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Cost-effectiveness of potential infant vaccination against respiratory syncytial virus infection in The Netherlands

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ABSTRACT

Introduction: Respiratory syncytial virus (RSV) infection is one of the major causes of respiratory illness in infants, infecting virtually every child before the age of 2 years. Currently, several Phase 1 trials with RSV vaccines in infants are ongoing or have been completed. As yet, no efficacy estimates are available for these vaccine candidates. Nevertheless, cost-effectiveness estimates might be informative to enable preliminary positioning of an RSV vaccine.
Methods: A decision analysis model was developed in which a Dutch birth cohort was followed for 12 months. A number of potential vaccination strategies were reviewed such as vaccination at specific ages, a two- or three-dosing scheme and seasonal vaccination versus year-round vaccination. The impact of the assumptions made was explored in various sensitivity analyses, including probabilistic analysis. Outcome measures included the number of GP visits, hospitalizations and deaths, costs, quality-adjusted life years and incremental cost-effectiveness ratios (ICERs).
Results: Currently, without vaccination, an annual number of 28,738 of RSV-related GP visits, 1623 hospitalizations, and 4.5 deaths are estimated in children in the age of 0–1 year. The total annual cost to society of RSV in the non-vaccination scenario is €7.7 million (95%CI: 1.7–16.7) and the annual disease burden is estimated at 597 QALYs (95%CI: 133–1319). In case all infants would be offered a potentially safe and effective 3-dose RSV vaccination scheme at the age of 0, 1 and 3 months, the total annual net costs were estimated to increase to €21.2 million, but 544 hospitalizations and 1.5 deaths would be averted. The ICER was estimated at €34,142 (95%CI: € 21,652–€ 87,766) per QALY gained. A reduced dose schedule, seasonal vaccination, and consideration of out-of-pocket expenses all resulted in more favorable ICER values, whereas a reduced vaccine efficacy or a delay in the timing of vaccination resulted in less favorable ICERs.
Discussion: Our model used recently updated estimates on the burden of RSV disease in children and it included plausible utilities. However, due to the absence of clinical trial data, a number of crucial assumptions had to be made related to the characteristics of potential RSV vaccine. The outcomes of our modeling exercise show that vaccination of infants against RSV might be cost-effective. However, clinical trial data are warranted.

1. Introduction

Respiratory syncytial virus (RSV) infection is one of the major causes of respiratory illness among infants, infecting virtually every child before the age of 2 years [1,2]. The epidemiology of RSV shows a recurrent seasonal incidence pattern, similar to that of influenza, with an incidence peak in the winter months [3–7]. A previous RSV-infection may provide transient protection but does not prevent subsequent infections later on in life [2,8,9]. The course of many RSV-related episodes is mild but in a number of cases it is associated with a lower respiratory tract infection [1]. In approximately 1–2% of the cases, RSV-infection may lead to pneumonia and bronchiolitis requiring hospitalization [1,2,5,6,10]. Risk factors for RSV-hospitalization include prematurity,

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congenital heart disease (CHD) and bronchopulmonary dysplasia (BPD). RSV-induced bronchiolitis is associated with severe episodes of recurrent wheezing in infancy and asthma in 8–70% of cases [11–13]. In school-aged children, wheeze is no longer associated with a history of RSV-hospitalization [11,12]. The low incidence of RSV-related mortality makes it difficult to obtain consistent data on excess RSV-mortality in epidemiological studies. Only in a very small number of studies RSV-mortality was studied prospectively. Indeed, the majority of studies used a retrospective study design and could not demonstrate significant rates of RSV-associated mortality [3]. Mortality was primarily observed in the youngest children, aged <12 months. Estimates range from 0.03 per 100,000 to 5.3 per 100,000 population. The Dutch National Institute for Public Health and the Environment (RIVM) reports a mortality rate of 0.03 per 100,000 for the total population corresponding to a total number of 4.5 deaths annually due to RSV (equaling 2.78 per 100,000 infants 0–12 months of age). This is in line with estimates from the UK, where RSV-incidence patterns are similar to those in the Netherlands [10,14]. In the UK, RSV-associated excess mortality has been estimated at 2.9 deaths per 100,000 infants per year [14].

Treatment options for severe cases of RSV are limited. Hospitalization occurs when oxygen supplementation or intravenous fluids as well as nasogastric feeding is required [15]. Antiviral drugs such as ribavirin are indicated only in infants with a compromised immune system. Primary prophylaxis with palivizumab or RSV-immunoglobulin is expensive, potentially not highly cost-effective and should be provided restrictively. Yet, despite that palivizumab prophylaxis was not judged cost-effective in the Netherlands, conditional reimbursement was granted and more than 1800 Dutch prematurely born infants receive it annually [16].

In the light of the burden of disease and the potential cost-effectiveness of the possible prophylactic regimens, ideally a vaccine should be available that protects infants at risk. Given the fact that the majority of hospitalizations occur before the age of 6 months, this vaccine should induce protective immunity at a very early age. The development of an RSV-vaccine for children has been hampered by the disastrous outcome of a clinical trail with formalin-inactivated whole-virus RSV-vaccine in the 1960s. It appeared that vaccination with the vaccine did not confer protection, but rather primed the vaccinees for enhanced disease upon subsequent exposure to live RSV, leading to the death of two children [17]. The enhanced disease was linked to severe immunopathology as a result of a Th2-type cellular immune response induced by the vaccine, as well as the induction non-neutralizing antibodies [17–19]. Currently, several Phase 1 trials with live attenuated vaccines against RSV infection in infants are running or have been completed (www.clinicaltrials.gov, accessed March, 2011). Such live attenuated vaccines are likely to induce a more balanced immune response as compared to unadjuvanted inactivated vaccines.

The number of papers modeling RSV vaccination is limited and all have become available rather recently. One study performed in Spain in 2009 reviewed potential vaccination strategies in infants <1 yr of age and in the Netherlands vaccination was analyzed in infants <2 yrs of age [20,21]. This paper presents an update of our previous cost-effectiveness estimate of RSV-vaccination of infants in the Netherlands [21]. In addition to our previously reported model, we now include quality-of-life estimates in the model making it possible to provide an estimate of the overall cost-effectiveness of infant vaccination against RSV, expressed in € per quality-adjusted life year (QALY) gained. Furthermore, epidemiological data were updated, based on the most recent information [3,4].

