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Cost-effectiveness of palivizumab in infants with congenital heart disease: a Swedish perspective

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Abstract

Background: Infants with congenital heart disease (CHD) have an increased risk of morbidity and mortality during a respiratory syncytial virus (RSV) infection. The aim of this study was to estimate the cost-effectiveness of palivizumab as RSV-prophylaxis among infants with CHD, including the effect of delayed heart surgery and asthma.

Methods: A simulation model with data from the literature and health care authorities including costs and utilities was developed to estimate costs and health effects over a lifetime for a cohort of CHD infants receiving palivizumab compared to no RSV-prophylaxis.

Results: The prophylaxis treatment incurred a cost of 3664 EUR per treated infant. However, due to cost-savings from primarily avoiding hospitalizations (5145 EUR/treated infant) and avoiding heart complications due to delayed heart surgery (2082 EUR/treated infant), the RSV-prophylaxis treatment resulted in a total cost-saving of 3833 EUR per treated infant. At the same time, the prophylaxis-treated cohort accumulated more life-years and higher quality of life than the non-prophylaxis cohort.

Conclusion: This study confirms that RSV-prophylaxis in severe CHD infants less than one year of age is cost beneficial. Avoiding delayed heart surgeries is an important benefit of prophylaxis and should be taken into consideration.

Keywords: Congenital heart defect, Cost-effectiveness analyses, Palivizumab, Prophylaxis, RSV-infection

Background

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections (LRTI) in infants and young children. Severe RSV may result in acute respiratory failure and hospitalization with supplemental oxygen, mechanical ventilation, and intensive care (ICU), especially for infants and children at risk [1, 2]. Infants with congenital heart disease (CHD) carry a risk of morbidity and mortality from RSV infection worldwide as well as in Scandinavia [3, 4]. Long-term sequelae from RSV-infections are wheezing and asthma [5–8].

Cardiac surgery performed during an ongoing RSV infection is associated with a high risk of postoperative complications, prolonged postoperative stay at the pediatric intensive care unit (PICU), and morbidity [9–11]. Postponing cardiac surgery is thus appropriate in infants with symptomatic viral respiratory infection. However, postponing will, on the other hand, increase the risk of morbidity and mortality induced by the cardiac disease.

Palivizumab (Synagis®, MedImmune) is a monoclonal antibody designed to provide passive immunity against RSV – thereby reducing the severity of RSV infection in infants at high risk, including infants with CHD [12–14].

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Cost-effectiveness analyses of palivizumab in infants and children with CHD have previously been done, where most studies compared palivizumab prophylaxis to no prophylaxis with the results suggesting cost effectiveness [15–19]. Most studies were performed in high-income countries and only one in Scandinavia for over 16 years ago [20]. Significant variance exist across these study characteristics such as age of the included children, duration of assessed RSV seasons, primary outcome measures evaluated, sensitivity analyses conducted, and other model assumptions [21].

The aim of the present study was to estimate the cost-effectiveness of palivizumab as RSV-prophylaxis according to national guidelines among Swedish infants with CHD, including delayed heart surgery, risk of asthma, and costs related to parental care (Additional file 1).

Methods

This analysis was based on a Markov model [22, 23] with annual cycles comparing the cost-effectiveness of palivizumab as RSV-prophylaxis to no prophylaxis for Swedish infants with CHD. The simulated population was treated with RSV-prophylaxis to infants aged up to one year with hemodynamic significant CHD and subject to the national Swedish prophylactic program for palivizumab [24]. The analysis was performed from a societal perspective with a lifetime time-horizon and quality-adjusted life-years (QALYs) as the health outcome. Results are expressed in incremental cost-effectiveness ratios (ICER; euros [EUR]/QALY). Costs and effects were discounted at 3% annually as per the Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds- och Läkemedelsförmansverket, TLV) guidelines [25]. All costs in this study were calculated in Swedish krona (SEK) based on the health-care price-level of 2019 and expressed in EUR in year 2019 values (1 EUR = 10.5892 SEK).

Model structure

The health states and possible transitions of the Markov model are shown in Fig. 1. The model structure was similar to the structure used in previously published cost-effectiveness analyses of RSV-prophylaxis [16, 23], but with the addition of possible complications from

