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Cost-Effectiveness of Pediatric Influenza Vaccination in The Netherlands

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ABSTRACT

Objective: This study evaluates the cost-effectiveness of extending the Dutch influenza vaccination program for elderly and medical high-risk groups to include pediatric influenza vaccination, taking indirect protection into account.

Methods: An age-structured dynamic transmission model was used that was calibrated to influenza-associated GP visits over 4 seasons (2010-2011 to 2013-2014). The clinical and economic impact of different pediatric vaccination strategies were compared over 20 years, varying the targeted age range, the vaccine type for children or elderly and high-risk groups. Outcome measures include averted symptomatic infections and deaths, societal costs and quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios. Costs and QALYs were discounted at 4% and 1.5% annually.

Results: At an assumed coverage of 50%, adding pediatric vaccination for 2- to 17-year-olds with quadrivalent live-attenuated vaccine to the current vaccination program for elderly and medical high-groups with quadrivalent inactivated vaccine was estimated to avert, on average, 401 820 symptomatic cases and 72 deaths per year. Approximately half of averted symptomatic cases and 99% of averted deaths were prevented in other age groups than 2- to 17-year-olds due to herd immunity. The cumulative discounted 20-year economic impact was 35 068 QALYs gained and €1687 million saved, that is, the intervention was cost-saving. This vaccination strategy had the highest probability of being the most cost-effective strategy considered, dominating pediatric strategies targeting 2- to 6-year-olds or 2- to 12-year-olds or strategies with trivalent inactivated vaccine.

Conclusion: Modeling indicates that introducing pediatric influenza vaccination in The Netherlands is cost-saving, reducing the influenza-related disease burden substantially.

Keywords: children, cost-effectiveness, dynamic transmission model, economic evaluation, influenza, vaccination.

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Introduction

Seasonal influenza epidemics are responsible for a considerable clinical and economic burden.[1,2] Although most severe outcomes occur among the elderly and chronically ill, increasing evidence shows that the influenza-related burden among children is also relevant.[3] Young children are frequently hospitalized, require an outpatient visit, or stay at home from school, causing work loss among caregivers.[4,5] Furthermore, children are thought to play a key role in the transmission of influenza because they have more close contacts than adults and limited preexisting immunity.[6] Ecological studies as well as mathematical modeling studies suggest that pediatric influenza vaccination would provide not only direct protection but also indirect protection to susceptible contacts due to herd immunity.[7-12]

Anticipating these direct and indirect benefits, several countries have issued positive recommendations for pediatric influenza vaccination.[13] For instance, the United Kingdom is rolling out a publicly funded vaccination program for 2- to 16-year-olds.[14] In The Netherlands, influenza vaccination is offered free of charge to individuals aged ≥60 years and those in high-risk groups due to chronic illnesses.[15] In 2007, pediatric influenza vaccination was not recommended by the Health Council of The Netherlands because the risk of severe complications and mortality was not considered high enough.[16] However, the discussion is ongoing, and the decision on pediatric influenza vaccination will be reassessed in 2020.[17]

Cost-effectiveness is a relevant aspect in the decision whether to implement vaccination programs in most countries, including The Netherlands.[18] Against this perspective, we conducted a cost-effectiveness analysis of inclusion of pediatric influenza vaccination in the current vaccination program for elderly and high-risk groups in The Netherlands. As pediatric influenza vaccination is expected to confer indirect effects on the wider community, a

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dynamic transmission model was used that accounts for herd immunity.

Methods

Overview

The analysis uses a probabilistic sensitivity analysis (PSA) approach, taking into account uncertainty in the transmission, clinical, and economic parameters. A deterministic transmission model was used to simulate the population-level dynamics of influenza infection (see Transmission Model section below). To incorporate uncertainty in the transmission parameters, a set of key transmission parameters was repeatedly sampled from input distributions. Those sets that fitted the observed information from The Netherlands were retained and are collectively referred to as the calibrated model (see Calibration section below). The updated sets of parameter distributions were then integrated with the transmission model to produce a PSA of the transmission parameter inputs. Results of the transmission model served as an input for the economic PSA in which clinical and economic parameters were sampled and outcomes were compared for a range of vaccination policies (see Expected Net Benefit Analysis section below).