2. Methods

2.1. Model

A Markov cohort model was developed in the decision analytic software package TreeAge Pro 2009 (see www.treeage.com for more information) and the model was analyzed using Monte Carlo simulation methods. The model is currently a static model, assuming a constant force of infection and no herd-immunity effects. The Markov cohort is a monthly Dutch birth cohort, which is followed for 12 months with a cycle length of one month.

In the analyses, a cohort of 180,000 newborns (approximating the Dutch birth cohort) is followed twice: once as a mainly vaccinated cohort and once as an unvaccinated cohort. The model outline is shown in Fig. 1. All newborns begin in the state "naïve/susceptible" at an age of 0 months. Each month the cohort faces a risk (transition probability) of a symptomatic RSV infection. This risk is dependent on the season (calendar month) and the age of the cohort (in months). A symptomatic infection may lead to health-care utilization such as a GP visit or hospitalization. Due to insufficient data on the actual number of symptomatic RSV infections, the model was calibrated to the number of GP visits. After having gone through a symptomatic RSV infection, the proportion of the cohort moves to either one of the states "acquired immunity" or "death". Dependent on the vaccination scenario, the cohort faces a monthly probability of being vaccinated. Vaccinated members of the cohort move to the state "vaccinated", which represents either full or partial immunity from symptomatic RSV infection, dependent on the specific parameter values for vaccine efficacy.

2.2. Baseline disease risks

In the Netherlands, infants with a clinical RSV infection are generally taken to a general practitioner (GP) by their parents or caretakers. The GP decides whether to refer the patient to a hospital. Hospitalized children may either be discharged or die. Estimating the magnitude of the health burden of RSV is challenging because a significant proportion of RSV-infections are asymptomatic, the size of RSV-epidemics varies across seasons, and outbreaks of RSV often coincide or overlap with outbreaks of influenza with comparable symptomatology [3,7,10]. Despite high incidence rates, mortality from RSV is very low in West-European countries, which hampers obtaining reliable mortality rates. Infants presented at the hospital with relevant symptoms are very often tested for RSV and therefore it is assumed that hospitalization and mortality rates are rather reliable for this hospitalized population. This is probably untrue for the GP data as patients are most often not clinically tested for RSV. Several authors have assessed the health burden from RSV. An overview of these assessments is presented and the result is discussed in Appendix A. The data from which the transition probabilities in the model are derived, are presented in Table 1.

Several authors have demonstrated an association between RSV-infection in infancy and chronic respiratory morbidity in childhood, such as asthma and episodes of recurrent wheezing [1,11–13]. However, it remains uncertain whether there indeed is a causal relationship between RSV-hospitalization and chronic respiratory morbidity. In addition, there is a wide range of estimates for both the proportion of RSV-hospitalizations associated with sequelae, and the duration and severity of the symptoms [1,13,22,23]. Because of the uncertainty in the association between RSV-infection and chronic respiratory morbidity later in life it was decided to model the occurrence of chronic respiratory morbidity as an alternative scenario. The assumptions for this scenario are presented in Table 1 and discussed in Appendix A.

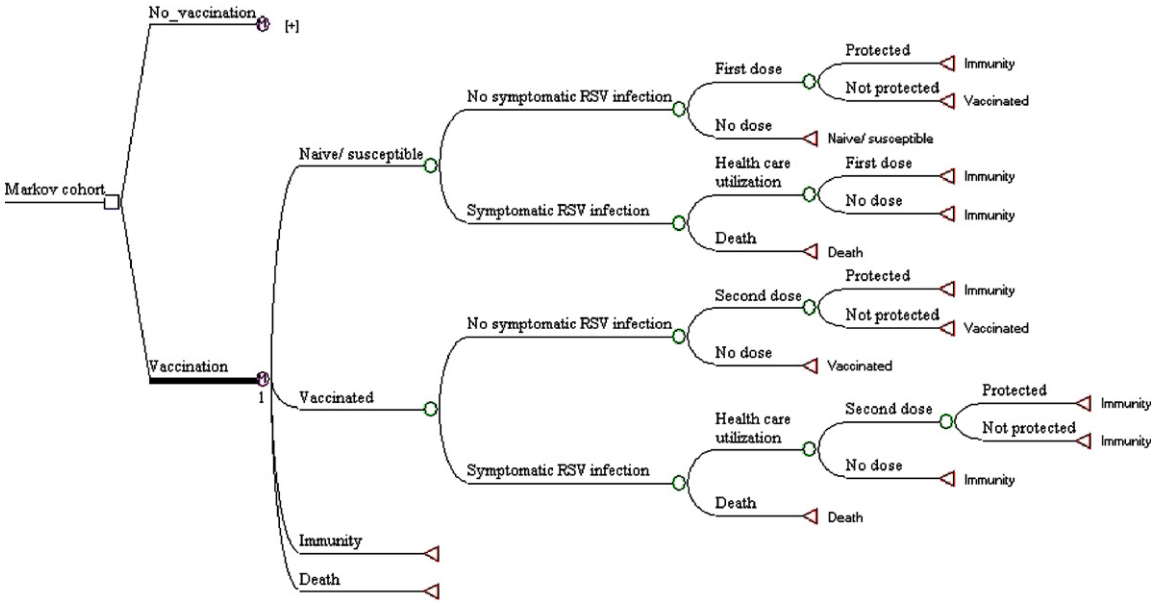

Fig. 1. Markov model for RSV vaccination in infants. A square denote decision branches (vaccination vs no vaccination). Circles represent chance nodes. Triangles denote end nodes.

2.3. Vaccine efficacy and vaccination strategies

As RSV-vaccines are still under development, assumptions had to be made regarding vaccine efficacy and dosing. Because RSV-vaccination is likely to be considered for inclusion in the National Immunization Program (NIP) in the Netherlands as well as in other countries, a vaccination strategy was considered in which all infants of a certain age are eligible for vaccination. Given the disease burden in the first year, vaccination was considered as early as possible. For a three-dose schedule vaccination was considered for infants

Table 1
Data used in the economic model. An overview of the consulted literature and supporting calculations is provided in Appendix A.