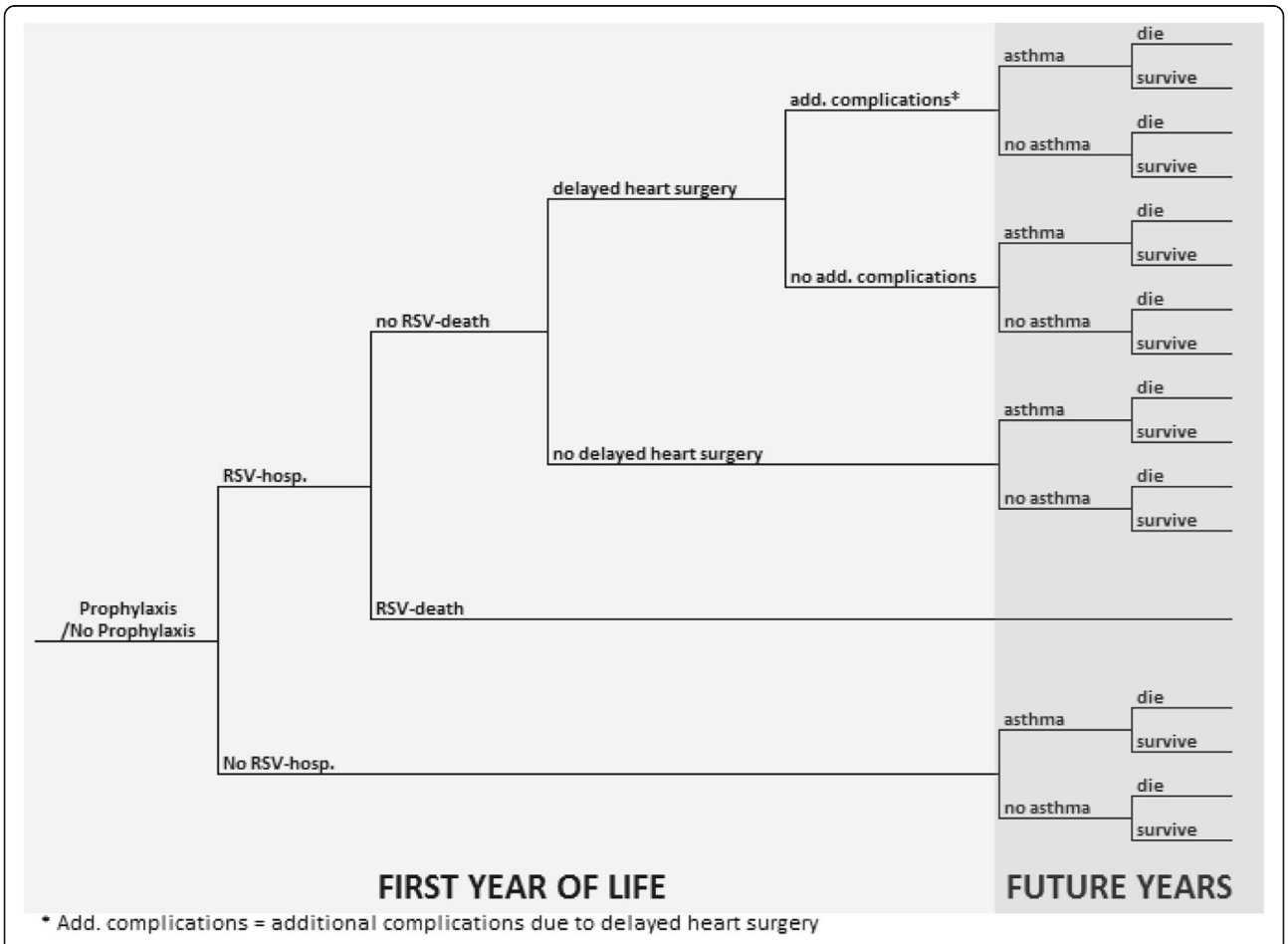

Fig. 1 The structure of the Markov model

delayed heart surgery, costs due to parental care and risk of asthma. The simulation was started during the first year of life for a cohort of Swedish infants with CHD subject to RSV-prophylaxis according to national guidelines [24]. At the start of the RSV-season, a proportion of these infants would be infected with RSV leading to RSV-hospitalization, and in some cases even death. RSV-hospitalization was modeled to delay the planned heart surgery in an estimated number of cases affected by RSV during the winter season, where the risk of CHD-associated complications, including death, would rise. During the future years of simulation, the infants were subjected to a risk of asthma – with a higher risk for those with a history of RSV-hospitalization. The prevalence of the CHD-associated complications was unchanged from the first year. Mortality risks were identical for all children with CHD after the first year. For the RSV-prophylaxis cohort, palivizumab was modeled to be administered only during the RSV season of the first year of simulation.

Risk data and treatment effects of palivizumab

For the palivizumab-treated cohort the following direct treatment effects were modeled based on the randomized clinical trial on palivizumab in CHD infants [13]:

- Lower risk of RSV-hospitalization
- Less severe RSV-infection if hospitalized

Data related to RSV-infection and hospitalization, continuous positive airway pressure (CPAP), extracorporeal membrane oxygenation (ECMO) and RSV-related death, as well as asthma following RSV, have been retrieved from well-known studies [7, 13, 26–31]; hospital economists at one of the hospitals (Linköping) were consulted when data was not available (Table 1). After 18 years of age, no further difference in the prevalence of asthma was assumed in the present analysis.

The risk of death has been estimated to a hazard ratio (HR) of 64 for the group of children born during the 1990's with the most severe defects and would be included in the national prophylactic program of palivizumab [40]. Survival rates have improved among children born as of 2010, and the survival rates are thus expected to improve to approximately 80% [41, 42].

The risk of delayed heart surgery due to RSV-hospitalization was 30%, based on information from a Swedish study from 2014 on adherence to guidelines of palivizumab – where 30% of children with prophylactic treatment had their operation delayed [43]. Among infants with delayed heart surgery, around 40% were estimated to have heart complications (expert opinion within the group).

Cost data

Cost of palivizumab

The cost of palivizumab was based on five injections with a dose of 15 mg/kg at a cost of 8.25 EUR per mg (Table 1). We assumed that some children were born late during season and therefore not in need of all five doses, but some were older at start of season and outgrew the national guidelines recommended age during season. Thus, we assumed for the calculations that the overall number of children during a season and we accounted for five doses during the season.

