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Passive immunisation against respiratory syncytial virus: a cost-effectiveness analysis

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ABSTRACT

Aim The cost-effectiveness of passive immunisation against respiratory syncytial virus (RSV) in the Netherlands was studied by assessing incremental costs to prevent one hospitalisation in high-risk children using a novel individualised monthly approach.

Methods Cost-effectiveness analysis was performed by combining estimates of individual hospitalisation costs and monthly hospitalisation risks, with immunisation costs, parental costs and efficacy of passive immunisation for a reference case with the highest hospitalisation risks and costs of hospitalisation during the RSV season (male, gestational age ≤ 28 weeks, birth weight ≤ 2500 g, having bronchopulmonary dysplasia (BPD), aged 0 months at the beginning of the season (October)). Various sensitivity analyses and a cost-neutrality analysis were performed.

Results Cost-effectiveness of passive immunisation varied widely by child characteristics and seasonal month. For the reference case it was most cost effective in December at €13 190 per hospitalisation averted. Cost-effectiveness was most sensitive to changes in hospitalisation risk. For the reference case, cost neutrality was reached in December, if acquisition costs of passive immunisation decreased from €930 to €375, monthly hospitalisation risk increased from 7.6% to 17%, or hospitalisation costs increased from €10 250 to €23 250 per hospitalisation. Even if passive immunisation prevented all hospitalisations, costs per hospitalisation averted in December would still exceed €2645.

Conclusions Although cost-effectiveness of passive immunisation varied strongly by child characteristics and seasonal month, incremental costs per hospitalisation averted were always high. A restrictive immunisation policy only immunising children with BPD in high-risk months is therefore recommended. The costs of passive immunisation would have to be considerably reduced to achieve cost-effectiveness.

INTRODUCTION

Respiratory syncytial virus (RSV) is a major cause of respiratory morbidity in infants. In general, hospitalisation risks are low (0.5–2% of all infected infants). Higher hospitalisation risks are reported for children with prematurity, bronchopulmonary dysplasia (BPD), low birth weight, congenital heart disease, male gender and young age. In addition, the seasonal pattern of RSV infections greatly influences the monthly hospitalisation risk.¹ In the absence of a safe and efficacious vaccine, passive immunisation against RSV is an alternative to prevent RSV hospitalisation. Palivizumab (Synagis), a humanised monoclonal antibody to RSV, is safe

What is already known on this topic

- ▶ Passive immunisation against respiratory syncytial virus (RSV) is safe, moderately effective and expensive.
- ▶ There is dispute about the cost-effectiveness of passive immunisation against RSV.

What this study adds

- ▶ Detailed cost-effectiveness data on passive immunisation against RSV in premature infants at different postnatal ages are provided.
- ▶ A novel individualised monthly approach facilitating more targeted use of passive immunisation against RSV is described.
- ▶ Since costs per hospitalisation averted are always high, passive immunisation against RSV is only indicated for infants with BPD in high risk months.

and effective in preventing RSV hospitalisation in children with prematurity, BPD and haemodynamically significant congenital heart disease.²⁻³ Palivizumab reduces the overall incidence of hospitalisation in children with prematurity and BPD by 55%.²

However, the costs of palivizumab are considerable. Treatment of one child during a complete RSV season costs approximately €3550 (mean weight 5 kg, five injections, no wastage).⁴ These costs, combined with the moderate efficacy and the generally low incidence of RSV hospitalisation, have led to a discussion concerning the cost-effectiveness of passive immunisation.⁵⁻¹⁰ Several economic analyses of palivizumab for prevention of RSV hospitalisation have been published.^{4 11-24} The results of these analyses show a wide variability that can partly be explained by differences in study methods (study perspective, source of cost data, economic outcome measure and setting) and assumptions (reduction of hospitalisation risk, reduction of developing asthma, hospitalisation risk without prophylaxis, hospitalisation costs, drug dosing). Six of these studies were analysed in a systemic review that identified several methodological shortcomings.²⁵ In one study cost per life-year saved was calculated on the basis of unproven assumptions of reduced mortality,⁴ two did not express the results in cost-effectiveness