Health burden related to RSV	Mean or range	Distribution	Reference
Excess GP visits per 100 K/y (age 0–12 m/o)	16,000 (9400 as alt. scen.)	n/a	[3]
Proportion of GP visits with bronchi(oli)tis	35%	Beta (SD = 0.035)	[3]
Excess hospitalizations per 100 K/y (age 0–12 m/o)	900	n/a	[4]
Excess mortality per 100 K/y (0–12 m/o)	2.5	n/a	[14,15]
Duration of chronic respiratory morbidity (y)	5	Gamma (sd = 0.6)	[1,11]
Probabilities of events in age group 0–12 months old (based on the health burden summarized above)			See Appendix A for details
RSV-related GP visit	0.160	Beta (SD = 0.0160)	
RSV-related hospitalization (as % of GP visits)	0.05625	Beta (SD = 0.005625)	calc. from incidence data
ICU admissions (as % of hospitalizations)	0.02606	Beta (SD = 0.002606)	
RSV-related mortality (as % of hospitalizations)	0.002778	Beta (SD = 0.000278)	calc. from incidence data
RSV hospitalizations leading to chronic respiratory morbidity	0.30	Beta (SD = 0.008)	[1,11]
Costs associated with RSV-infections			
Cost of GP visit	€ 22.17	Fixed	[27]
Cost of RSV-hospitalization	€ 3749.36	Gamma (SD = 2000)	[5]
Productivity loss per GP visit (workdays)	0.25	Fixed	[29]
Productivity loss per hospitalization (workdays)	2.00	Fixed	[29]
Cost of lost workday (not corrected for productivity elasticity)	€ 250.48	Fixed	[27,29]
Productivity elasticity	30–45%	Uniform (1)	[27]
QALY decrements			
GP-treated RSV bronchi(oli)tis	0.01	Gamma (SD = 0.001)	[25]
RSV hospitalization	0.04	Gamma (SD = 0.004)	[25]
Chronic respiratory morbidity	0.08	Gamma (SD = 0.007)	[25,33]
Parameters related to vaccination program			
Level of protection against infection	scenario dependent	Beta	NVI, p.c.
Vaccination coverage rate	0.96	Beta (SD = 0.096)	NVI, p.c.
Price of vaccine per dose	€ 37.50	Fixed	NVI, p.c.
Price of administration costs	€ 5.00	Fixed	NVI, p.c.
Proportion of infections covered under various vaccination scenarios			
Year-round vaccination of all <3 m/o	0.62	Beta (SD = 0.062)	[5,6]
Vaccination in October, age groups 3–6 m/o	0.176	Beta (SD = 0.0176)	[5,6]
Vaccination in November, age groups 3–6 m/o	0.207	Beta (SD = 0.0207)	[5,6]
Vaccination in November, age groups 3–9 m/o	0.270	Beta (SD = 0.0270)	[5,6]
Vaccination in November, age groups 3–12 m/o	0.301	Beta (SD = 0.0301)	[5,6]

at the ages of 0, 1 and 3 months with vaccine efficacies of 30%, 60% and 75%, respectively. For a two-dose schedule, vaccination was considered at 0 and 3 month of age with vaccine efficacies of 30% and 70%. On immunological grounds, it is assumed that a three-dose schedule would result in a somewhat higher vaccine efficacy than a two-dose schedule, and that a one-dose schedule would be insufficient to provide adequate protection. In accordance with the coverage rate of the Dutch NIP, coverage for the total cohort was assumed to equal 96%. In the base case analysis, no waning effect related to the vaccine efficacy was taken into account.

In scenario analyses, several alternative scenarios were explored. A "seasonal" strategy was explored in which vaccination takes place only in the winter months, in order to protect the age groups at risk against the seasonal incidence peak. This would result in a lower coverage rate for the total birth cohort. However, as the approach is targeted at a high-risk condition, cost-effectiveness may be expected to be better. The age at which the vaccination schedule was completed was varied, and the effect of reaching a 70% vaccine efficacy already after the second dose was investigated. Also, the protective effect of vaccination wanes over time and therefore a linear and a plateau waning effect was explored in the analyses to review the potential impact on the ICER. The time period to look at the waning effect was ten years. The baseline disease risks with respect to the number of RSV-related GP visits was varied (9400 per 100,000 children <12 m/o per year) as was the occurrence of chronic respiratory morbidity. In addition to the average cost-effectiveness of immunization of all monthly birth cohorts before the age of 3 months, the cost-effectiveness of vaccination of each monthly birth cohort before the age of 3 months was investigated.

2.4. Utilities (QALYs)

Quality-of-life losses were included in the model as quality-adjusted life years (QALYs) which were connected to all health states. Five health states were distinguished: (1) asymptomatic or home-cared RSV-infection (no QALY decrement), (2) RSV-related bronchi(oli)tis treated at the GP, (3) RSV-related pneumonia or severe bronchiolitis requiring hospitalization, (4) chronic respiratory morbidity following RSV-hospitalization, and (5) death. Both QALYs and DALYs reported in literature were reviewed [24]. The Dutch National Institute for Public Health and the Environment (RIVM) assigns decrements to bronchi(oli)tis of 0.01 DALY, to pneumonia of 0.04 DALY and to asthma of 0.08 DALY [25]. These estimates were obtained by the RIVM by extrapolating daily quality decrements for a respiratory episode to a 365-day period.

Two papers present an assessment of quality of life after RSV-related hospital discharge [22,26]. One paper presents actual QALY scores [26]. In this study, quality-of-life in children, aged 2–4 years, with a history of preterm birth and RSV-hospitalization were compared with a control group of preterm children without a history of RSV-hospitalization. The median HUI 2 multi-attribute utility function was 0.88 in children with a confirmed RSV-infection, as compared to 0.95 in the control group. This would imply that the decrease in quality-of-life related to RSV is 0.07. The estimate of the utility (0.07) is in the same order of magnitude as the DALY (0.08) decrement for asthma and therefore the most conservative estimate of 0.07 was applied in the model.