Data on weight of infants were retrieved from 30 patients with severe CHD receiving RSV-prophylaxis according to national guidelines at Linköping Children's Hospital. In this dataset, the mean weights at dose 1, 2, 3, 4, and 5 of palivizumab were 5.0 kg, 5.4 kg, 5.8 kg, 6.4 kg and 7.0 kg, respectively. The resulting cost of RSV-prophylaxis per infant and season was 3664 EUR (Table 1).

Cost of RSV-hospitalization

Data on cost of hospitalization, supplementary oxygen, mechanical ventilation, CPAP, and ECMO are presented in Table 1. In Sweden, parents are provided parental allowance if the child is hospitalized. The cost for the society for this was estimated to be 118 EUR per day based on data from Statistics Sweden [35]. Mean length of hospitalization (10.8 days with prophylaxis vs. 13.3 days without prophylaxis) and ICU days (3.0 days with prophylaxis vs. 7.3 days without prophylaxis) were calculated based on Feltes et al. [13]. The resulting total costs per RSV-hospitalization, when combined with the length of stay data, was 96,918 EUR for prophylaxis treated infants and 106,344 EUR for non-treated infants (Table 1).

Cost of CHD-associated complications following postponed operation and RSV-sequalae as asthma

The costs of a general CHD-associated complication following delayed heart surgery was calculated as the value of 100% productivity loss, assuming that one parent would initially need to be at home full-time with the infant, and that all the individuals with these heart complications do not enter the labor market as adults. The resulting annual cost of a general CHD-associated complication using these assumptions was 21,506 EUR (Table 1). The annual cost of asthma per infant has been gathered from estimations [23] building on studies on adults [44] and preschool children [45].

Utility data

The utility of the modeled CHD-infants was assumed to be equal to the utility of premature infants as previously described by Greenough et al. [37]. The base utility was accordingly set to 0.89 for all infants, with a decrement

Table 1 Input data used in the model

	Cohort		
	RSV-prophylaxis	No Prophylaxis	Source
Palivizumab as RSV-prophylaxis			
Dose	15 mg/kg		
Price	8.25 EUR/mg		
Weight (cost per injection):			
1st injection	5 kg (619 EUR)		
2nd injection	5.4 kg (668 EUR)		
3rd injection	5.8 kg (718 EUR)		
4th injection	6.4 kg (792 EUR)		
5th injection	7 kg (866 EUR)		
Total prophylaxis costs per treated infant:	**3664 EUR**		
RSV-hospitalization			
Annual risk of RSV-hospitalization (1st year of life)	5.34% (RR = 0.55)	9.70%	Feltes et al. [13]
Risk of death during RSV-hospitalization	3.72%	3.72%	Feltes et al. [13]
Mean length of stay, RSV-hospitalization	10.8 days	13.3 days	Feltes et al. [13]
Mean length of stay, ICU	3.0 days	7.3 days	Feltes et al. [13]
Mean length of...			
supplemental oxygen	5.2 days	10.4 days	Feltes et al. [13]
mechanical ventilation	1.2 days	5.6 days	Feltes et al. [13]
ECMO	8.2 days	8.2 days	Khan et al. [27]
CPAP	3.5 days	3.5 days	Greenough et al. [32]
Cost per day			
RSV-hospitalization	1197 EUR	1197 EUR	SSVR County Council Price List [33]
ICU	1802 EUR	1802 EUR	SSVR County Council Price List[1] [33]
Supplemental oxygen	344 EUR	344 EUR	SÖSVR County Council Price List [34]
Mechanical ventilation	344 EUR	344 EUR	SÖSVR County Council Price List [34]
ECMO	8592 EUR	8592 EUR	SSVR County Council Price List [33]
CPAP	3338 EUR	3338 EUR	SÖSVR County Council Price List[a] [34]
Hotel (1 parent)	96 EUR	96 EUR	SSVR County Council Price List [33]
Productivity loss (1 parent)	118 EUR	118 EUR	Statistics Sweden [35]
Resulting total costs per RSV-hospitalization	**96,918 EUR**	**106,344 EUR**	
CHD-associated complications			
Risk of delayed surgery, if RSV-hospitalized	30%	30%	Granbom et al. [36]
For infants with delayed surgery: Risk of …			
general complication	40%	40%	Assumed
death (during first year)	1%	1%	Assumed
Annual cost of general heart complication	21,506 EUR	21,506 EUR	Assumed
Asthma			
Annual risk of asthma	(Depending on age and history of RSV-hospitalization)		Sigurs et al. [7, 28, 29]
Annual cost of asthma	1440 EUR	1440 EUR	Neovious et al. [23]
Utilities			
Base utility	0.89	0.89	Greenough et al. [37]
Utility decrement of RSV hospitalization	0.10	0.10	Assumed
Utility of asthma	0.79	0.79	Chiou et al. [38]

Table 1 Input data used in the model *(Continued)*

	Cohort		
	RSV-prophylaxis	No Prophylaxis	Source
Utility decrement of heart complication	0.10	0.10	Assumed
Discount rates			
Costs (annual)	3.0%	3.0%	TLV guidelines [39]
QALYs (annual)	3.0%	3.0%	TLV guidelines [39]

CPAP Continuous positive airway pressure, *ECMO* Extracorporeal membrane oxygenation, *ICER* incremental cost-effectiveness ratio, *ICU* Intensive care unit, *Proph* prophylactic, *RSV* Respiratory syncytial virus, *SSVR* Södra sjukvårdsregionen, *SÖSVR* Sydöstra sjukvårdsregionen, *TLV* Tandvårds- och läkemedelsförmånsverket, *QALY* quality-adjusted life year, *y* years
[a]This price includes hospital stay which was accounted for in calculations

of 0.10 (assumed) for those RSV-hospitalized. Asthma and CHD-complications further decreased the utility, as shown in Table 1.