Transmission Model

The dynamic transmission model is a compartmental model, stratified by age in months. The model uses a $SEIR_FR_LS(V)$ structure (susceptible, exposed, infectious, recovered with short-term immunity, recovered with long-term immunity, vaccinated). The short-term and long-term immunity states should be viewed as a single immunity state, but chaining such 2 states together allows for greater flexibility in the distribution of time individuals stay in the immunity state. Aging was simulated on a monthly basis, informed by Dutch population data.[19-21] The Netherlands-specific contact rates[22] informed an age-stratified matrix of transmission coefficients, which were assumed to vary sinusoidally over time.

Influenza A and influenza B were simulated independently with strains from H1N1 and H3N2 subtypes for influenza A, and from Victoria and Yamagata lineages for influenza B. Both strains were modeled simultaneously with the flows of individuals between compartments described by a set of linked differential equations (see Appendix 1, Figure 1.3 and Equation 1). Patients could not be infected with 2 strains at once.

Further details are provided in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.011.

Calibration

The transmission model was run for the 2010-2011 through 2013-2014 seasons for sets of input parameter samples. The main source for the model calibration was a set of The Netherlands–specific general practitioner (GP) consultation rates obtained from a regression of influenza-like-illness (consultation data against laboratory-confirmed influenza reports).[23] Influenza-associated GP consultation rates were stratified by influenza strain, age group (0-4, 5-19, 20-59, and ≥60 years), and season (2010-2011, 2013-2014). Whether a set of parameter samples provided a good fit is decided by comparing the Poisson deviance between the model results and the observed influenza-associated GP visits, together with a set of heuristic criteria (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.011), retaining the best-fitting runs.

Key inputs of transmission parameters were drawn from assigned input distributions (Table 1). The model simulated vaccination with trivalent inactivated vaccine (TIV), which includes antigens against both influenza A subtypes (H1N1 and H3N2) and 1 influenza B lineage (either Victoria or Yamagata). Vaccine composition was obtained from WHO recommendations.[24] Efficacy of TIV by age was obtained from the literature.[25,26] Age-specific vaccine uptake rates from the seasons 2010-2011 to 2013-2014 were used (see Appendix 1: Table 1.6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.011).[27] The duration of vaccine-induced protection was much shorter than that of naturally acquired immunity. No cross-immunity from infections or vaccines were assumed.

Further details are provided in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.011.

Expected Net Benefit Analysis

The calibrated model was used to compare the clinical and economic impact of a range of vaccination strategies. For each set of parameter samples of the calibration, the model was run forward from 2010-2011 to 2034-2035. Explored vaccination strategies diverged from the 2015-2016 season, and results from the period 2015-2016 to 2034-2035 were used (20-year time horizon). The initial output of the model integration concerned incidence of infection. Risk functions of clinical outcomes were applied to the incidence of infection in order to estimate the number of symptomatic cases, GP visits, hospitalizations, and deaths. Estimates of costs and quality-adjusted life-years (QALYs) lost were then applied to the clinical outcomes. Costs were discounted at 4% per year and QALYs at 1.5% per year from the start of the 2015-2016 season.[28]

Further details are provided in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.011.

Vaccination strategies

Vaccines considered for elderly and high-risk groups were TIV and quadrivalent inactivated vaccine (QIV). QIV includes antigens of both influenza B lineages (Victoria and Yamagata) and has been used in the Dutch influenza vaccination program since the 2019-2020 season.

Pediatric vaccination strategies were assumed to be implemented in addition to the current program for elderly and high-risk groups and considered vaccination with TIV and the intranasally administered quadrivalent live-attenuated influenza vaccine (Q-LAIV) for the age groups 2-6 years, 2-12 years, and 2-17 years. Given that postlicensure studies comparing the effectiveness between LAIVs and inactivated vaccines (IVs) show equivocal results,[29-31] we assumed the efficacy of LAIV to be equal to IV. Consequently, results of pediatric strategies with Q-LAIV are also representative for pediatric strategies with QIV. The combination of TIV in children and QIV in elderly and high-risk groups was not considered. Finally, a strategy of no influenza vaccination at all was added.

