Cost-effectiveness of inactivated influenza vaccination in children with medical risk conditions in the Netherlands

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ARTICLE INFO

ABSTRACT

Background: In many countries, annual immunization with inactivated influenza vaccine (IIV) is recommended for children with medical risk conditions. Prior cost-effectiveness analyses found such immunization to be cost saving, but assumed effectiveness against non-severe influenza outcomes and a higher effectiveness against severe influenza outcomes than recent studies would suggest. However, recent vaccine studies do not indicate any reduction in community or outpatient disease episodes in IIV immunized individuals. We therefore evaluated cost-effectiveness of IIV immunization in children with medical risk conditions in the Netherlands, assuming that IIV reduces influenza-related hospitalization and death, but has no meaningful impact on non-severe health outcomes.
Methods: A health economic decision tree model was developed to evaluate health effects and costs of annual IIV immunization versus no immunization. Model inputs were based on our study on influenza-related primary care visits and other literature. Immunization was considered cost effective if associated costs were less than €20,000 per quality-adjusted life year (QALY) gained. Probabilistic sensitivity analyses were performed to assess robustness of results, and one-way sensitivity analyses and scenario analyses were done to assess the influence of individual parameters.
Results: Annual IIV prevents an average of 1.59 influenza-related hospitalizations and 0.02 deaths per 1,000 children with medical risk conditions. This results in an expected QALY gain of 0.43 at incremental costs of €21,564 per 1,000 children, corresponding to an incremental cost-effectiveness ratio (ICER) of €50,297/QALY compared to no immunization. Under base case assumptions, immunization had a 5% probability of being cost effective. Results were most influenced by vaccine efficacy against fatal influenza, QALY loss due to death, and mortality rate.
Conclusions: If IIV only reduces severe disease outcomes, as current evidence suggests, annual immunization of medical risk children is unlikely to be cost effective. Results should however be interpreted with caution as cost-effectiveness is largely dependent on incidence and QALY losses for fatal influenza, for which evidence is scarce.

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1. Introduction

Influenza is a major cause of respiratory disease and complications, in particular in individuals with underlying medical conditions, such as chronic respiratory disease, diabetes mellitus and cardiovascular conditions. To control the influenza disease burden, annual immunization with inactivated influenza vaccine (IIV) of medical risk groups from six months of age is recommended in many countries, including the Netherlands [1]. The recommenda-tion to vaccinate children with medical risk conditions annually with IIV relies on a thin evidence base [2]. Prior cost-effectiveness analyses found such immunization to be cost saving [3–5], but assumed vaccine effectiveness to be around 70%, while recent studies have shown a vaccine effectiveness of 51% against influenza-related death [6] and of 57% against influenza-related hospitalization [7]. More importantly, earlier cost-effectiveness analyses assumed vaccine effectiveness against non-severe disease outcomes. However, there is a lack of convincing evidence that IIV immunization reduces non-severe health outcomes, including community or outpatient episodes of acute respiratory illness. This fuels debate on whether the current policy actually qualifies as an efficient allocation of healthcare budgets.

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Although IIV immunization reduces influenza incidence in case of adequate antigenic match between the vaccine and circulating influenza strains [2,8], the estimated impact on respiratory disease incidence and severity varies widely between studies and across seasons [2,8–11]. Several studies found no, or a very limited, impact of IIV immunization on seasonal respiratory illness occurrence [8,9,11–15]. Of these, two studies were performed in medical risk children in the Netherlands, and found no impact of IIV immunization on the occurrence of upper respiratory tract infections and asthma exacerbations [11] or primary care attended respiratory illness episodes during influenza epidemic periods [12]. It is hypothesized that this lack of impact results from viral interference, where prevention of one respiratory virus infection (i.e. influenza) influences the risk of infection by another respiratory virus [16,17]. By contrast, effectiveness against severe influenza outcomes, such as hospitalization or death, has been widely demonstrated [6,18–21], possibly because immunization also reduces influenza disease severity. Prior cost-effectiveness analyses evaluating IIV immunization in children considered a reduction in disease from prevention of non-severe influenza episodes. It is unknown whether immunization would still be cost effective if no reduction in non-severe disease outcomes is assumed. Therefore, we performed a health economic evaluation to assess the cost-effectiveness of IIV immunization of children with medical risk conditions, assuming immunization is effective against severe influenza outcomes, defined as those requiring hospitalization or resulting in death, but has no impact on non-severe outcomes occurring in the community or primary care.

2. Methods

The health and economic impact of immunization in children with medical risk conditions was evaluated as compared to no immunization using a decision tree-type model developed in Excel (Version 2010, Microsoft). This static type of model was chosen because the decision to vaccinate is a yearly choice without long-term illness consequences. Medical risk conditions included respiratory (e.g. recurrent wheeze/asthma) and (congenital) cardiovascular disease, diabetes mellitus, chronic kidney disease or immunocompromising conditions (e.g. primary immunodeficiency, auto-immune disease, HIV or use of immunosuppressive medication), according to Dutch primary care guidelines [22]. Children with medical risk conditions who develop influenza may be admitted to the hospital, which may either result in influenza-related death or full recovery from disease (Fig. 1). The remainder

of the Methods section first provides a detailed description of the input parameters used in the health economic evaluation, and then discusses model outcomes and analyses.

