11</sup>

Studies in the United States have used decision analysis to compare the societal cost effectiveness—that is, both medical and work loss costs—of palivizumab in a hypothetical cohort using data from a large network.<sup>27</sup> Sensitivity analysis showed that even for the highest risk infants ( $\leq 32$  weeks gestation and still in oxygen at 28 postnatal days) palivizumab was projected to cost US\$12 000 (UK£ 6725) per hospital admission averted. Infants lost to follow up and under-representation of lower socioeconomic groups may limit the generalisability of this study to United Kingdom populations.<sup>21</sup>

Similar costs to those in the United Kingdom have been determined by studies in New Zealand,<sup>28</sup> and other centres in the United States.<sup>29</sup> The lowest costs in an analysis of non-United Kingdom published studies that we identified came from a German study, where costs of €6639 (UK£4400) to prevent hospital admission in male infants with CLD,

discharged between October and December, and with siblings in a day care group were determined.<sup>30</sup> A number of other non-United Kingdom cost studies have been included in a systematic review<sup>31</sup> that highlights the divergent results and differing methodologies and assumptions. As the drug costs are so high, changing the estimated infant weights has a major effect on cost, but over half of the studies did not explicitly state the infant weights.<sup>31</sup> In the United Kingdom studies reviewed in this paper, the actual weights were not used, but assumptions about whether a 50 mg or 100 mg vial would be needed. Few other studies have performed a sensitivity analysis that examined the effects of changing dose or number of doses, although in one, opting to give four doses instead of the recommended five, resulted in a 20% reduction in drug costs but still provided coverage for 94% of hospital admissions.<sup>29</sup>

Hospital admission was chosen as one of the primary outcomes in the original trial<sup>9</sup> and is also the major cost to the healthcare system of RSV infection,<sup>27</sup> but to base cost effectiveness analysis on this alone ignores the numerous other direct—for example, outpatient visits, etc—and indirect—for example, parental time lost from work—costs. The thresholds for admission to hospital and criteria for ventilation are also likely to differ between populations, and this was one of the main reasons for restricting our systematic review of cost effectiveness to United Kingdom studies. Deshpande *et al*<sup>7</sup> noted that RSV associated rates of admission to intensive care units in Shropshire in the United Kingdom were less than a quarter, and ventilation rates less than a half, of those of comparable North American populations. Greater cost effectiveness may be demonstrated in regions covering remote areas where hospital admission presents a greater burden for the family.<sup>24</sup>

It is unclear whether all hospital admissions reported in the IMPact and other studies were due to RSV illness or whether in some cases simply associated with RSV infection. Most studies have focused on the prevention of the initial admission episode, thereby ignoring the subsequent re-admissions that may be more common in the next two years in preterm infants,<sup>25 32</sup> but there is, as yet, no evidence that allows us to determine whether palivizumab prophylaxis will have any effect on this.<sup>33</sup>

Clinicians need to be aware of how the data are presented. The IMPact study presents benefit in terms of a 55% relative risk reduction, but if this is presented as just a 5.8% absolute risk reduction (95% confidence interval 3% to 9%) and a number needed to treat of 17, the effect may appear less impressive.<sup>34</sup> Most initial research involving expensive drugs is funded, at least in part, by the manufacturers, and many of the studies considered here received some funding from the manufacturers or an affiliated company.<sup>9 11–17 20 25 28 30</sup> In the systematic review of Kamal-Bahl *et al*,<sup>31</sup> an association between manufacturer funding and study results of favourable cost effectiveness was identified,<sup>31</sup> but only one of the seven United Kingdom RSV related cost studies we identified received any funding from the manufacturer.<sup>25</sup>

The American Academy of Pediatrics (AAP) has advocated the use of palivizumab in preterm infants.<sup>35</sup> There are no comparable national guidelines in the United Kingdom, but the use of palivizumab has been recommended by the Joint Committee on Vaccination and Immunisation.<sup>36</sup> The latter recommendations preceded the recently published randomised controlled trial on the use of palivizumab in infants with congenital heart disease.<sup>11</sup>

## CONCLUSIONS

There are major difficulties in setting the criteria to determine which infants (if any) should receive palivizumab. Analysis is

### Box 1: key messages from this review

- Palivizumab prophylaxis is safe and efficacious in preterm infants
- The primary demonstrated benefit is a reduction in rates of hospital admission
- Studies have not shown a reduction in requirement for ventilation or mortality, or any longer term benefit
- Cost effectiveness has yet to be shown for any risk group in a United Kingdom healthcare setting
- There are no published studies that comprehensively assess the healthcare costs and benefits of palivizumab prophylaxis

**Box 2: indications and/or recommendations for the use of palivizumab in preterm infants****British National Formulary (2004)**

- Preterm infants  $\leq 35$  weeks gestation and  $< 6$  months old at start of RSV season, or those less than 2 years old with BPD in last six months

**Joint Committee on Vaccination and Immunisation (2002)**

- Infants  $< 2$  years of age with CLD on home oxygen, or babies with rare conditions—for example, severe multiple congenital abnormalities including congenital lung disease

**Recommendations of this review**

- Preterm infants with ongoing significant CLD requiring home oxygen or those with haemodynamically significant cardiac disease

complicated by apparently discrepant responses with more vulnerable infants—that is, those with CLD—achieving less risk reduction of hospital admission with RSV than others (ex-preterm infants without CLD).<sup>9</sup> The overall burden of RSV disease for the health provider is enormous, and prophylaxis with palivizumab will have little overall impact on most admissions as most of these are term babies. Palivizumab is currently too highly priced for the outcomes it prevents when given according to current licensed indications, but reduction in the unit price would have a dramatic effect on cost effectiveness.<sup>3 7 23 26</sup> Nevertheless, it remains an efficacious and safe treatment with the potential to save lives and prevent tremendous morbidity. New treatments for existing diseases are rarely cost neutral. When considered from a broad societal perspective,<sup>5</sup> we consider its use for the most vulnerable infants—that is, those with active CLD—to be justified (see box 2), but its use should be part of a package of care that includes minimising viral exposure by careful hand washing and avoiding potentially infectious contacts. We accept that there is not a strong evidence base for our opinion. Palivizumab will have virtually no impact on the pattern of RSV related admissions seen by paediatricians—only 2% of admission are for those with CLD.<sup>3</sup> It is currently far too expensive to justify its use in preterm infants without additional risk factors.

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