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terms,^{11 14} five did not mention the year in which costs were measured,^{11 12 14 15 20} and three did not perform a sensitivity analysis.^{12 14 20} In addition, an association between manufacturer sponsored studies and a favourable outcome of study results was found.^{25 26}

The aim of the present cost-effectiveness analysis of passive immunisation against RSV was to assess the incremental costs to prevent one hospitalisation for severe RSV disease in high-risk children from a societal perspective. Since palivizumab must be administered on a monthly basis, we analysed its cost-effectiveness per month using individualised risk and cost estimates to determine more detailed indications for passive immunisation.

METHODS

We analysed data from a retrospective cohort of children born in the southwest of the Netherlands. This mixed urban-rural region has a population of approximately 4 million people and an annual birth cohort of approximately 47 000 children.²⁷ All 29 hospitals in the region with a paediatric ward participated in this study. Two of these hospitals have paediatric intensive care facilities. We assumed that all children living within the study region are referred to these hospitals. None of the children received passive immunisation against RSV.¹

We defined BPD as the need for supplemental oxygen on day 28 after birth or at a postconceptional age of 36 weeks, in the presence of typical abnormalities on the chest x-ray.^{28 29} We corrected age (being the time the child is exposed to RSV in the community) of children born prior to 38 weeks of gestation to a postconceptional age of 38 weeks.¹

We report costs in Euros (€) as of the year 2000, rounded to €5. The institutional review board of the Erasmus MC approved the study.

RSV hospitalisation risk

We described the development of a clinical prediction model which estimates individual monthly hospitalisation risks in a previous paper.¹ In short: children born between 1 January 1996 and 31 December 1998 and hospitalised with RSV during the seasons 1996/1997 to 1998/1999 (n=2469) were related to children born during the same period (n=140 661; 1 181 790 months at risk). We constructed a logistic regression model, which estimates individual monthly RSV hospitalisation risks, using five clinical predictors (gestational age, presence of BPD, birth weight, gender and age) and the mean seasonal pattern of RSV infections (see appendix A).¹

Medical costs

RSV hospitalisation costs

We described the development of a clinical prediction model which estimates individual hospitalisation costs in a previous paper.³⁰ In short, the total costs per RSV hospitalisation were calculated by multiplying volumes of healthcare use with corresponding real costs in children hospitalised with RSV during the seasons 1996/1997 to 1999/2000 (n=3458).³⁰ Mean hospitalisation costs were €3110 per hospitalisation at a mean duration of hospitalisation of 6 days. Mean hospitalisation costs were higher for children with a low gestational age (≤ 28 weeks; €5550 per hospitalisation), low birth weight (≤ 2500 g; €3900 per hospitalisation), BPD (€5800 per hospitalisation) and young age (first month of life; €4730 per hospitalisation). We used these data to construct a linear regression model which estimates anticipated individual RSV hospitalisation costs for children at risk, using four predictors: gestational age, presence of BPD, birth weight and age (see appendix B).³⁰

Costs of palivizumab

The costs of one vial of 50 or 100 mg of palivizumab were €560 or €930, respectively, according to the Dutch price system for pharmaceutical care. We used the mean weight of children hospitalised with RSV during the seasons 1996/1997 to 1999/2000 (6255 g) to calculate the dose per immunisation. Given a dose of 15 mg/kg, assuming drug wastage, a 100 mg vial would be required. We assumed that the costs of administration of palivizumab equalled the costs of a visit to the general practitioner, that is €20. We also assumed total compliance.

Non-medical costs

Parental costs

We estimated the parental costs of hospitalisation to be 15.5% of the medical hospitalisation costs.³¹ We further assumed that parents lost two working hours for each administration of passive immunisation.^{4 17} With an average wage of €16 per hour, these parental costs were €32 per administration.