2.1. Influenza-related hospitalization parameters

Data on the contribution of influenza to hospitalizations in medical risk children are scarce. Jansen et al. used two indirect methods to estimate influenza-related hospitalizations in all children (both with and without medical risk conditions) aged 0–1 year, 2–4 years, and 5–17 years. Age-stratified hospitalization rates for all-cause respiratory tract infections and pulmonary disease during influenza epidemic periods were either compared to (i) summer baseline or (ii) peri-seasonal baseline periods [23], while adjusting for co-circulation of respiratory syncytial virus (RSV) based on virus surveillance data. Given a lack of consensus on the most accurate comparator, we used the average estimate of the two baseline periods for each age group. Next, we calculated age-specific relative risks (RRs) of influenza-related hospitalization for children with versus without medical risk conditions using stratified hospitalization rates from a US-based study [24]. The overall influenza-related hospitalization rates from Jansen et al. were then subdivided into rates for children with and without medical risk conditions using those RRs [24] and the age-specific prevalence of medical risk conditions from De Hoog et al. [12] (see Appendix Table 1 for details). Using this methodology, we derived base case hospitalization rates of 578 per 100,000 for 0–1 year-olds, 348 per 100,000 for 2–4 year-olds, and 111 per 100,000 for 5–17 year-olds (Table 1).

2.2. Influenza-related mortality parameters

As for hospitalizations, influenza-related mortality estimates for children with medical risk conditions were not available from literature and we used mortality estimates including all children from Jansen et al. [23] instead. For children aged 2–17 years, we averaged the influenza-related mortality rate estimated from summer and peri-seasonal baseline. For 0–1 year-olds, Jansen et al. estimated zero influenza-related mortality and argued that this may be due to a lack of power, given that other studies did observe influenza-related deaths in infants, with generally highest mortality in children < 1 year of age [25,26]. We therefore used the mortality rates in Shang et al. [27] to calculate the RR of dying at 0–1 years of age versus at 2–17 years of age. We then multiplied this RR with the average influenza-related mortality at ages 2–17 years
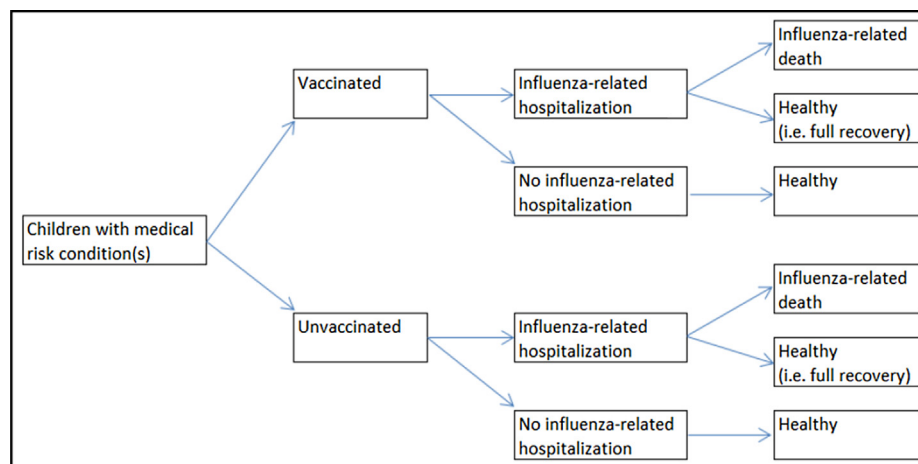

Fig. 1. Decision tree of influenza vaccination in children with medical risk conditions.

from Jansen et al. to determine the mortality rate for 0–1 year-olds in the general population. Mortality rates were then converted to rates for children with medical risk conditions using the age-specific percentage of influenza-related pediatric deaths found in children with medical risk conditions from Flannery et al. [6], and the age-specific prevalence of medical risk conditions from De Hoog et al. [12] (see Appendix Table 2 for details). Using this methodology, we derived base case mortality rates of 9.1 per 100,000 for 0–1 year-olds, 2.3 per 100,000 for 2–4 year-olds, 2.6 per 100,000 for 5–12 year-olds, and 3.5 per 100,000 for 13–17 year-olds (Table 1).

As influenza-related mortality in children is rare and difficult to measure, the uncertainty around published estimates is large. In scenario analysis, we used mortality estimates from Wijngaard et al. [28], who used the incidence of influenza-like illness rather than the conventional influenza positivity rate as a measure of influenza activity, without correction for co-circulating other respiratory viruses. This provides an upper bound on influenza-related mortality. For base case and scenario analyses we also performed probabilistic sensitivity analyses (PSA) assuming a wide range of influenza-related mortality rates, including zero.

2.3. Utility parameters

A small loss in quality of life (0.0001 QALYs, equivalent to ~ 1 h) was assumed for getting vaccinated, of which the associated pain is a source of anxiety and distress for many children [29]. For influenza-related hospitalization, an average QALY loss of 0.016 (equivalent to 5.84 days) was assumed (Table 1) [30].

Table 1
Input parameters of decision tree model of influenza vaccination.