Sensitivity analysis and scenario analysis

One-way sensitivity analysis was used to test the robustness of the results for alterations in individual input data items by separately increasing/decreasing each variable by ±50%, except for the utilities, which generated a range of the ICER for each variable.

Probabilistic sensitivity analysis using Monte-Carlo simulation [22, 23] was used to investigate the uncertainty around the ICER, presented as an ICER scatter plot.

The effect on the ICER of shorter time horizons of the analysis; excluding the consequences of delayed heart surgery; excluding asthma and RSV-mortality; and using the mortality of the general population was investigated in scenario analyses.

Results

The results of incidence in different outcomes from the simulation model are shown in Fig. 2. Palivizumab had the greatest impact compared to the non-prophylaxis cohort in terms of hospitalizations. There was an increased incidence in other outcomes, but with less of a difference to prophylactically treated children with CHD.

Cost-effectiveness

The mean costs, effects, and ICER per infant in the base case scenario are shown in Table 2. The prophylaxis treatment incurred a cost of 3664 EUR per treated infant. By avoiding RSV-hospitalizations and morbidity associated with RSV infection as a result of prophylaxis, substantial savings mainly due to fewer days in the ICU and fewer days with ECMO were generated. The lower incidence of asthma and complications due to delayed surgery in the prophylaxis-treated cohort also generated savings. Over a lifetime, the prophylaxis was estimated to result in a cost-saving of 3833 EUR per CHD infant. In addition, the prophylaxis-treated cohort accumulated more life-years and higher quality of life than the non-prophylaxis cohort, resulting for the base case in a gain of 0.06 QALYs.

Sensitivity analysis and scenario analysis

Results from the one-way sensitivity analysis of the base case are shown in Table 3. When changing the variable values by ±50%, respectively, the prophylaxis treatment arm remained dominant (lower costs and higher

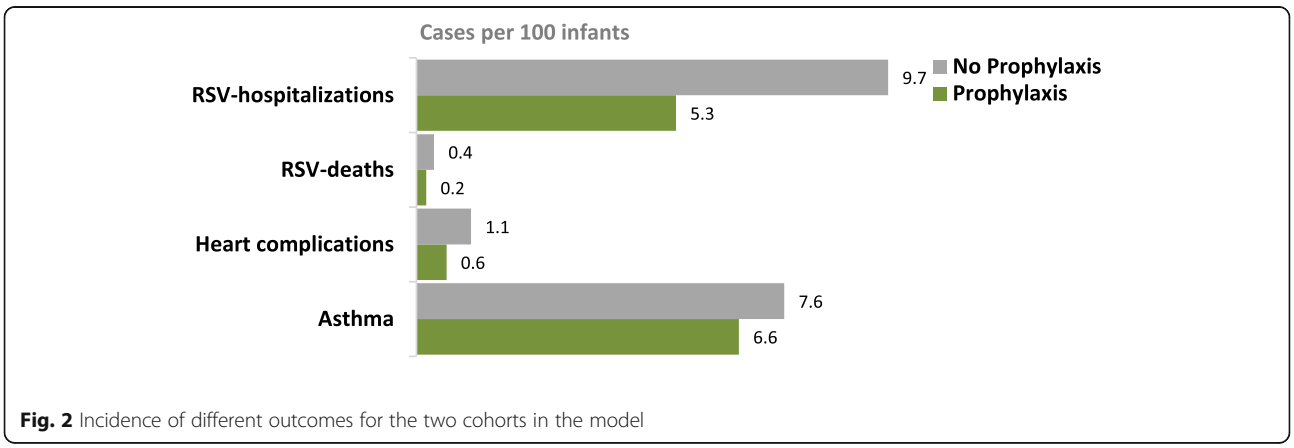

Fig. 2 Incidence of different outcomes for the two cohorts in the model

Table 2 Costs, effects and incremental cost-effectiveness ratios (ICER) for the base case scenario. Data indicate mean values per infant

	Prophylaxis	No Prophylaxis	Difference
Prophylaxis	**3664 EUR**	**0 EUR**	**3664 EUR**
RSV-hospitalizations	**5171 EUR**	**10,315 EUR**	**−5145 EUR**
General	499 EUR	691 EUR	− 191 EUR
ICU	286 EUR	1279 EUR	− 993 EUR
Supplemental oxygen	96 EUR	349 EUR	− 253 EUR
Mechanical ventilation	23 EUR	188 EUR	− 165 EUR
CPAP	400 EUR	727 EUR	− 327 EUR
ECMO	3744 EUR	6806 EUR	− 3063 EUR
Hotel nights	55 EUR	124 EUR	−69 EUR
Productivity losses	68 EUR	152 EUR	−84 EUR
Heart complications	**2544 EUR**	**4626 EUR**	**−2082 EUR**
Asthma	**1470 EUR**	**1739 EUR**	**− 270 EUR**
Total costs	**12,848 EUR**	**16,681 EUR**	**−3833 EUR**
Total QALYs	**17.82**	**17.75**	**0.06**
Total LY	**20.15**	**20.12**	**0.03**
ICER (QALY)			**DOMINANCE**
ICER (LYG)			**DOMINANCE**