Efficacy of palivizumab

The IMpact trial with palivizumab reports a relative risk (RR) reduction of 55% (95% confidence interval (CI) 38% to 72%) for the incidence of hospitalisation because of severe RSV disease in children with prematurity and BPD, favouring passive immunisation.² The RR reduction is 78% (95% CI 66% to 90%) in premature children alone and 39% (95% CI 20% to 58%) in children with BPD.²

Cost-effectiveness analysis

We performed the primary cost-effectiveness analysis for children with prematurity and BPD. We programmed the linear regression models for monthly RSV hospitalisation risks and monthly RSV hospitalisation costs, with data on immunisation costs, parental costs, and efficacy of passive immunisation, in an Excel spreadsheet.^{4 17} We calculated monthly costs and effects with and without prophylactic treatment. The primary outcome measure, the incremental costs to prevent one hospitalisation, was calculated for every month of the RSV season by dividing the costs difference by the risk difference. We calculated the risk difference by subtracting the estimated monthly RSV hospitalisation risk with passive immunisation from the estimated monthly RSV hospitalisation risk without passive immunisation (using a RR reduction of 55% for efficacy of passive immunisation). We calculated the costs difference by subtracting the costs without passive immunisation from the costs with passive immunisation. We calculated the costs without passive immunisation according to the common two-part methodology by multiplying the estimated hospitalisation costs with the hospitalisation risk without passive immunisation. We calculated the costs with passive immunisation by multiplying the estimated hospitalisation costs with the hospitalisation risk with passive immunisation and adding the immunisation costs. For illustrative purposes we used a reference case. This is a child with the highest hospitalisation risk and hospitalisation costs during the complete season (male, gestational age ≤ 28 weeks, birth weight ≤ 2500 g, having BPD and an age of 0 months at the beginning of the season (October)).

Our analysis focuses on the short-term outcome of RSV infection (hospitalisation within 1 year). Therefore no discounting was applied.

Sensitivity analysis

To account for uncertainty in the estimates used in the cost-effectiveness analysis, we performed univariate sensitivity

analyses allowing changes of one variable at a time. These sensitivity analyses were performed for the reference case in the 4 months that passive immunisation was most cost effective (November–February). We changed RSV hospitalisation risk, hospitalisation costs, immunisation costs and efficacy of immunisation from half to double their values, and within the 95% CIs of the estimates. We also explored for which values the incremental costs per hospitalisation averted would be €0 (cost neutrality).

RESULTS

Detailed results of the cost-effectiveness calculations across the RSV season for the reference case are shown in table 1. Costs per hospitalisation averted varied between €13 190 in December and €833 695 in October. Every month costs per hospitalisation averted were higher for children without BPD and children with higher gestational ages (figure 1). Costs per hospitalisation averted were also higher for girls and decreased with decreasing birth weight and age. Passive immunisation was always most cost effective in December, but was never cost saving.

Sensitivity analysis

The sensitivity analyses for the reference case for the four most cost-effective months (November–February) are shown in figure 2. The estimated cost-effectiveness of passive immunisation for the reference case in December (€13 190 per hospitalisation averted) was most sensitive to changes in hospitalisation risk, followed by efficacy of passive immunisation, immunisation costs and hospitalisation costs. Changes in monthly RSV hospitalisation risk between 3.8% and 15.2% resulted in an exponential decrease in costs per hospitalisation averted from €36 625 to €1470. For the 95% CI of the risk estimate (5.1–11.3%), costs per hospitalisation averted ranged from €24 485 to €5565. The monthly hospitalisation risk had to exceed 17% to reach cost neutrality.

Changes in efficacy of passive immunisation to RSV (RR reduction 28–100%) resulted in an exponential decrease in costs per hospitalisation averted from €36 625 to €2645 when passive immunisation would prevent all hospitalisations. For the 95% CI of the efficacy estimate (RR reduction 38–72%), costs per hospitalisation averted ranged from €23 675 to €7655.

Changes in monthly immunisation costs between €490 and €1960 resulted in a linear increase in costs per hospitalisation averted from €2095 to €35 380. For children with weights below 3300 g, who could be immunised with the 50 mg vial at a cost of €560, costs per hospitalisation averted were €4405. Acquisition costs of passive immunisation had to be decreased to €375 to reach cost neutrality.