Parameter		Base-case value	Distribution in PSA	Source(s)
INFLUENZA SEVERITY				
Influenza-related hospitalizations per 100,000 children with medical risk conditions				
Ages 0–1 years		**578.0**	*	
Ages 2–4 years		**348.3**	*	
Ages 5–17 years		**110.8**	*	
Influenza-related mortality per 100,000 children with medical risk conditions				
Ages 0–1 years		**9.1**	*	
Ages 2–4 years		**2.3**	*	
Ages 5–12 years		**2.6**	*	
Ages 13–17 years		**3.5**	*	
VACCINE EFFICACY				
Influenza-related hospitalization		**57%**	100-Gamma(43/2,2)[†]	Restivo et al. [18]
Influenza-related death		**51%**	100-Gamma(49/3,3)[†]	Flannery et al. [6]
QALY LOSS				
Vaccination		**0.0001**	Normal (0.0001,0.00005)[‡]	Assumption
Influenza-related hospitalization		**0.016**	Normal (0.016,0.00082)[‡]	Baguelin et al. [30]
Influenza-related death (discounted) – overall (2/3 limited; 1/3 normal)		**21.20**	Gamma ($\sqrt{21.20}$,$\sqrt{21.20}$)	Flannery et al. [6][§]
Influenza-related death (discounted) – limited life expectancy	13.69			Bruijning-Verhagen et al. [31]
Influenza-related death (discounted) – normal life expectancy	36.22			Statistics Netherlands [32]
COSTS OF VACCINATION				
Vaccine		**10.71**	‖	National Health Care Institute [34]
GP reimbursement		**11.36**	‖	National Influenza Prevention Program [54]
Productivity loss parents		**3.64**	¶	
Productivity loss per parent (in hours)	2			Prosser et al. [55]
% of parents with productivity loss	5%			Portegijs and Van den Brakel [36]
Productivity loss per hour (2017 €)	36.41			Hakkaart-van Roijen et al. [35], Statistics Netherlands [41]
Total cost per vaccine		**25.71**		
Total cost per vaccinated child[**]		**29.21**		De Hoog et al. [12]
COSTS OF HOSPITALIZATION				
GP		**9.93**	††	
% of children who visit their GP prior to hospitalization	29.5%			Uijen et al. [37]
GP cost per hour (2017 €)	33.66			Hakkaart-van Roijen et al. [35], Statistics Netherlands [40]
Stay at ICU		**1,781.31**		
% of hospitalized children admitted to ICU	19.3%		Beta(19.3,100–19.3)	Ampofo et al. [38], De Hoog et al. [12]
Median length of stay at ICU (in days)	4.5		Gamma($\sqrt{4.5}$,$\sqrt{4.5}$)	Ampofo et al. [38]
ICU cost per day (2017 €)	2,055.25			Hakkaart-van Roijen et al. [35], Statistics Netherlands [40]
Stay at pediatric ward		**1,918.58**		
Median length of stay at pediatric ward (in days)	3		Gamma($\sqrt{3}$,$\sqrt{3}$)	Ampofo et al. [38]
Ward cost per day (2017 €)	639.53			Hakkaart-van Roijen et al. [35], Statistics Netherlands [40]
Transportation by ambulance		**85.45**		
Cost per emergency transport (2017 €)	625.25			Hakkaart-van Roijen et al. [35], Statistics Netherlands

(*continued on next page*)

Table 1 (continued)

Parameter	Base-case value	Distribution in PSA	Source(s)
% of hospitalized children admitted to ICU[‡‡]	19.3%	Beta(19.3,100–19.3)	Ampofo et al. [38], De Hoog et al. [12]
Ambulance use in hospitalized children admitted to ICU	50%		Assumption
Ambulance use in hospitalized children not admitted to ICU	5%		Assumption
Productivity loss parents	**994.02**		
Length of hospitalization (in days)	3	Gamma($\sqrt{3},\sqrt{3}$)	Ampofo et al. [38]
Productivity loss per hospitalization day (in hours)[§§]	9.1		Friesema et al. [39]
Productivity loss per hour (2017 €)	36.41		Hakkaart-van Roijen et al. [35], Statistics Netherlands [41]
Total cost per hospitalization	**4,789.29**		

GP = general practitioner; ICU = intensive care unit; PSA = probabilistic sensitivity analyses.

[*] We simulated hospitalization and death rates for children in the general population instead of for children with medical risk conditions, because for the latter, associated distributions could not be retrieved from literature. See Appendix Table 1 for the derivation of influenza-related hospitalization rates based on the assumed distributions within the general population, the calculation used to determine the rates for children with medical risk conditions, and sources used. Appendix Table 2 provides a similar overview for influenza-related mortality rates.

[†] Neither a Gamma distribution with alpha = mean and beta = 1, nor a Gamma distribution with alpha = beta=$\sqrt{mean}$ gave a proper fit, so parameters were slightly adjusted. Vaccine efficacy against influenza-related hospitalization was assumed to be 70% correlated with vaccine efficacy against influenza-related death. One shared random number was drawn for both parameters, which accounted for 70% of the final random number, and one unique random number was drawn for both parameters, which accounted for 30% of the final random number.

[‡] A value of 0 was assumed if simulated values were negative.

[§] Based on the medical risk conditions observed in deceased children, we suspect that two thirds of deceased children with medical risk conditions would have had a (severely) limited life expectancy otherwise.

[‖] The vaccine price and the GP visit that is considered in the vaccination price are fixed reimbursement values, and were therefore not varied.

[¶] The productivity loss of parents due to vaccination was not varied because it is both a small fraction of the total cost per vaccinated child and it is based on three inputs that are characterized by limited uncertainty. We assumed 2 h of productivity loss per parent, which is in line with findings from Prosser et al. [55] and seems reasonable given the time needed to visit a GP in the Netherlands. The assumption that 5% of parents need to take time off from work is based on the fact that vaccination hours are often flexible, and that in only 10% of households with minors, both parents work full time [36] and thus potentially have to take time off. The average hourly wage was taken from the Cost manual of the Netherlands Health Care Institute [35], which prescribes reference prices for health economic evaluations, and was updated to 2017€ using the development of wages in collaborative labor agreements.

[**] Vaccination protocol prescribes that children below the age of 6 years, who are vaccinated for the first time, should receive two influenza shots, one month apart. Approximately 14% of all children with a medical risk condition did not have a medical risk condition one year earlier and is below the age of six years. Costs per vaccinated child were therefore 1.14 times the cost per vaccine shot.