CPAP Continuous positive airway pressure, *ECMO* Extracorporeal membrane oxygenation, *ICER* incremental cost-effectiveness ratio, *ICU* Intensive care unit, *LY* Life year, *LYG* Life year gained, *Proph* prophylactic, *RSV* Respiratory syncytial virus, *QALY* quality-adjusted life year, *y* years

utilities) in all cases except when the HR for RSV hospitalization of children treated with prophylaxis was increased by 50%. In that case, the ICER was 7875 EUR/QALY which, with a high margin, still would be regarded as very cost-effective [46].

The results from the probabilistic sensitivity analysis (Fig. 3 in Appendix) showed that the probability of RSV-prophylaxis to be cost-saving compared to no prophylaxis was close to 100%, given the joint uncertainty of the input data (Table 3 in Appendix).

In scenario analyses, a shorter time horizon of the analysis was shown to have the greatest impact on the cost-effectiveness of RSV-prophylaxis (Table 4 in Appendix). The prophylactic treatment was however still dominant when the time horizon was set to only 1 year as opposed to lifetime in the base case. Excluding asthma and RSV-mortality had a clear impact on QALYs but only minor effects on the costs, still leading to cost-savings and higher utility. If the effect of delayed heart surgeries due to RSV-hospitalization was removed from the model, the cost savings were lowered to 1751 EUR and the incremental QALYs to 0.05. If using the mortality from the general population in the model instead of the adjusted mortality for CHD infants used in the base case, the cost-savings and utility of prophylaxis would be even greater.

Discussion

The cost-effectiveness for RSV-prophylaxis with palivizumab as compared to no prophylaxis among Swedish CHD-infants aged less than 1 year during RSV-season and with cardiac defects adherent to the current national guidelines of prophylaxis showed that RSV-prophylaxis was associated with not only improved health effects, but also cost-savings of 3833 EUR per infant. The analysis included hospitalization, delayed surgery, asthma, and death as well as cost associated with parental care due to a child being hospitalized for RSV.

RSV-prophylaxis was cost-effective in CHD-infants who are included in the prophylactic program in this present study. In addition to more commonly used cost-driving entities such as hospitalization and mechanical ventilation in the ICU, we included an effect of delayed surgery, parental productivity loss, and asthma. The results remained unaltered when the robustness was tested, and these characteristics were excluded from the analysis. There has been notable variance in included study characteristics, analytic models utilized, duration of RSV seasons assessed, primary outcome measures evaluated, and sensitivity analyses conducted along with other model assumptions in other studies on cost-effectiveness on palivizumab in children with CHD. Thus, comparing results can be difficult and the cost effectiveness may to some extent still be inconclusive [21, 26]. Some of the earlier studies have evaluated short-term benefits, such as reducing hospitalizations and associated costs, while more recent studies have included long-term benefits such as asthma, QALYs, or life-years gained (LYG). Most of the studies performed in the high-income countries have shown that palivizumab in children with hemodynamically congenital heart disease is cost effective [16–19, 47, 48].

Congenital cardiac surgery performed during RSV infection is associated with a high risk of peri- and post-operative complications and mortality [9, 11]. These risks are of higher severity among the youngest patients and with more severe types of CHD. Thus, if a child is infected by RSV less than 6 weeks prior to heart surgery, this operation is often delayed. A delayed operation may however further increase the cardiac morbidity with increased cyanosis and/or heart failure. Previous cost-effectiveness studies of RSV-prophylaxis for children with CHD have not included the impact of delayed surgery. We found the cost-effective impact as well as health and quality of life factors in children with CHD were improved by RSV-prophylaxis.