2.5. Health-care resource use, productivity losses and corresponding costing

The analysis was performed from a societal perspective including both direct medical costs and indirect costs of production losses, all updated to 2009 (source: Central Bureau of Statistics of the Netherlands). Health-care costs include costs of GP-visits and costs of hospitalization (see also Table 1). Over the counter medications, such as nasal washes, have not been taken into account. The average costs of a GP-visit were estimated at €22.17 [27]. Based on a study by Rietveld et al. the cost of RSV-hospitalization was estimated at €3749 [6]. Societal costs included productivity losses by caretakers as a result of care giving to children suffering from RSV-infections. The Dutch modeling guidelines were followed and to calculate productivity losses, the friction-cost method was used [28]. Compared to the human capital method, the friction cost method conservatively estimates the productivity losses. It has been estimated that on average two parental workdays are lost as the result of an RSV-related hospitalization [29]. An RSV-related GP visit leads to a loss of 0.25 workdays. An average hourly wage of €31.31 was used for people in the age group 25–34 years old (young parents) with an average number of hours per workday of 8 [27]. The resulting figure of €251 per workday was corrected for a productivity elasticity of 80%. In the sensitivity analysis, the impact of a lower productivity elasticity was explored (30–45%) assuming that RSV-episodes will last no longer than 14 days [27]. In particular, research has shown that absence from work shorter than 14 days resulted in productivity losses of only 30–45% of the work time absenteeism.

The price of the vaccine was assumed to be fixed at €37.50 per dose plus administration costs of € 5.00 (personal communication,

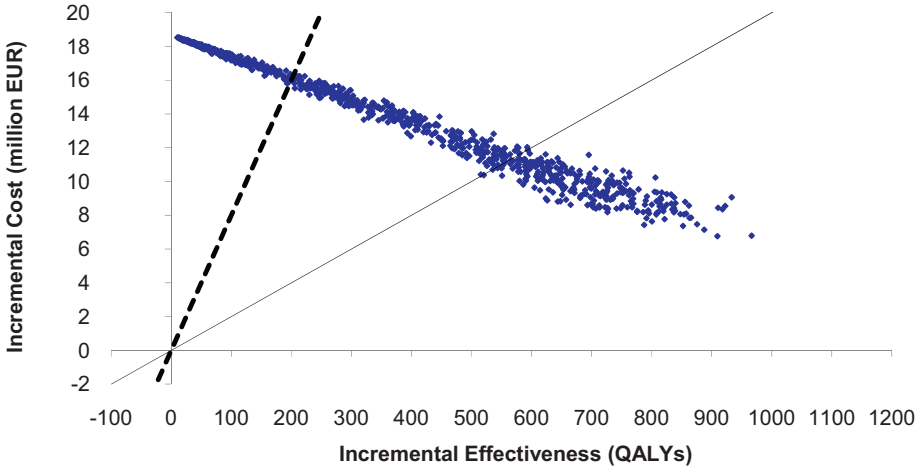

Fig. 2. Incremental cost-effectiveness scatterplot for RSV-vaccination versus no vaccination. The straight lines represent willingness-to-pay curves of € 20,000/QALY (solid) and € 80,000/QALY (dotted).

W. Luytjes). It was assumed that vaccination against RSV would be included in the existing infants NIP.

2.6. Outcome measures and cost-effectiveness analysis

The simulation model tracks the cases of RSV, deaths, costs and QALYs. Summing all the costs, life years and QALYs and consequently calculating the differences for the respective outcomes for the evaluations without and with vaccination rendered net costs and QALYs gained. Dividing the net costs by the health effects defined the cost-effectiveness ratio. Health effects and cost were discounted according to the Dutch guidelines for cost-effectiveness research at 1.5% and 4%, respectively. Cost-effectiveness ratios (CERs) were calculated for routine vaccination using different vaccination schedules compared to no vaccination.

2.7. Sensitivity analysis

Univariate, scenario and probabilistic sensitivity analyses were performed to explore parameter uncertainty. Transition probabilities were inserted as beta distributions and utility decrements as gamma distributions [30]. Cost-related parameters were inserted as fixed values when prices were fixed (GP-visit, vaccine-price), and as gamma distribution where they were estimated from a sample (hospitalization costs) or as uniform distributions (productivity elasticity in productivity loss estimation). Outcome values were generated by running the model 10,000 times. In the univariate sensitivity analyses, all relevant parameters were varied with 25% to explore the impact of each parameter relative to each other.

3. Results

3.1. Cost-effectiveness of RSV vaccination

In the current situation in which no vaccine is available, a total annual number of 28,738 of GP visits are estimated in children in the age of 0–1 year. The expected number of hospitalizations in this scenario is 1623 (95%CI: 356–3635) and the number of RSV-related deaths is 4.5 (95%CI: 0.96–10.5). The total annual cost to society of RSV disease is € 7.7 million if no vaccination is undertaken (95%CI: 1.7–16.7) and the annual disease burden is estimated at 597 QALYs (95%CI: 133–1319). In case all infants would be offered a three-dose vaccination scheme at the age of 0,1 and 3 months of age, this would result in higher costs of €21.2 million (95%CI: 19.1–25.1), but significantly lower numbers of hospitalizations (544–95% CI: 95.4–1386) and deaths (1.5–95%CI: 0.25–3.99). Vaccination would thus result in a cost per QALY of € 34,142 (95% CI: € 211,652–€ 87,766).

Table 2 shows the results of various options that can be considered, such as introduction of the vaccination at a somewhat later stage, for example when infants are 0, 2 and 4 months of age, and the effects of waning immunity. The results show that most health gains are obtained when the vaccine is offered as early as possible. Delaying the second and third dose both with one month already increases the ICER to € 40,900 per QALY. Furthermore, when a waning effect for the vaccine efficacy was taken into account this obviously negatively affected the incremental cost effectiveness ratio (ICER). Assuming a plateau waning effect in the base case resulted in a somewhat higher ICER of €38,544 per QALY and inclusion of a linear waning effect resulted in an ICER of €52,250 per QALY. Fig. 2 shows the scatterplot of the incremental cost effectiveness ratio for RSV-vaccination versus no vaccination.