[††] The GP costs per hospitalization were not varied because it is both a small fraction of the total cost per hospitalization and it is based on two inputs that are characterized by limited uncertainty. The percentage of children who visit their GP prior to hospitalization was taken from a Dutch study, where 23 out of 78 hospitalized children with diagnosed pneumonia or influenza had consulted their GP (Uijen et al. [37]). The GP price per hour was taken from the Cost manual of the Netherlands Health Care Institute [35], which prescribes reference prices for health economic evaluations, and was updated to 2017€ using the consumer price index for health care expenditures.

[‡‡] The probability of ICU admittance during hospitalization was calculated based on findings from a US-based study (Ampofo et al. [38] and a Dutch study (De Hoog et al. [12]). The former study showed that 13% of the 6–23 month-old and 20.3% of the >2 year-old children who were hospitalized due to influenza, were admitted to the ICU during hospitalization. Based on results from the latter study, we estimated that from all medical risk children that were hospitalized due to influenza-related disease, 14.2% was <2 years old and 85.8% was ≥2 years old.

[§§] No data available on parental productivity loss due to influenza-related hospitalizations in children in the Netherlands, so data on gastroenteritis hospitalizations was used instead.

Based on the distribution of underlying medical risk conditions among fatal influenza cases as described in Flannery et al. [6], we assumed that two thirds of the deceased children with medical risk conditions would otherwise have had a limited life expectancy (i.e. comparable to Bruijning-Verhagen et al. [31]), and one third would otherwise have had a normal life expectancy [32]. We further assumed that given their chronic medical conditions, the quality of life for children who die from influenza would have been 10% lower than the average age-specific quality of life in the Netherlands for the remainder of their lives [33].

2.4. Cost parameters

The analysis was performed from a modified societal perspective, including both direct health care costs and productivity losses for work absenteeism among parents.

The average costs per influenza dose equaled €25.71, consisting of costs of the vaccine (€10.71) [34], general practitioner (GP) (€11.36), and average productivity loss for parents (€3.64). For the latter, we assumed that a parent would be absent from paid work (for a period of 2 h of €36.41 each, according to Dutch cost guidelines [35]) in only 5% of cases, because a vast majority of children lives with at least one parent that does not work full time [36] and both immunization hours and working hours may be flexible. Each year, approximately 14% of all children with medical risk conditions are aged < 6 years and are invited for influenza immunization for the first time [12]. These children are recommended to receive two doses, one month apart, and hence total costs per vaccination were increased by 14% to €29.20.

The average costs per influenza-related hospitalization were derived from item costs, multiplied by their resource consumption. On average 29% of children were assumed to visit their GP prior to hospitalization [37], at costs of €33.66 per visit [35]. Median length of stay at the pediatric ward was assumed to be 3.0 days [38], at costs per day of €639.53 [35]. An estimated 19.3% of hospitalized children were assumed to require intensive care unit (ICU) admission for a median duration of 4.5 days [38], at costs of €2,055.25 per day [35]. We assumed that 50% of children admitted to ICU, and 5% of hospitalized children not requiring ICU, were transported by ambulance (€625.25 per ride [35]). Average parental productivity loss was estimated using the average length of hospitalization (3.0 days) and assuming 9.1 h of work leave per hospitalization day [39], at a cost of €36.41 per hour [35]. Thus, total hospitalization costs were estimated at €4,789.30 (GP: €9.94, pediatric ward days: €1,918.58, ICU stay: €1,781.31, ambulance use: €85.45, parental productivity losses: €994.02).

All healthcare costs were updated to 2017 euros, using the consumer price index for education, healthcare and social security for all healthcare-related costs [40]. Costs for productivity losses were updated based on the development of salaries within collective

labor arrangements wages [41]. An overview of all base case costs, their sources, and distribution in PSA, is provided in Table 1.

2.5. Vaccine efficacy parameters

A recent systematic review and meta-analysis estimated the average vaccine effectiveness against influenza-related hospitalization in children at 57% (95% confidence interval (CI): 30–74%) [18]. A recent Australian study found that the efficacy of influenza immunization against severe disease (i.e. visit to an emergency department) was similar in children with and without medical risk conditions [42]. Hence, we assumed an average vaccine effectiveness of 57% against hospitalization for our population of medical risk children (Table 1).

Flannery et al. found that influenza immunization (inactivated or live-attenuated) in children with a medical risk condition reduces risk of influenza-related death by 51% (credibility interval: 31–67%) [6]. No separate estimate was provided per vaccine type, but the majority (81%) of children was vaccinated with the inactivated influenza vaccine, which is also used in the Netherlands. To our knowledge, this is the only study providing estimates on vaccine effectiveness against mortality.

The model did not allow for any herd effect, i.e. a reduction of influenza incidence in non-immunized children as a result of immunizing others. We believe that such an effect would be small, given that healthy children and adults below age 60 are not routinely vaccinated in the Netherlands.

2.6. Model outcomes

Model outcomes include the number of vaccines, hospitalizations, and deaths, as well as the associated costs and health effects per 1,000 vaccinated, and per 1,000 unvaccinated children with medical risk conditions. Vaccination impact and (cost-)effectiveness was calculated using the difference in costs and health effects between those groups. In the Discussion, the findings are extrapolated to the Netherlands, using the child population size from Statistics Netherlands [43], and the prevalence of medical risk conditions and IIV immunization coverage from De Hoog et al. [12]

2.7. Analyses

We estimated the difference in costs and QALYs comparing a strategy of annual IIV immunization of children with medical risk conditions to a strategy of no immunization. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs of immunization by the incremental QALYs, and compared to a willingness-to-pay (WTP) threshold of €20,000 per QALY, which is generally recommended for preventive interventions in the Netherlands [44]. QALYs lost due to influenza-related death were discounted at an annual rate of 1.5%. For all other outcomes, no long term effect was assumed, and hence no discounting was required.