Annual vaccine uptake in the pediatric vaccination program was assumed at 50%, in accordance with emerging uptake data from the UK's pediatric influenza vaccination program.[32] The receipt of 1 dose per year was assumed irrespective of whether influenza vaccine had been received before. Vaccine uptake in elderly and high-risk groups was assumed to be unchanged, and the latest data of the 2013-2014 season were carried forward (overall uptake of approximately 3% in 0-17 years, 8% in 18-59 years, and 65% in ≥60 years).

Outcome probabilities

Outcome probabilities are shown in Table 1. The probability of symptoms, given influenza infection, was obtained from the

Table 1. Key model inputs of the dynamic transmission model and the economic model.

Parameter	Input	Range/SE	Distribution	Source
R0				
Transmission coefficient*	Min – Max:	2.76E-08 to 8.29E-08	Uniform	See Appendix 1‖
Latent period (days)*	Min – Max:	0.01-3	Uniform	See Appendix 1‖
Infectious period (days)*	Min – Max:	0.5-5	Uniform	See Appendix 1‖
Immunity				See Appendix 1‖
Duration of initial naturally acquired* immunity (years)*	Min – Max:	Influenza A: 0.5-10 Influenza B: 0.5-30	Uniform	See Appendix 1‖
Duration of long-term naturally acquired immunity (years)*	Min – Max:	10-70	Uniform	See Appendix 1‖
Probability of acquiring long-term immunity*	Min – Max:	0-1	Uniform	See Appendix 1‖
Duration of vaccine-induced immunity (years)*	Min – Max:	0.5-3	Uniform	See Appendix 1‖
Vaccination				See Appendix 1‖
Vaccination campaign duration (days)†	Min – Max:	30-40	Uniform	See Appendix 1‖
Vaccine efficacy‡				
0-17 y	48	95% CI: 31-61	Lognormal	Diazgranados, 2012[25]
18-64 y	59	95% CI: 50-66	Lognormal	
≥65 y	50	95% CI: 39-59	Lognormal	Rivetti, 2006[26]
Probabilities				
Probability of symptoms given infection	0.669	0.0413	Beta	Carrat, 2008[33]
Probability of GP visit given infection	Intrinsic to calibrated model			
Probability of hospitalization given GP visit				
0-4 y	0.0148	0.000879	Beta	Van den Wijngaard, 2010[35]
5-9 y	0.0040	0.000264	Beta	
20-64 y	0.0062	0.000752	Beta	
65-99 y	0.0352	0.002182	Beta	
Probability of death given infection				
0-44 y	0.000003	2.96E-07	Beta	Van den Wijngaard, 2012[36]
45-64 y	0.000035	0.000004	Beta	
65-74 y	0.000320	0.000049	Beta	
75-99 y	0.003502	0.000534	Beta	
Costs				
Healthcare costs				
TIV	3.59			SNPG, 2017[66]
QIV/Q-LAIV	5.38			Assumption, 50% higher than TIV
Vaccine administration	11.36			
Influenza GP visit§				
0-9 y	52.19	1.55	Gamma	Enserink, 2014[67]
≥10 y	82.86	2.69	Gamma	Mangen, 2015[41]
Influenza hospitalization costs				
0-9	2332	19	Normal	Rozenbaum, 2015[68] Dutch cost-effectiveness guideline, 2016[28]
10-17 y	3030	103	Normal	
18-44 y	3125	28	Normal	
45-59 y	3953	33	Normal	
60-74 y	4618	36	Normal	
≥75 y	4412	28	Normal	
Indirect healthcare costs				