3.2. Uncertainty and sensitivity analysis

Univariate sensitivity analyses showed that a number of changes in the model parameters resulted in less favorable ICERs. This is

Table 2
Results of the cost-effectiveness analysis. In brackets the 2.5–97.5th percentiles.

Scenario	Doses	Dosing schedule	Waning vaccine efficacy	Vaccine Efficacy	ICER (€/QALY)	Cost (mln €)	Effect (QALYs lost)	Hospitalizations	Deaths
No vaccination	n/a	n/a	n/a	n/a	n/a	7.7 (1.7–16.7)	597 (133–1319)	1623 (356–3635)	4.5 (0.96–10.5)
Year-round	3	0, 1, 3 m/o	None	30%, 60%, 75%	34,143	21.3 (19.1–25.1)	200 (35–504)	544 (95–1386)	1.5 (0.25–3.99)
Including waning vaccine efficacy									
Year-round	3	0, 1, 3 m/o	Plateau	30%, 60%, 75%	38,758	21.7 (19.2–25.0)	232 (77–645)	630 (97–1379)	1.75 (0.27–3.92)
Year-round	3	0, 1, 3 m/o	Linear	30%, 60%, 75%	51,606	22.7 (19.7–27.3)	309 (82–672)	840 (220–1865)	2.3 (0.60–5.3)
Alternative 3 dose schedule									
Year-round	3	0, 2, 4 m/o	None	30%, 60%, 75%	40,900	21.9 (19.1–27.1)	245 (36–663)	1611 (357–3635)	4.49 (0.96–10.4)
Year-round	3	0, 2, 4 m/o	Plateau	30%, 60%, 75%	43,917	22.2 (19.5–27.2)	269 (61–663)	73 (163–1829)	2.03 (0.45–5.21)
Year-round	3	0, 2, 4 m/o	Linear	30%, 60%, 75%	58,601	23.0 (19.7–28.7)	334 (36–254)	909 (206–2192)	2.5 (0.56–6.2)

the case, for example, when the incidence rates of RSV-related GP-visits are lowered, when – after a full dosing scheme – a lower expected vaccine efficacy is considered or when the time of vaccination is delayed (for example to 0, 2 and 4 months). The disease burden as such and the distribution of the disease burden over the age groups considered highly influence the incremental cost-effectiveness ratios. Consideration of an equal distribution of the GP-visits over the age groups of 0–12 and 13–24 months (in the base case 86% in the 0–12 months and 14% in the 13–24 months of age), results in a lower number of GP-visits in the youngest age group and this lower incidence results in a higher ICER. When all other parameters remain equal, this would result in an ICER of € 77,775.

In the base case, the majority of the disease burden is in children under the age of 6 months and this is also confirmed by the ICER when considering a three dose vaccination scheme for infants when they are 6, 7 and 8 months of age. This would result in an incremental cost effectiveness ratio of around € 287,000 per QALY.

The vaccine price has a moderate influence on the ICER. A vaccine price of € 25 in the base-case analysis results in an ICER of around €18,600 per QALY and a vaccine price of € 60 euro result in an ICER of around € 60,000 per QALY.

The base-case analysis did not include waning immunity for vaccine efficacy but when this is included this would also have a negative impact on the ICER (see for the results Table 2). On the other hand there are also a number of changes in model parameters that would have a positive impact on the ICER. These include, for example, a highly efficacious 2-dose vaccination schedule, offering the vaccine in a seasonal vaccination schedule, like – for example – for influenza, or consideration of out-of-pocket payments.

4. Discussion

This paper addresses the challenges which a potential RSV-vaccination strategy for children will have to face when it is considered for inclusion into national vaccination programs. In addition to the previous study by Bos et al. [21], our model includes updated estimates on the burden of RSV-disease from Jansen et al. [3,4] and it also includes quality of life data. Because RSV-vaccines are still in development, few clinical studies are available and, in the Netherlands as well as elsewhere, large-scale clinical trials are not expected before 2012. Based on (i) available epidemiological data in children and on (ii) a number of assumptions that had to be made in the absence of, for example, vaccine efficacy data, the potential cost-effectiveness of RSV-vaccination of children has been estimated. The base-case analysis showed a potential for RSV-vaccination to be cost-effective according to current standards. Our study shows that the continuous interest in development of effective RSV-vaccines is relevant from a health-economic perspective, which is important for the decision-making process in the Netherlands and elsewhere. As soon as more data become available, for example from vaccine trials, the model will be re-analyzed in order to review the impact of the updated evidence.

Taking the current model into account, our study has several limitations.

First, the current Markov model is a static model, assuming a constant force of infection and no herd-immunity effects. Increasingly, dynamic models are being used and advocated in cost-effectiveness analyses of vaccination programs [31]. These models enable the analysis of herd-immunity effects, possible age shifts in epidemiology and changing forces of infection, but are generally highly complex and require extensive information to parameterize them. Therefore, in the present situation, with as yet only limited available information on the characteristics of a potential RSV-vaccine, the initial use of a static approach is justified. A dynamic approach is warranted when further information on the efficacy of RSV-vaccination becomes available from epidemiological studies, subsequent clinical trials and observational studies on the consequences of RSV-vaccination in routine daily practice [32].

Second, in databases symptomatic RSV infections are registered whereas it is known that most RSV infections are asymptomatic infections which also lead to (partial) protection. The effect these infections have on the total disease burden is unknown but expected to be significant due to the duration of the illness, the costs involved in it; both direct medical cost as well as productivity losses for the parents. The exclusion of these infections from the model is expected to lead to an underestimation of the potential benefit of vaccination.

Third, epidemiological data show that around 90% of infants experience their first RSV infection before the age of two and that the incidence of RSV related hospitalizations and LRTI's decreases with age. The highest disease burden is observed in children 1–6 months of age. It is suggested that there is little protective effect after the first infection, although there are indications that the primary infection is the most severe and that the course of subsequent infections is milder [3,4]. The epidemiological data used in the model only include the primary infection and therefore the data are all independent observations. Taking only the primary symptomatic infection into account is expected to lead to an underestimation of the total disease burden but a straightforward extrapolation based on a higher number of infections per person is not possible due to the milder course of the disease for subsequent infections [3,4].