We performed PSA with 10,000 simulations, in which we took into account the uncertainty in vaccine efficacy against influenza-related hospitalization and death, hospitalization and mortality rates, costs of hospitalization, and QALY loss due to immunization, hospitalization and death. The assumed distributions for these parameters and the assumptions for correlation between vaccine efficacy against hospitalization and vaccine efficacy against death, and those between hospitalization rates and death rates, are given in Table 1. For each of the parameters varied in the PSA, we also performed one-way sensitivity analyses in order to assess their individual impact on the estimated outcomes. In these analyses, parameter values were decreased and increased by 50%, in line with best practices identified by the ISPOR-SMDM Modeling Good Research Practices Task Force [45].

In the base-case scenario we assume hospitalization and mortality rates based on Jansen et al. [23] and a reduced life expectancy and quality of life for medical risk children who die from influenza (as described in the utilities section). Given the uncertainty in these assumptions, we also performed scenario analyses in which we assumed:

(1) Mortality estimates from Wijngaard et al. [28] instead of from Jansen et al. [23], and that
(2) Children who die from influenza were assumed to otherwise have had a normal life expectancy and normal quality of life. For this analysis, we used the life expectancy of the average 8-year-old child in the Netherlands [32] (i.e. the average age at death due to influenza in children [12,23,27]), and the average age-specific quality of life in the Netherlands [33].

Furthermore, we performed an analysis from the healthcare perspective, excluding parental productivity losses.

3. Results

Influenza immunization of medical risk children is expected to prevent an average of 1.59 influenza-related hospitalizations (95%

Table 2
Expected health effects and costs of influenza vaccination and no influenza vaccination per 1,000 children.

	Unvaccinated cohort (N = 1,000)		Vaccinated cohort (N = 1,000)	
	Mean	95% CI	Mean	95% CI
Numbers				
Vaccination	0	NA	1136	NA
Hospitalization	2.747	2.360–3.155	1.154	0.899–1.422
Death	0.047	0.006–0.096	0.023	0.003–0.047
Costs (€)				
Vaccination	0	NA	29,208	NA
Hospitalization	13,181	9,849–17,034	5,538	3,892–7,502
Total Costs	13,181	9,849–17,034	34,746	33,099–36,710
QALY losses				
Vaccination	0.000	NA	0.114	0.001–0.225
Hospitalization	0.044	0.037–0.052	0.018	0.014–0.023
Death	1.000	0.120–2.290	0.483	0.059–1.107
Total QALY loss	1.044	0.160–2.335	0.615	0.172–1.240
Overall Costs of Vaccination (€)			21,564	17,842–24,674
Overall QALYs gained by Vaccination			0.429	−0.052–1.169
Average Cost per QALY gained (€)			50,297	NA

CI = confidence interval; NA = not applicable; QALY = quality-adjusted life year.

CI: 1.01–2.20) and 0.02 influenza-related deaths (95% CI: 0.00–0.05) per 1,000 children annually, as compared to no immunization (Table 2). This results in an expected QALY gain of 0.43 (95% CI: −0.05–1.17) and additional costs of €21,564 (95% CI: €17,842–24,674) per 1,000 children, corresponding to an average ICER of €50,297/QALY (Fig. 2A). Applying the Dutch recommended WTP threshold of €20,000/QALY, there is a 5% probability that annual immunization is cost effective compared to no immunization (Fig. 3A).