Changes in RSV hospitalisation costs between €5125 and €20 500 resulted in a linear decrease in costs per hospitalisation averted from €18 315 to €2940. For the 95% CI of the hospitalisation costs estimate, ranging from €8920 to €11 575, costs per hospitalisation averted ranged from €14 515 to €11 862. A hospitalisation had to cost over €23 250 to reach cost neutrality.

DISCUSSION

The cost-effectiveness of passive immunisation with palivizumab varied widely by child characteristics and seasonal month. This variation was caused by variation in hospitalisation costs and hospitalisation risk. Passive immunisation was most cost effective in December, but even in this month the costs per hospitalisation averted were high (at least €13 190). The sensitivity analysis showed that cost-effectiveness could be improved by lowering the acquisition costs of passive immunisation. For the reference case, cost savings were only reached when acquisition costs were below €375. Changes in hospitalisation risk, efficacy of passive immunisation and hospitalisation costs also influenced cost-effectiveness.

Current guidelines of the Dutch Society of Pediatrics recommend passive immunisation against RSV during the whole RSV season from October to March for children with a gestational age of <32 weeks, chronic lung diseases or haemodynamically significant congenital heart disease. Based on our findings, we recommend a more restrictive immunisation policy, only immunising children with BPD in their first year of life during the highest-risk months (November–January). Even with this restricted policy, the costs per hospitalisation averted remain high. If this restricted immunisation policy were implemented in the Netherlands, the immunisation costs would approximate €1 029 000 per year. Since our study did not address children with congenital heart disease, we cannot advise on passive immunisation in this group.

Several economic analyses of palivizumab have been published.^{4 11–24} We are the first to use detailed

Table 1 Calculation of incremental costs per hospitalisation averted (€) per seasonal month for the reference case (male infant, gestational age ≤28 weeks, birth weight ≤2500 g, with bronchopulmonary dysplasia and age* = 0 months at the start of the season)

	Seasonal month						
	October	November	December	January	February	March	April
Age* (months)	0	1	2	3	4	5	6
Hospitalisation risk without passive immunisation (%)	0.2	4.0	7.6	4.5	3.2	1.6	0.4
Hospitalisation risk with passive immunisation† (%)	0.1	1.8	3.4	2.0	1.5	0.7	0.2
Risk difference (%)	0.1	2.2	4.2	2.5	1.7	0.9	0.2
Hospitalisation costs‡ (€)	21290	13010	10250	8865	8040	7485	7090
Immunisation costs§ (€)	980	980	980	980	980	980	980
Costs without passive immunisation (€)	45	525	780	400	260	120	30
Costs with passive immunisation (€)	1000	1215	1330	1160	1095	1030	995
Costs difference (€)	955	690	550	760	835	910	965
Incremental costs per hospitalisation averted (€)	833695	31055	13190	30795	47145	105120	395860

*Age of children born prior to 38 weeks of gestation was corrected to a postconceptional age of 38 weeks.

†Assuming a relative risk reduction for incidence of hospitalisation of 55% favouring passive immunisation.²

‡Including 15.5% parental costs.³¹

§100 mg vial of palivizumab (€930), administration costs (€20) and parental costs (€32).

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Symbol	Gestational age	Age*	BPD	Seasonal month							Total season
				Oct	Nov	Dec	Jan	Feb	Mar	Apr	Nov - Mar
■	28	0	Yes	833,695	31,055	13,190	30,795	47,145	105,120	395,860	32,590
△	28	12	Yes	513,870	102,525	51,845	91,835	130,095	271,460	985,995	98,850
○	28	0	No	847,730	44,290	24,950	53,570	88,335	212,725	884,555	53,330
◇	34	0	No	1,149,065	63,005	36,720	75,325	122,250	290,300	1,198,060	75,070

* Age of children born prior to 38 weeks of gestation was corrected to a postconceptional age of 38 weeks.