Table 3 Results from one-way sensitivity analysis of the base case

	Value			ICER (SEK/QALY)		
Variable	Low	Base case	High	Low	Base case	High
Risk of RSV-hospitalization	4.9%	9.7%	14.6%	Dominance	Dominance	Dominance
HR RSV hospitalization (proph)	0.28	0.55	0.83	Dominance	Dominance	7875
Death from RSV hospitalization	1.9%	3.7%	5.6%	Dominance	Dominance	Dominance
Proportion delayed surgeries due to RSV-hosp	15.0%	30.0%	45.0%	Dominance	Dominance	Dominance
Proportion general complication from delayed surgery	20.0%	40.0%	60.0%	Dominance	Dominance	Dominance
Death (compl., delayed surgery)	0.5%	1.0%	1.5%	Dominance	Dominance	Dominance
LOS, RSV hospitalization	6.6	13.3	19.9	Dominance	Dominance	Dominance
LOS, RSV hospitalization (proph)	5.4	10.8	16.2	Dominance	Dominance	Dominance
LOS, ICU	3.7	7.3	11.0	Dominance	Dominance	Dominance
LOS, ICU (proph)	1.5	3.0	4.5	Dominance	Dominance	Dominance
Days with suppl. Oxygen	5.2	10.4	15.7	Dominance	Dominance	Dominance
Days with suppl. Oxygen (proph)	2.6	5.2	7.9	Dominance	Dominance	Dominance
Days with mechanical ventilation	2.8	5.6	8.4	Dominance	Dominance	Dominance
Days with mechanical ventilation (proph)	0.6	1.2	1.9	Dominance	Dominance	Dominance
Days with ECMO	4.1	8.2	12.3	Dominance	Dominance	Dominance
Days with ECMO (proph)	4.1	8.2	12.3	Dominance	Dominance	Dominance
Days with CPAP	1.8	3.5	5.3	Dominance	Dominance	Dominance
Days with CPAP (proph)	1.8	3.5	5.3	Dominance	Dominance	Dominance
RSV hosp (cost per day)	598	1197	1795	Dominance	Dominance	Dominance
ICU (cost per day)	302	605	907	Dominance	Dominance	Dominance
Suppl. oxygen (cost per day)	172	344	517	Dominance	Dominance	Dominance
Mechanical ventilation (cost per day)	172	344	517	Dominance	Dominance	Dominance
ECMO (cost per day)	4296	8592	12,888	Dominance	Dominance	Dominance
CPAP (cost per day)	1071	2141	3212	Dominance	Dominance	Dominance
Hotel (cost per night)	48	96	144	Dominance	Dominance	Dominance
Productivity loss (value per day)	59	118	177	Dominance	Dominance	Dominance
Cost of prophylaxis, per infant	1832	3664	5496	Dominance	Dominance	Dominance
Dose, Synagis	8	15	23	Dominance	Dominance	Dominance
Cost per mg, Synagis	4	8	12	Dominance	Dominance	Dominance
Weight factor, OWSA	0.50	1.00	1.50	Dominance	Dominance	Dominance
Annual cost asthma	720	1440	2160	Dominance	Dominance	Dominance
Cost of general CHD-complication (annual)	10,753	21,506	32,260	Dominance	Dominance	Dominance
Base utility	0.79	0.89	1.00	Dominance	Dominance	Dominance
Utility decrement of RSV hospitalization	5.0%	10.0%	15.0%	Dominance	Dominance	Dominance
Asthma utility	65.0%	79.0%	100.0%	Dominance	Dominance	Dominance
Utility decrement of heart complication	0.05	0.10	0.15	Dominance	Dominance	Dominance
Discount rate, costs	0.0%	3.0%	5.0%	Dominance	Dominance	Dominance
Discount rate, effects	0.0%	3.0%	5.0%	Dominance	Dominance	Dominance

CPAP Continuous positive airway pressure, *ECMO* Extracorporeal membrane oxygenation, *ICU* Intensive care unit, *HR* hazard ratio, *LOS* Length of stay, *OWSA* One-way sensitivity analyses, *Proph* prophylactic, *RSV* Respiratory syncytial virus

The risk of RSV-hospitalization and the treatment effect of RSV-prophylaxis among CHD-infants in our study were retrieved from a large randomized control trial [13]. The impact of these variables was tested in sensitivity analyses in the present study. The results showed that even if the risk of RSV-hospitalization or

the effect of RSV-prophylaxis were very low (half of the base case value), the ICERs were still well below the threshold of being very cost effective given the high disease severity of this patient population.

As a long-term complication to RSV infection, asthma has been included in previous studies of cost-effectiveness analyses covering RSV-prophylaxis with palivizumab in sensitive children [16, 17, 47]. Specific data of the risk of asthma following RSV among children with CHD is lacking. The risk for asthma following RSV infection in otherwise healthy Swedish infants was used in the analysis [28]. However, CHD infants may have a different risk of asthma. A scenario analysis was performed to rule out this risk, showing that even if asthma would be completely excluded from the analysis, palivizumab as RSV-prophylaxis would still result in cost-savings. One previous study in premature infants has suggested that prophylactic treatment with palivizumab may reduce subsequent recurrent wheezing [49]. The effect on asthma and wheezing following RSV infection on children with CHD with palivizumab is not known.

Productivity costs due to temporary parental allowance and productive loss was included in the analysis but had a minor impact on the outcome. Swedish parents are provided parental benefit when their child is sick at home or hospitalized. Given the lack of robust evidence regarding the extent of parental care or short-term absence to take care of the child when hospitalized, our estimates should be interpreted with caution. Some other studies have included costs related to parental care of the child with similar results. However, these studies are performed in countries with different socioeconomic systems and the only study in Scandinavia did not include this as well as several other cost components in the analysis [17, 19, 20, 47].

The results from the analysis in this study may be underestimating the cost-effectiveness of RSV-prophylaxis, as only the effect on very severe RSV-infections leading to hospitalization was included. Costs associated with outpatient RSV bronchiolitis and treatment is difficult to ascertain but may have influenced our results. Furthermore, a decreased quality-of-life while waiting for a delayed heart surgery was not included in the calculation which if included would have contributed to higher QALY gains. Palivizumab is injected monthly intramuscularly by pediatric nurses at each pediatric cardiac center at a university- or county hospital. Costs associated with travel for clinic visits, injections, or nurse consultations have not been included in the analysis. Further, when the sterile seal of a vial is broken there may be some surplus of the drug not being used, and should maybe have been included in the costs. In our hospitals (Crown Princess Victoria Children's Hospital University Hospital and Sahlgrenska University Hospital) this is a minor issue, as nurses often collect all children for prophylactic treatment timely to reduce the costs. Although some of the above mentioned issues have been accounted for in some other studies, an inclusion of these data is not likely to alter our results [17, 19].