The impact of increasing and decreasing individual input parameters by 50%, while leaving all other parameters at their base case value, is shown in Fig. 4. Varying the vaccine efficacy against death had the largest impact on the ICER. Results varied from €25,509/QALY at 77% efficacy to €187,204/QALY at 26% efficacy. Mortality rate and QALY loss due to influenza-related death were also highly influential on the ICER, with values ranging from €33,208 to €136,615 per QALY in one-way sensitivity analyses. In none of the one-way sensitivity analyses, the lower end of the ICER range was below the €20,000/QALY threshold.
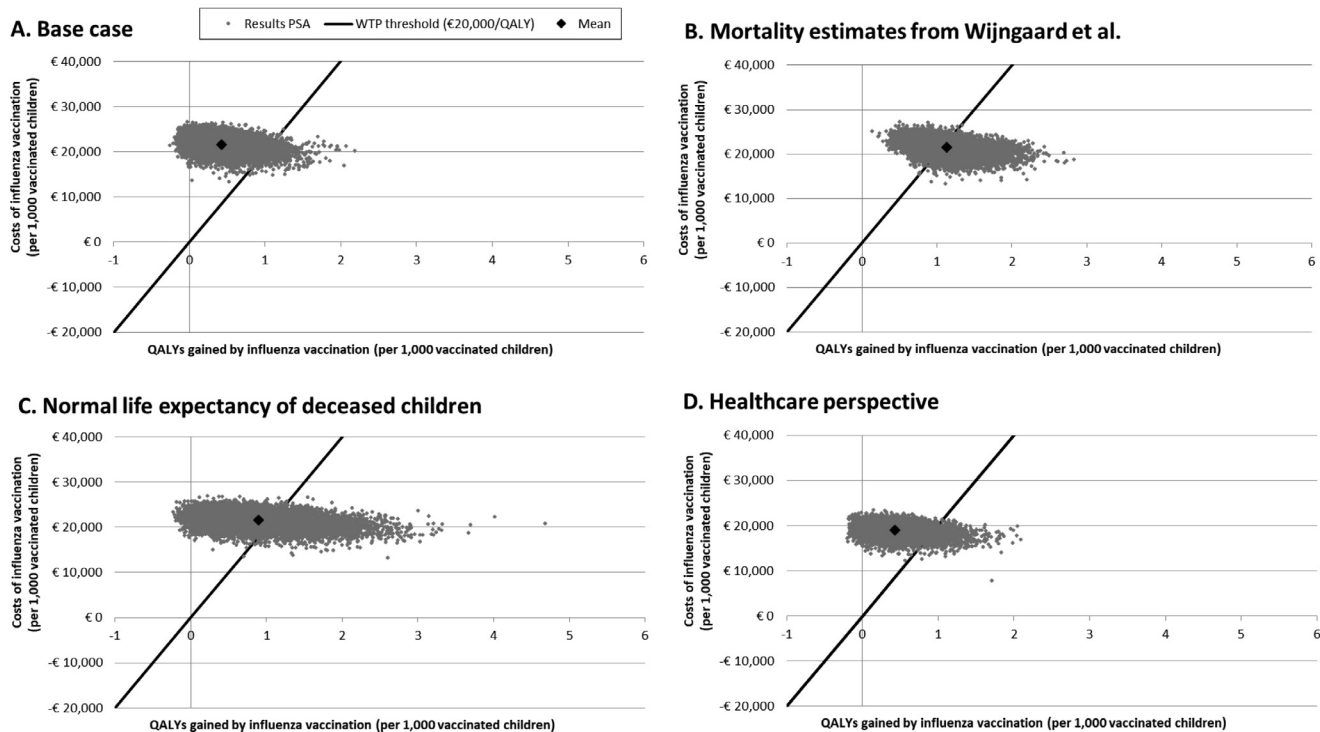
Compared to the base-case analysis, cost-effectiveness of immunization was more favorable in the scenario analyses. When influenza-related mortality estimates from Wijngaard et al. were used, 0.70 more QALYs were gained per 1,000 children and, as such, the average ICER decreased to €19,104/QALY (Fig. 2B). Cost-effectiveness of immunization was still uncertain as the probability of the ICER being below the €20,000/QALY threshold was 52% (Fig. 3B). Assuming both a normal life expectancy and a normal quality of life for children who deceased from influenza resulted in 0.47 more QALYs gained compared to the base case, resulting in an average ICER of €24,108/QALY (Fig. 2C). Annual immunization then had a 35% probability of being cost effective (Fig. 3C).

When productivity losses for parental absenteeism from work were excluded, costs decreased by €2,567 per 1,000 children, resulting in an average ICER of €44,392 (Fig. 2D). In this analysis, using a healthcare perspective, immunization had a 8% probability of being cost effective (Fig. 3D).
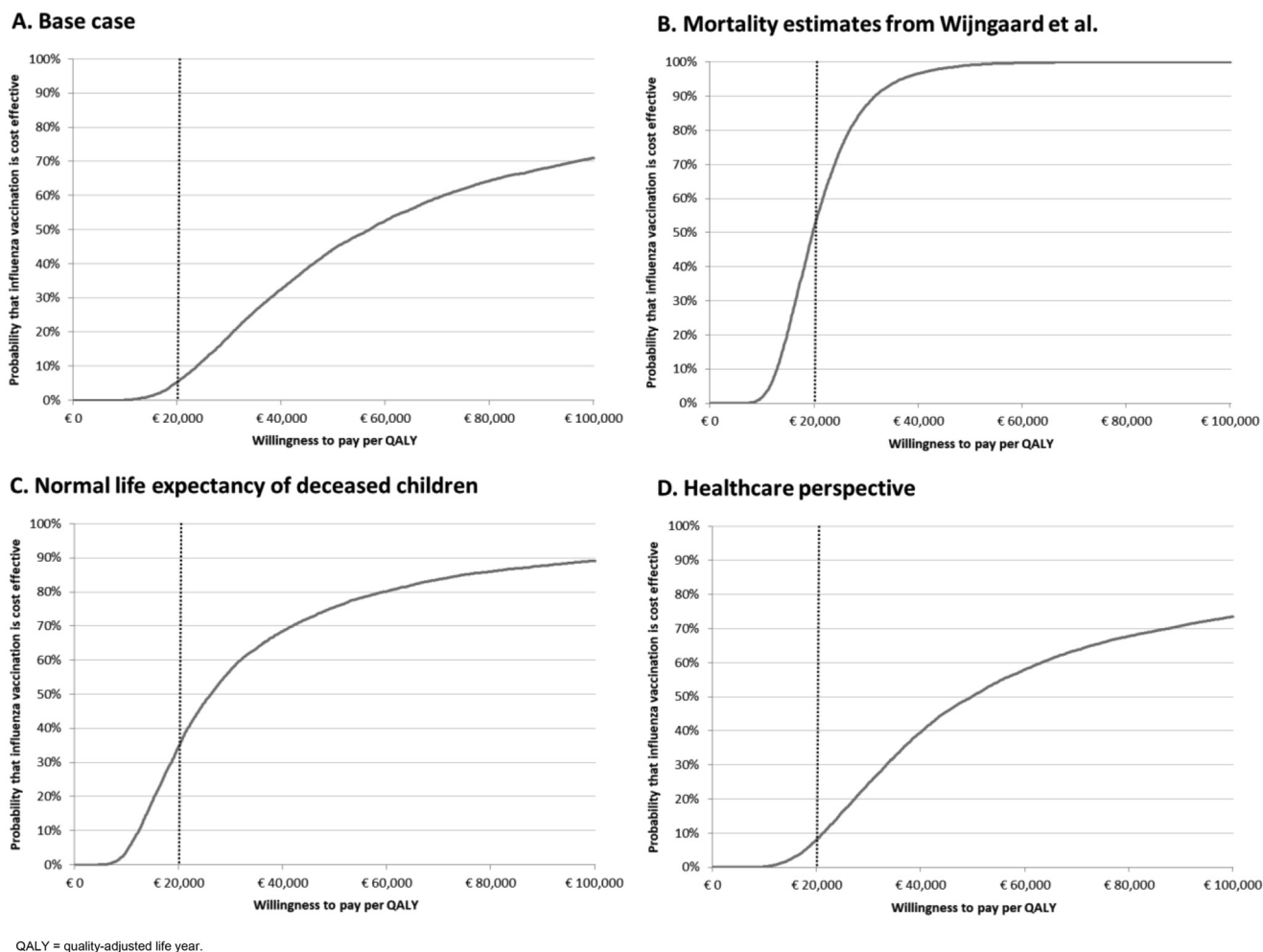
4. Discussion