Fourth, the epidemiological study that has been the primary source of the epidemiological data in the model considered the excess mortality due to RSV and did not report any significant excess mortality in the study sample. Other studies report a mortality rate of between 0.5 and 8 per 100,000 infants. Due to the variety of mortality data reported, the influence of this model parameter is reviewed critically in the sensitivity analyses. Because of the significant influence it has on the incremental cost-effectiveness ratio, it is important to gather long-term, detailed national mortality data on RSV.

Fifth, it is unknown whether hospitals regularly test for RSV-infection when very young infants are brought into the hospital with respiratory-tract illness. Therefore, missing cases are certainly expected from these registries, and it will also remain a challenge in the future to obtain reliable national hospital data on infants with an RSV-infection.

Lastly, the model did not assess the potential cost-effectiveness of RSV-vaccination when only high-risk groups or groups which are currently receiving prophylactic therapy (palivizumab) are targeted. Assuming that 1800 infants (1% of the birth cohort) receive prophylactic therapy at a cost of €3645 euro per person (for five injections), we estimate that the yearly RSV-related costs of palivizumab amount to 6.6 million euro in the Netherlands. This is highly significant, taking into account that the total RSV-related costs in the absence of vaccination are estimated at 7.7 million euro, of which hospital-related costs are around 3.7 million euro (48%). Considering that part of the infants currently receiving prophylactic therapy might shift to vaccination might further improve cost-effectiveness of vaccination.

The results of the study show that there is a need for promoting, improving and extending the European RSV surveillance system. Future research might focus on the potential effect of clustering because of the possibilities for subsequent infections. To obtain a better overview of the total burden of RSV-disease, it would be valuable to have a detailed insight in the proportion of children experiencing one or more RSV-infections. Also, more research is needed to estimate the protective effect of a primary RSV-infection. In addition, it is important to know whether there is some level

of indirect protection of young infants when older infants/siblings are immunized. Furthermore, the use of a dynamic model should be considered when additional information on these aspects of RSV-infection and -vaccination becomes available. An alternative vaccination strategy that might be considered is the immunization of pregnant women in order to provide a degree of passive protection to the babies via transplacental immunity. Antibodies are the main mediators of protective immunity (which is the case with RSV) and therefore maternal antibodies will also protect the baby.

Finally, it will be of interest to review the burden of RSV-disease and the cost-effectiveness of RSV-vaccination among the elderly.

Decision-makers usually review all available data. However, soon after a vaccine is available on the market, mainly efficacy data from randomized clinical trials can be considered. The effect of vaccination in an uncontrolled environment has to be shown afterwards, including potential herd-immunity effects. The results of this study indicate that depending on vaccination efficacy, RSV-vaccination might be more cost-effective than the previously Dutch pneumococcal vaccination program with the seven-valent pneumococcal vaccine [32]. Cost-effectiveness analyses for the pneumococcal vaccine have recently been updated and resulted in less favorable ICERs than the ICERs that were considered when it was decided to include the vaccine in the NIP. At the same time, the results also show that RSV-vaccination might be less cost-effective than other potential vaccination programs which are not yet implemented in the Netherlands. It is important to keep in mind that, among others, the quality of epidemiological data, the disease burden, the availability of alternative treatments for a disease, the relationship with the compliance to the other vaccines included in the national scheme are all important parameters to consider. Ergo, cost-effectiveness is only one of many aspects to be taken into account by decision-makers when they consider a particular vaccination for inclusion in the national immunization scheme.

Appendix A.

This appendix describes the background of the probabilities for RSV-related health care utilization that are presented in Table 1 of the main text in more detail in order to justify the choices made (*Data used in the economic model*). The overall strategy was to build our model on incidence data estimated for the Netherlands. Available international data was presented to reflect on the choices which were made when national data was lacking, available data from other countries were used in the model.

A.1. GP visits related to RSV

Table A1 summarizes the literature search performed assessing the RSV-associated primary health care burden. Five studies were included in the research, two studies retrospectively looked at the RSV figures and two studies used a prospective study design and three studies were performed in the Netherlands. In addition, one report was available from the Dutch National Institute for Public Health and the Environment but unfortunately no references were used in this document. The data show considerable variation in the estimates. Notably, the estimate by the Dutch National Institute for Public Health and the Environment [15] is much lower than the estimate for the Netherlands provided by Jansen et al [4]. The study of Jansen is valued higher than the report by the institute for public health and the environment due to the fact that no study design and references were available for the report of the later institute and the study from Jansen covers an eight-year period which reduces the risk of outliers (e.g. regression to the mean). RIVM estimates the number of hospitalizations at 209 per 100 K <60 m/o (see below). If the number of GP visits would be 413 per 100 K <60 m/o, this would imply that >50% of RSV-cases presented at the GP is referred for hospital admission, which we consider to be an unlikely high estimate. In their conservative scenario, Jansen et al. [4] estimate the number of GP visits at 9400 GP visits per 100,000 children under 24 m/o. The proportion of the under 12 months olds in this figure is not provided and could not be retrieved from the available data. When the same age distribution as for hospitalizations is applied (84–86% of total hospitalizations occur in the age groups 0–12 months and the remainder in the age group 13–24 months), the number of GP visits in the age group 0–12 months of age would approximately be 16,000 per 100 K per year ($0.85 \times (9401 + 9401) = 16{,}000$. Assuming that the GP visits are equally distributed among the age groups 0–12 months and 13–24 months, the number of GP visits under 12 months would be 9400 per 100 K per year. These two scenarios were tested in the model.

A.2. Hospitalizations related to RSV

Table A2 summarizes the literature search performed on hospitalizations related to RSV. The studies are performed in the USA,

Table A1
Overview of the literature regarding GP visits caused by RSV.