Figure 1 Influence of variation in gestational age (weeks), age* at the start of the season (months) and bronchopulmonary dysplasia (BPD) on costs per hospitalisation averted (€) per seasonal month and for the total respiratory syncytial virus season (male gender and birth weight ≤ 2500 g). *Age of children born prior to 38 weeks of gestation was corrected to a postconceptional age of 38 weeks.

individualised monthly risks and costs. Ten studies report cost increases,^{4 12–14 17–22} of which five report incremental costs per hospitalisation averted ranging from \$7000 to \$420 000.^{4 12 17 19 21} Three studies report cost savings.^{11 15 16} These savings were only reached when high hospitalisation costs (over \$15 000) were combined with high seasonal hospitalisation risks (28% or higher), high efficacy of passive immunisation (>80%), and low costs of immunisation (\$2500 per season),¹⁵ when high hospitalisation costs (>\$50 000) and high seasonal hospitalisation risks (>20%) were assumed,¹¹ or when a very restrictive prophylaxis policy was followed.¹⁶

To appreciate our results, some aspects need to be addressed. Instead of using mean hospitalisation costs we used a linear regression model to estimate anticipated individual hospitalisation costs.³⁰ This allowed for higher costs for children with BPD, low birth weight and young age. However, anticipated individual hospitalisation costs may depend on more characteristics than considered in our regression model.

If the reference case had a weight below 3300 g in December, a 50 mg vial of palivizumab would have been sufficient for immunisation, leading to a reduction of costs per hospitalisation averted from €13 190 to €4405. However, only 9% (9/101) of the hospitalised infants with a gestational age below 35 weeks and birth weight below 3000 g had a weight on admission in December below 3300 g.

Wastage of palivizumab is the most likely condition in actual practice, because the reconstituted drug has to be used within hours. A decrease in wastage by clustered administration would increase the cost-effectiveness of passive immunisation.

We advocate immunisation of the highest-risk children during the highest-risk months only. However, children born very prematurely (gestational age ≤ 30 weeks) seem to achieve optimal protective serum levels of antibodies only after the second dose of palivizumab. This has important implications for the timing and dosing of palivizumab in these children.^{32 33}

We used a logistic regression model to estimate individual monthly hospitalisation risks.¹ Every estimate is accompanied by a 95% CI. Should the actual risk for the reference case in December equal the upper boundary of this interval (11.3%), then costs per hospitalisation averted would be reduced by 58% (from €13 190 to €5565). Cost neutrality would only be reached at very high monthly risks (>17%). The highest monthly risk estimated in our population was 8.1% (95% CI 5.4% to 12.2%). Monthly hospitalisation risks exceeding 3.8% (the lower boundary of our sensitivity analysis, corresponding to costs per hospitalisation averted of €36 625) were predicted for only 4% (422/10 652) of all at-risk months of children with a gestational age below 35 weeks or BPD in our study.

We consider the overall RR reduction reported in the IMPact trial (55%) for our effect estimate of passive immunisation against RSV. When we apply the subgroup-specific RR reductions for premature children without BPD and children with BPD (78% and 39%, respectively), passive immunisation is more cost effective in premature children without BPD because of a higher efficacy (€22 805 vs €15 950 in December; reference case with and without BPD).²

No deaths were observed in our large study (n=3458) covering four RSV seasons (1996/1997 to 1999/2000). In other

Figure 2 Sensitivity of costs per hospitalisation averted (€) to changes in estimates of respiratory syncytial virus hospitalisation risk, hospitalisation costs, immunisation costs and efficacy of immunisation, from half to double their values in the primary analysis and the 95% confidence intervals of the values used in the primary analysis for the reference case in November (A), December (B), January (C) and February (D).

studies, overall mortality due to RSV was very low.^{34,35} Passive immunisation has not shown to have an effect on mortality caused by RSV. Therefore, in contrast to others,⁴ we did not analyse costs per life-year saved.