Omitting or delaying palivizumab prophylaxis has been linked to increased rates of re-hospitalization. A previous Swedish study has found a delay in the start of prophylactic treatment among almost half of the children in the prophylactic program [43]. The results from our study indicate that timing and correct diagnosis of CHD is essential to benefit from cost-effectiveness of prophylactic treatment.

The cost-effectiveness shown in our study is based on the national guidelines on prophylactic treatment with palivizumab for children with CHD in Sweden [24] but the cost of the drug is a major concern. Our study used current Swedish guidelines in the analysis, which includes prophylactic treatment to the most severe types of CHD. Strict patient selection criteria are essential and use of palivizumab in a broader population than recommended in the guidelines is not justified by our study. In a recent Swedish study, the risk of RSV hospitalization for less severe cardiac defects was equal to that of severely ill children [36]. A cost-effectiveness study for that patient group would be the next logical step.

Delayed heart surgery is difficult to quantify due to limited available data. Data on risk of RSV-hospitalization might be different for Sweden compared to the multicentered study used in our analysis, which may further limit the study. Other risk factors for RSV infection, such as premature birth, prenatal exposure to maternal smoking and exposure to environmental tobacco smoke, lack of breastfeeding, living in crowded households, low birth weight, day care attendance among older siblings in the household, and increased risk for nosocomial infections have not been considered in this study, which may limit the overall aspects of RSV-prophylatic treatement [50–52]. Prophylactic treatment can therefor include information to parents and healthcare staff of the risk for severe viral infection in children with all types of CHD, and with special attention to the risk of nosocomial infection. The effect of this precaution is difficult to evaluate but may also reduce hospitalization rates.

Conclusion

This study confirms that Swedish guidelines on RSV-prophylaxis with severe CHD in infants less than 1 year of age is cost effective. Avoiding delayed heart surgeries is an important aspect of the prophylaxis' benefits and should be taken into consideration. However, further studies on the frequency and costs of delayed heart surgery are also needed to gain a better understanding of the impact RSV on society.

Appendix

Table 4 The variables used in the probabilistic sensitivity analysis, with their associated uncertainty and distributions

Variable	Mean value	Standard error (SE)	Distribution
Risk of RSV-hospitalization	9.7%	0.010	beta
HR RSV hospitalization (proph)	0.55	0.055	lognormal
Death from RSV hospitalization	3.7%	0.004	beta
Proportion delayed surgeries due to RSV-hosp	30.0%	0.030	beta
Proportion general complication from delayed surgery	40.0%	0.040	beta
Death (compl., delayed surgery)	1.0%	0.001	beta
LOS, RSV hospitalization	13.27	1.33	gamma
LOS, RSV hospitalization (proph)	10.79	1.08	gamma
LOS, ICU	7.32	0.73	gamma
LOS, ICU (proph)	2.97	0.30	gamma
Days with suppl. Oxygen	10.44	1.04	gamma
Days with suppl. Oxygen (proph)	5.24	0.52	gamma
Days with mechanical ventilation	5.62	0.56	gamma
Days with mechanical ventilation (proph)	1.24	0.12	gamma
Days with ECMO	8.17	0.82	gamma
Days with ECMO (proph)	8.17	0.82	gamma
Days with CPAP	3.50	0.35	gamma
Days with CPAP (proph)	3.50	0.35	gamma
RSV hosp (cost per day)	1197 EUR	120	gamma
ICU (cost per day)	605 EUR[1]	60	gamma
Suppl. oxygen (cost per day)	344 EUR	34	gamma
Mechanical ventilation (cost per day)	344 EUR	34	gamma
ECMO (cost per day)	8592 EUR	859	gamma
CPAP (cost per day)	2141 EUR	214	gamma
first injection (kg)	5.00	0.50	normal
second injection (kg)	5.40	0.54	normal
third injection (kg)	5.80	0.58	normal
fourth injection (kg)	6.40	0.64	normal
fifth injection (kg)	7.00	0.70	normal
Annual cost asthma	1440 EUR	144	gamma
Cost of general CHD-complication (annual)	21,506 EUR	2151	gamma
Base utility	0.89	0.089	beta
Utility decrement of RSV hosp	0.10	0.010	beta
Asthma utility	0,79	0,079	beta
Utility decrement of heart complication	0,10	0,010	beta

Table 5 Costs, effects and incremental cost-effectiveness ratios (ICER) for different scenarios. Data are expressed as mean value per infant