Using a decision tree-type of model and considering vaccine effects on influenza hospitalizations and deaths, we found that annual IIV in children with medical risk conditions is unlikely to be cost effective, when assuming a WTP threshold of €20,000/QALY. The overall impact of annual immunization of medical risk children is limited with 1.59 fewer influenza-related hospitalizations and 0.02 fewer deaths per 1,000 children, resulting in an expected QALY gain of 0.43 per 1,000 children. These estimates correspond to a number needed to vaccinate (NNV) of 628 to prevent one hospitalization and a NNV of more than 40,000 to prevent one death. Costs of immunization were on average €21,564 per 1,000 children, resulting in an average cost-effectiveness ratio of €50,297/QALY. Results were highly influenced by vaccine efficacy against death, influenza-related mortality rates, and QALY loss due to death. However, even when assuming mortality rates based on ILI incidence, the probability of IIV immunization being cost effective was not higher than 52%.

On January 1st 2017, there were 3.4 million children under 18 in the Netherlands [43]. Based on the age-specific prevalence of medical risk conditions in GP data obtained by De Hoog et al. [12], approximately 129,000 children (3.8% of total) were eligible for influenza immunization in 2017. In an average influenza sea-

Fig. 2. Incremental cost-effectiveness of influenza vaccination versus no influenza vaccination – Results of probabilistic sensitivity analyses under base case assumptions and three alternative scenarios.

PSA = probabilistic sensitivity analyses; QALY = quality-adjusted life year; WTP = willingness to pay.

A. Base case

B. Mortality estimates from Wijngaard et al.

C. Normal life expectancy of deceased children

D. Healthcare perspective

QALY = quality-adjusted life year.

Fig. 3. Probability that influenza vaccination is cost effective for different willingness-to-pay thresholds – Results of probabilistic sensitivity analyses under base case assumptions and three alternative scenarios.

son, vaccinating all these children could potentially prevent an estimated 200 influenza-related hospitalizations and 3 influenza-related deaths. This would result in 53 QALYs gained at an annual cost of €2,809,000. With ~29% vaccination coverage as observed in De Hoog et al. [12], an estimated 59 hospitalizations and 1 death are prevented each year, resulting in 15 QALYs gained at an annual cost of €828,000.

Results of any cost-utility analysis are dependent on utility assumptions. For any simulated health intervention or disease state, average disutility and duration should be defined for the population of interest. For (small) children, utility values are difficult to elicit [46]. However, one-way sensitivity analyses showed that varying the assumed utility loss for vaccination and hospitalization does not affect our conclusions. Utility loss assumed for death did have a larger impact. If deceased children would otherwise have had a normal quality of life, the ICER of influenza vaccination in medical risk children was more favorable but it was still unlikely to be cost effective. One may argue that severe outcomes like hospitalization and in particular the death of a child will affect quality of life of parents as well. To our knowledge, there is no consensus on how this parental QALY loss should be addressed in economic evaluations of vaccination strategies and it is generally not included. Including such parental utility losses would likely improve cost-effectiveness of IIV in medical risk children.

Cost-effectiveness of influenza vaccination may be more favorable in one year versus another, because IIV effectiveness can vary substantially from year-to-year depending on the antigenic match between the vaccine and circulating influenza strains. However, policy makers are forced to make decisions based on expected effectiveness and cost-effectiveness, which depend on average outcomes and their potential variation. We accounted for this by using parameter values based on average season outcomes. For example, we excluded the pandemic year 2009/2010 from the mortality estimates obtained from Wijngaard et al. [28], which were assumed in one of the scenario analyses. The impact of the potential variation in vaccine effectiveness and severity of the influenza season was explored in PSA.

Vaccine efficacy estimates used in this study are mostly based on trivalent inactivated influenza vaccines, which are currently in use in the Netherlands, and the reported efficacy against any influenza, irrespective of influenza strain or subtype. The use of quadrivalent inactivated or live-attenuated vaccines could improve overall vaccine efficacy against hospitalization and death in children, since they include a second influenza B strain. However, in our one-way sensitivity analysis, increased vaccine efficacy up to 77% did not result in a mean ICER below the €20,000/QALY threshold.