Paper	Country	Period	Study type	Study size	Age group	Clinical event	Incidence per 100 K/y
[15]	Netherlands	n.s.	n.s.	n.s.	<60 m/o	RSV-GP	413
[3]	Netherlands	1997–2003	Retrospective	47,000	<24 m/o	RSV-URTI-GP	Peri-seasonal: 5477 Summer: 9772
						RSV-LRTI-GP	Peri-seasonal: 3924 Summer: 5275
[29]	Netherlands	1998–2000	Prospective surveillance	Parent questionnaire 73 RSV-H	9–537 d/o; median 79	RSV-GP	n.s. Average of 2 RSV-GP visits per RSV-H
[34]	Netherlands	2003–2006	Prospective birth cohort	668 samples in 305 subj.	<12 m/o	RSV-GP	n.s. RSV-GP in 30% of 31 single-pathogen RSV
[10]	UK	1994–2004	Retrospective virological/incidence data	Population 650,000	<12 m/o	RSV-GP	12,000
[35]	USA	n.s.	n.s.	n.s.	<24 m/o	RSV-ED	6440

RSV-H: Hospitalization for RSV.
RSV-GP: GP visit attributed to RSV infection.
RSV-LRTI-GP: GP visit for lower respiratory tract infection (bronchiolitis or pneumonia) attributed to RSV infection.
RSV-URTI-GP: GP visit for upper respiratory tract infection (bronchiolitis or pneumonia) attributed to RSV infection.
N.s.: Not specified.

Table A2
Overview of literature regarding RSV-related hospitalizations.

Paper	Country	Period	Study type	Study size	Age group	Clinical event	Incidence per 100 K/y
[15]	Netherlands	n.s.	n.s.	n.s.	<60 m/o	RSV-H	209
Netherlands Statistics, 2009	Netherlands	2006–2007	Registration	National	<12 m/o	LRTI-H	2006: 1932 2007: 2322
Netherlands Statistics, 2009	Netherlands	2006–2007	Registration	National	<12 m/o	URTI-H	2006: 3578 2007: 3507
[4]	Netherlands	1997–2003	Retrospective	47,000	<12 m/o	RSV-LRTI-H	Peri-seasonal: 870 Summer: 1063
					<24 m/o	RSV-URTI-H	Peri-seasonal: 34.7 Summer: 90.6
[36]	UK	2000–2001	Retrospective	613	<12 m/o	RSV-H	1906
[37]	UK	1993–1996	Retrospective	n.s.	<12 m/o	RSV-H	2440
[38]	USA	2000–2004	Retrospective	n.s.	<6 m/o	RSV-H	1700
					7–12 m/o	RSV-H	500
[39,40]	USA	1989–1993	n.s.	n.s.	<12 m/o	RSV-H	3000
[40]	USA	n.s.	n.s.	n.s.	<12 m/o	RSV-H	1290–3000
[41]	USA	2000–2001	Prospective surveil-lance	812	<6 m/o	RSV-H	1850
					7–12 m/o	RSV-H	740
					<12 m/o	RSV-H	1290
[42]	USA	1997–1999	Retrospective	297,684 records	<12 m/o	RSV-H	2520
[43]	Denmark	1995–1996	Retrospective	459 records	<6 m/o	RSV-H	3400
[44]	Germany	1996–1999	Prospective surveillance	1241 samples	<12 m/o	RSV-H	1214

RSV-H: Hospitalization for RSV infection.
RSV-URTI-H: Hospitalization for upper respiratory tract infection caused by RSV.
RSV-LRTI-H: Hospitalization for lower respiratory tract infection caused by RSV.
LRTI-H, URTI-H: Hospitalization for lower, upper respiratory tract infection, etiology not specified.
n.s.: not specified

the UK and the Netherlands, they cover different study periods and use various study design such as registration, retrospective cohort studies and two used a prospective surveillance study design. The age groups generally included in the studies are either below 12 or below 24 months of age and the main outcome parameter is RSV-hospitalization. Since the latest studies are performed in the Netherlands, they also cover either the total population or have included a very significant part of the population the model will make use of the available Dutch estimates. RIVM estimates the number of RSV-hospitalizations at 209 per 100 K <60 m/o. If we apply the age distribution estimated by Jansen to this figure, (79–84% of RSV-related hospitalizations in <12 m/o), we arrive at an estimate of 826–878. This estimate is quite in line with the conservative estimate by Jansen et al. of 901 hospitalizations per 100 K <12 months old, which was used as the default value in the model [4].

A.3. Mortality related to RSV

Table A3 summarizes the results of the literature search performed on the mortality of RSV. Only a very small number of studies looked at RSV mortality, the majority of studies used a retrospective study design and did not find significant mortality rates. Mortality was primarily observed in the youngest children, age <12 months and the study with the largest study sample was performed in the Netherlands. Estimates range from 0.03 per 100,000 to 5.3 per 100,000 population. RIVM reports a mortality rate of 0.03 per 100,000 for the total population corresponding to a total number of 4.5 deaths per year due to RSV. However, no reference was made to an article for this figure. Assuming that all mortality occurs in the youngest age group, this estimate would equal a mortality of 2.7 per 100 K <12 m/o (the size of the birth cohort in the Netherlands is approximately 180,000). This figure is however not confirmed by other Dutch papers, where no mortality was found [4,6]. Fleming and colleagues estimated the mortality rate for the UK at 2.9 per 100,000 and Howard and colleagues was at the high end with a mortality rate of 5.3 per 100,000 for the USA.

For the base case analysis, taking into account the variability in mortality data, the model uses an average of 2.5 per 100,000 population for the 0–12 months of age group. The influence the mortality rate has on the outcomes of the study will be looked at using sensitivity analyses.

Table A3
Overview of literature regarding RSV-related mortality.

Paper	Country	Period	Study type	Study size	Age group	Mortality per 100 K/y
[4]	Netherlands	1997–2003	Retrospective	47,000	<12 m/o	none
[15]	Netherlands	n.s.	n.s.	n.s.	Population	n.s. 0.03
[14]	UK	1989–1999	Retrospective	National	<12 m/o	2.9
[2]	USA	n.s.	Review	n/a	n.s.	n.s. 0.5–2% mortality in RSV-H
[1]	Netherlands	n.s.	Review	n/a	n.s.	n.s. <1% mortality in acute bronchiolitis
[45]	USA	1976–1999	Retrospective	n.s.	<12 m/o	3.1
[6]	Netherlands	1996–1998	Retrospective cohort	2469 RSV-H	<12 m/o	none
[46]	USA	1993–1995	Retrospective	10,767 RSV-H	<4 yrs of age	n.s. 5.3(390 deaths)

Table A4
Overview of literature regarding age and seasonal distribution of RSV-infections.