Scenario		Costs	QALYs	Incremental		ICER
				Costs	QALYs	
Base case	Prophylaxis	12,848 EUR	17.82	−3833 EUR	0.06	**Dominance**
	No Prophylaxis	16,681 EUR	17.75			
Time horizon = 1y	Prophylaxis	8834 EUR	0.88	− 1481 EUR	0.01	**Dominance**
	No Prophylaxis	10,315 EUR	0.88			
Time horizon = 5y	Prophylaxis	9341 EUR	3.76	− 1868 EUR	0.01	**Dominance**
	No Prophylaxis	11,209 EUR	3.74			
Time horizon = 10y	Prophylaxis	9964 EUR	6.84	− 2292 EUR	0.02	**Dominance**
	No Prophylaxis	12,255 EUR	6.81			
No asthma	Prophylaxis	11,378 EUR	17.92	− 3563 EUR	0.04	**Dominance**
	No Prophylaxis	14,941 EUR	17.88			
No RSV-death	Prophylaxis	12,962 EUR	17.85	− 3925 EUR	0.03	**Dominance**
	No Prophylaxis	16,887 EUR	17.82			
No RSV-death, no asthma	Prophylaxis	11,477 EUR	17.95	− 3643 EUR	0.01	**Dominance**
	No Prophylaxis	15,120 EUR	17.94			
No delayed heart surgeries	Prophylaxis	10,304 EUR	17.83	−1751 EUR	0.05	**Dominance**
	No Prophylaxis	12,055 EUR	17.78			
Mortality = general population	Prophylaxis	15,337 EUR	27.30	− 5137 EUR	0.10	**Dominance**
	No Prophylaxis	20,474 EUR	27.21			
No productivity loss	Prophylaxis	10,236 EUR	17.82	− 1667 EUR	0.06	**Dominance**
	No Prophylaxis	11,903 EUR	17.75			
Productivity loss of both parents	Prophylaxis	12,916 EUR	17.82	− 3916 EUR	0.06	**Dominance**
	No Prophylaxis	16,832 EUR	17.75			

ICER incremental cost-effectiveness ratio, *RSV* Respiratory syncytial virus, *QALY* quality-adjusted life year, *y* years

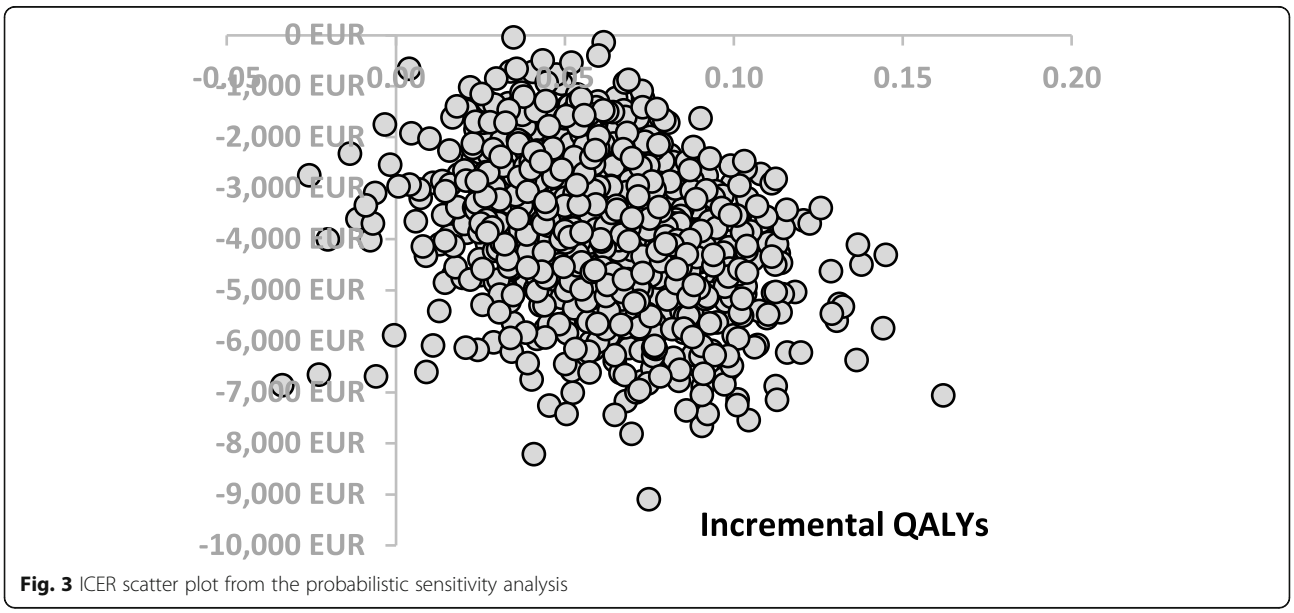

Fig. 3 ICER scatter plot from the probabilistic sensitivity analysis

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s40949-020-00036-w.

Additional file 1.

Abbreviations

CHD: congenital heart disease; CPAP: continuous positive airway pressure; ECMO: extracorporeal membrane oxygenation; ICER: incremental cost-effectiveness ratios; ICU: intensive care; LRTI: lower respiratory tract infections; PICU: pediatric intensive care unit; QALYs: quality-adjusted life-years; RSV: Respiratory syncytial virus

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Authors' contributions

AbbVie participated in the study design, retrieval of data, data analysis, review and approval of the publication. The authors interpreted the results and determined the final content. Dr. Estelle Naumburg had primary responsibility for study, protocol development, and writing the manuscript. Martin Eriksson had the performed the health economic analysis with input from Dr. Jonas Söderholm and contributed to the writing of the manuscript. Dr. Eva Fernlund and Jan Sunnegardh participated by acquisition of county council price list and clinical data, in the analytical framework for the study and contributed to the writing of the manuscript.

Availability of data and materials

The data that support the findings of this study are available in/from sources referred to in the manuscript, reference-list and Table 1.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

EF, JaS, and EN have nothing to disclose. ME and JoS are employed by AbbVie and may hold AbbVie stocks or stock options.

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