We assumed that children who are not hospitalised because of severe RSV infection do not benefit from passive immunisation. Passive immunisation might decrease primary care costs and parental loss of income in this group of children. However, these overall costs are very low compared to the hospitalisation costs. There is also some evidence suggesting that passive immunisation decreases the incidence of recurrent wheezing in non-hospitalised premature born children until the age of 24 months.³⁶ Exploratory analyses showed that these costs had only a small impact on the cost-effectiveness. Other studies support this conclusion.^{22,37}

Neither did we consider the costs of adverse events, because no serious adverse events related to palivizumab were reported and the incidence of non-serious adverse events was low.²

Other potential predictors for RSV hospitalisation risk such as environmental factors (smoking in the household, day-care attendance, etc), could not be included in the current analysis because they were not registered for the children at risk. Additional predictors might further refine the analysis of the cost-effectiveness of passive immunisation against RSV if combined with the predictors used in the current analysis.

Generalisability of our results is limited to geographical regions with comparable infection rates, seasonality and costs. However, cost-effectiveness of passive immunisation against RSV can be more accurately estimated by the use of more risk factors, and especially seasonality, in any population.

Since healthcare budgets are limited, economic analyses exploring the balance between the costs and benefits of medical interventions are essential to make choices about their reimbursement. Unfortunately, there is no established threshold for cost-effectiveness expressed in costs per hospitalisation averted. This threshold should, however, be well below standards for costs per life-year saved (eg, \$50 000).³⁸ Robbins *et al*³⁹ asked a small sample of physicians and nurses what they would be willing to pay for a treatment that could prevent a high-risk child from being admitted to hospital with severe RSV disease. Responses ranged from \$1325 to \$8700 (mean \$5787) but did not include savings resulting from preventing hospitalisation.

We conclude that although the cost-effectiveness of passive immunisation with palivizumab varied strongly by child characteristics and seasonal month, the costs per hospitalisation averted were always high. We therefore recommend a restrictive immunisation policy, only immunising children with BPD in high-risk months. Additional studies investigating the optimal dosing of palivizumab in very prematurely born children are needed. The costs of passive immunisation would have to be considerably reduced to achieve cost-effectiveness.

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Competing interests None.

Ethics approval The institutional review board of the Erasmus MC approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

APPENDIX A

The monthly RSV hospitalisation risk was estimated as: $\text{risk} = (1 / [1 + \exp(-\text{lp})])$, with $\text{lp} = -7.013 + 0.335 \times \text{gender} + 0.545 \times \text{bw1} + 0.234 \times \text{bw2} + 1.150 \times \text{ga1} + 1.042 \times \text{ga2} + 0.849 \times \text{ga3} + 0.447 \times \text{ga4} + 1.398 \times \text{aged} - 0.075 \times \text{age} \times \text{bpd} - 0.207 \times \text{age} \times (1 - \text{bpd}) + 0.851 \times s$, where *gender* is 1 if male, 0 if female; *bw1* is birth weight ≤ 2500 g, *bw2* is from 2501 to 3000 g; *ga1* is gestational age ≤ 28 weeks, *ga2* is from 29 to 32 weeks, *ga3* is from 33 to 34 weeks, *ga4* is from 35 to 36 weeks; *aged* is 0 if age = 0 months, 1 if age > 0 months; *age* in months (age of children born prior to 38 weeks of gestation was corrected to a postconceptional age of 38 weeks); *bpd* is 1 if BPD yes, 0 if BPD no; *s* is seasonal month at risk with the values: -1.40 for October, 0.53 for November, 1.36 for December, 0.83 for January, 0.53 for February, -0.22 for March and -1.63 for April.

APPENDIX B

The RSV hospitalisation costs were estimated as: $\text{costs} = 2274 + 591 \times \text{bw1} + 284 \times \text{bw2} + 1226 \times \text{ga1} + 313 \times \text{ga2} + 14344 \times \text{bpd} \times (1 / (\text{age} + 1)) + 2192 \times (1 - \text{bpd}) \times (1 / (\text{age} + 1))$, where *bw1* is birth weight ≤ 2500 g, *bw2* is from 2501 to 3000 g; *ga1* is gestational age ≤ 28 weeks, *ga2* is from 29 to 34 weeks; *bpd* is 1 if BPD yes, 0 if BPD no; *age* in months (age of children born prior to 38 weeks of gestation was corrected to a postconceptional age of 38 weeks).

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