In recent years, economic evaluations of influenza immunization in children have predominantly focused on universal immu-
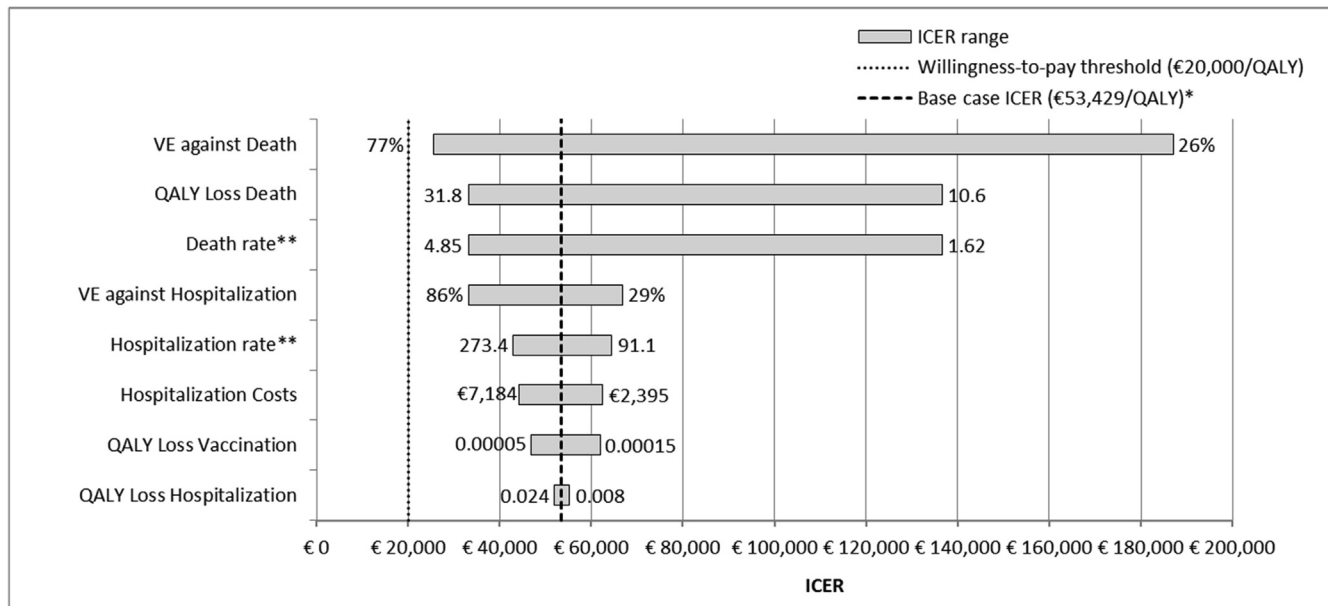
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; VE = vaccine efficacy.
*Base case ICER in deterministic analysis.
**Rate per 100,000 children with medical risk conditions.

Fig. 4. Tornado diagram showing the impact of reducing (−50%) and increasing (+50%) input parameter values one-by-one on the incremental cost-effectiveness ratio (ICER) of vaccination versus no vaccination.

nization, comparing strategies that target various age groups or that use different influenza vaccines. Some have also evaluated universal versus risk-group strategies, but none have recently compared immunization versus no immunization within a group of children with medical risk conditions as was done in the current analysis. Such studies have been performed in the early days of influenza immunization, and generally concluded that immunization of medical risk children was cost saving [3–5]. However, the estimated number of influenza-related hospitalizations and deaths that would be prevented by immunization of medical risk children was substantially higher than the more recent estimates from developed countries suggest [47–51]. In addition, these studies all included immunization benefits on non-severe influenza outcomes, which were not considered in the current analysis because of the lack of evidence already described.

Some limitations are noteworthy. First, limited evidence was available specifically for children with medical risk conditions in the Netherlands. While some parameters might not differ between children with or without medical risk conditions, parameters like hospitalization and mortality rates are likely to differ. We accounted for this by adjusting the rates for the general population using the increased hospitalization risk and the proportion of pediatric influenza-related deaths that is found in children with medical risk conditions in US-based studies [6,24] as a proxy for the Netherlands (Appendix Tables 1 and 2). If the risk difference between children with and without medical risk conditions were very different in the Netherlands compared to the US, then this assumption may have biased the results of the PSA. However, a 50% increase in either the hospitalization or mortality risk did not result in an ICER below €20,000 per QALY. In one-way sensitivity analyses, we evaluated which parameters were most influential for the anticipated cost-effectiveness of IIV immunization, providing directions for further research. A formal value of information analysis would be helpful in directing future research funds. Second, the static model structure did not allow for interactions between simulated individuals, which are needed to estimate the impact of herd protection. However, without an annual IIV pro-

gram for children without medical risk children in the Netherlands, and with imperfect coverage among children with medical risk conditions, the annual IIV coverage among Dutch children is only ~1%. At such low coverage levels, estimated vaccination impact is hardly influenced by model structure [52], and the use of a dynamic model is unlikely to have changed our conclusions. Of note, if universal child immunization is considered as alternative scenario, herd protection effects should be considered, as dynamic modeling studies suggest this has significant impact on cost-effectiveness estimates [53]. In fact, herd protection could render universal vaccination a more favorable scenario compared to the risk-group based pediatric program for the Netherlands, but this should be further evaluated.

5. Conclusions

Based on our health economic evaluation, the current policy of IIV immunization of children with medical risk conditions is unlikely to be cost effective in the Netherlands. Whether IIV immunization is cost effective largely depends on influenza-related hospitalization and mortality estimates, for which evidence is scarce. More research on these outcomes is required to come to a final conclusion on whether annual IIV immunization in children with medical risk conditions is cost effective, and if so, under what specific circumstances.

in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CRediT authorship contribution statement

Steffie K. Naber: Formal analysis, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Patricia C.J.L. Bruijning-Verhagen**: Conceptualization, Funding acquisition, Methodology, Supervision, Writing - review & editing. **Marieke L.A. de Hoog**: Conceptualization, Data curation, Funding acquisition, Project administration, Writing - review & editing. **Anoukh van Giessen**: Methodology, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.01.057.

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