Paper	Country	Period	Study type	Study size	Clinical event	Age/seasonal distribution
[5,6]	Netherlands	1996–1998	Retrospective	2469 RSV-H	RSV-H	Cumulative distribution of cases: <3 m/o 38%, <6 m/o 68%, <9 m/o 82%, <12 m/o 90%.
[4]	Netherlands	1997–2003	Retrospective	47,000	<12 m/o	Cumulative distribution of cases: <12 m/o 79–84%
[41]	USA	2000–2001	Prospective	812	RSV-H	Cumulative distribution of cases: <6 m/o 56%, <12 m/o 78%
[46]	USA	1993–1995	Retrospective	10,767 RSV-H	RSV-H	70% of all RSV-H <12 m/o
[5,6,46]	Netherlands	1996–1998	Retrospective	2469 RSV-H	RSV-H	O (4%) N (23%) D (33%) J (21%) F (11%) M (6%) A (2%)
[47]	Netherlands	1992–2003	Retrospective	15 RSV-ICU	RSV-ICU	N = 15. O (1) N (1) D (6) J (4) F (2) M (1) A (0)

RSV-H: Hospitalization for RSV infection.
RSV-ICU: Treatment in Intensive Care Unit for RSV infection.
The letters O, N, D, J, F, M and A stand for the months of the RSV season, starting in October.

Table A5
Overview of literature regarding RSV-related chronic respiratory symptoms.

Paper	Country	Period	Study type	Study size	Age group	Clinical event	Risk
[12]	n/a	n/a	Review	n.s.	n.s.	Recurrent wheezing after RSV-H	42–71% until 13 y/o
[22]	Netherlands	1999–2002	Prospective	140 RSV-H	start <12 m/o followed 3 y	Wheezing after RSV-H	55% after 3 m 10% 18 m
[11]	n/a	1978–1998	Review	n.s.	start <12 m/o followed 10 y	Wheezing after RSV-H	40% until 5 y after RSV-H (11% control)
[1]	n/a	n/a	Review	n/a	7–11 y/o	Recurrent episodes of asthma	>50% of ex-RSV-H
[23]	Sweden	n.s.	Retrospective	46 ex-RSV-H	13 y/o	Asthma-like symptoms	43% with symptoms vs. 8% control
[48]	n.s.	1980–1997	Prospective birth cohort	207 RSV-URTI	0–13 y	Wheezing after RSV-URTI	Association significant until 13 y/o

A.4. Age and seasonal distribution of RSV-infections

Table A4 summarizes the literature search performed on hospitalizations related to RSV specifically looking at age and seasonal distributions of RSV infections. All studies indicate that the majority of all RSV hospitalizations (70–90%) occur in infants <12 m/o, and that the largest disease burden falls upon <6 months olds which is in line with the epidemiology of RSV The majority of studies used a retrospective study design and a study period of 3 years was very common. One study included a much longer study period but only looked at the cases treated in the ICU and one retrospective cohort study looked at all RSV related cases including hospitalizations. Generally, it is expected that the data presented on hospitalized cases in infants is reliable as it is one of the most likely causes for hospitalization in infants and is therefore regularly performed. In the model, estimates of RSV hospitalizations by Rietveld et al. [6] and Jansen et al. [4] are used. Both authors performed their studies in the Netherlands. The estimate was included in the model as a multinomial Dirichlet distribution. The seasonal distribution of cases used in the model was also derived from Rietveld and also inserted as a multinomial Dirichlet distribution in our model. In Figs. 3 and 4 the attack rate per calendar month and the attack rate per month during the first year of life is presented. The information from both figures is used in the model to calculate the attack rate per age group per month.

A.5. Chronic respiratory morbidity

Table A5 summarizes the literature search performed on the occurrence of sequelae after severe RSV infection. There is a wide range of estimates regarding the proportion of former RSV cases that suffer from chronic respiratory symptoms, the duration of symptoms, and the severity of these symptoms. But also the study types differ, study sizes are relatively small and the clinical events evaluated are not always similar. However, despite these differences, most studies find a gradual decrease in symptoms as

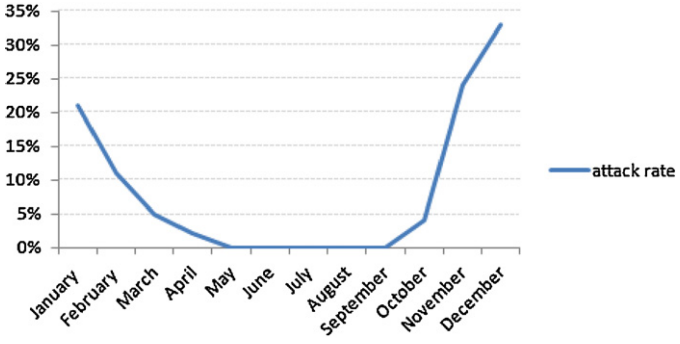

Fig. 3. Attack rate per calendar month.

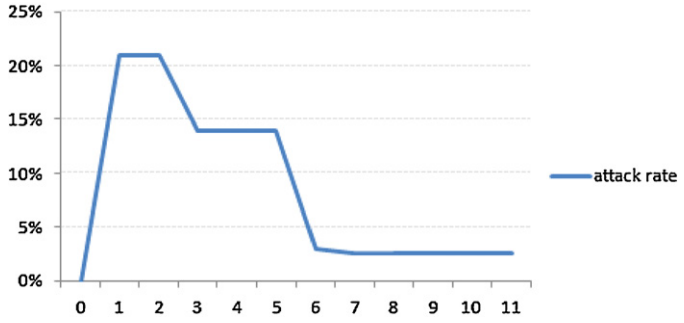

Fig. 4. Attack rate per month during first year of life.

children progress into school age. As indicated in the Methods section of the paper, due to the uncertainty regarding the causal relationship, the occurrence of sequelae was only included in the model as an alternative scenario. Assuming a baseline disease risk of recurrent wheezing of approximately 10% [11], an excess risk of 30% for recurrent wheezing was taken into account in the model, with an expected duration of symptoms of 5 years.

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