continued on next page

Table 1. Continued

Parameter	Input	Range/SE	Distribution	Source
Lifetime healthcare costs unrelated to influenza per death averted	Age-specific			See Appendix 1
Patient costs				
Vaccination	0.43			
Non–medically attended influenza (€)	7.04	0.16	Gamma	Bilcke, 2014[69]
Medically attended influenza (€)	21.45	1.97	Gamma	Mangen, 2015[41]
Hospitalized influenza (€)	128.21	25.58	Gamma	Van Werkhoven, 2017[70]
Productivity losses				
Caregiver of 0-14 y, nonhospitalized (€)	125	16	Normal	See Appendix 1¶
Caregiver of 0-14 y, hospitalized (€)	406	52	Normal	See Appendix 1¶
Influenza, non–medically attended (€)				
15-24 y	571	25	Normal	See Appendix 1¶
25-44 y	1849	20	Normal	
45-59 y	1971	28	Normal	
60-74 y	463	30	Normal	
Influenza, GP visit (€)				
15-24 y	901	52	Normal	See Appendix1¶
25-44 y	3361	65	Normal	
45-59 y	3487	81	Normal	
60-74 y	794	66	Normal	
Influenza, hospitalizations (€)				
15-24 y	956	11	Normal	See Appendix 1¶
25-44 y	2806	25	Normal	
45-59 y	3194	27	Normal	
60-74 y	951	7	Normal	
Influenza, death (15-74 y) (€)	Age-specific			See Appendix 1¶
QALY loss				
Non-medically attended	0.0038	0.00043	Normal	Mangen, 2015[27]; Bilcke, 2014[31]
Medically attended	0.0045	0.00051	Normal	Mangen, 2015[27]
Hospitalized	0.0118	0.00030	Normal	Mangen, 2013[41]
Death	Age-specific			See Appendix 1

QALY indicates quality-adjusted life-year; R0, basic reproduction number; SE, standard error; y, years of age.
*Stratified by virus.
†The annual vaccination campaign was assumed to start in mid-October.
‡Efficacy against laboratory-confirmed influenza of the inactivated vaccines by age was obtained from a meta-analyses of clinical trial data. We assumed the efficacy of inactivated and live-attenuated influenza vaccines to be the same. Vaccine efficacy in those 65 and older was assumed at 50%, based on efficacy estimates against pneumonia, hospitalizations, and death in care home residents.
§GP costs include also costs of prescribed drugs and specialist visits.
‖Wide distribution around plausible previous values were chosen from the literature and sampled uniformly within this range, to allow the model itself to coalesce to a distribution.
¶Productivity losses were calculated by multiplying the number of work days lost per clinical event (adjusted for labor participation rates) with age-specific average daily wages. For parental work loss we used labor participation rates and wages of the age group 25-44 years. For deaths, we estimated the productivity loss using the friction method, assuming the number of work days lost at 85 days.[28]

literature.[33] Age-specific probabilities of a GP consultation, given infection, was calculated as part of the calibration using the GP consultation rates and the modeled incidence of infection. Prescription of antiviral medication by Dutch GPs is restrained[34] and therefore not considered in the model. Age-specific probabilities of hospitalization were based on Dutch estimates of the relationship between respiratory-associated hospitalization and influenza-like–illness incidence at the GP.[35] Age-specific probabilities of death were based on Dutch incidence rates of respiratory-associated influenza death.[36]

Economic input

Economic input is shown in Table 1. As recommended by the Dutch cost-effectiveness guideline,[28] the analysis adopted a societal perspective. Results from a payer's perspective are also provided. All costs were converted to 2017 euros using the Dutch consumer price index.[37] We distinguished healthcare costs (vaccine, administration, GP visits including prescribed medication and specialist visits, hospitalizations, and indirect healthcare costs in life-years gained), patient costs (over-the-counter medication and travel), and productivity losses (missed work days of cases aged 15-74 years, parents of sick children aged <15 years, and premature deaths using the friction method).

We used the tendered price of TIV from the national vaccination program.[38] Vaccine prices of QIV and Q-LAIV were assumed to be 50% higher than that of TIV, based on the relative price difference of the list price of QIV and TIV.[39] Administration costs were based on the tariff that GPs receive for influenza vaccination

in the current program.[38] Age-specific costs of influenza disease were obtained from published sources or national datasets. Since the update of the Dutch cost-effectiveness guideline in 2016, the inclusion of indirect healthcare costs (ie, healthcare costs unrelated to influenza that occur in gained life-years) is recommended.[28] These costs were estimated using the life expectancy at age of death and annual healthcare costs unrelated to influenza or pneumonia from the Practical Application to Include Disease Costs tool.[40]

QALY losses due to influenza illness were based on studies using the validated EuroQol-5 Dimensions (EQ-5D) instrument.[41] QALYs lost due to premature death were calculated using the life expectancy at age of death multiplied by age-specific population norms of quality of life.[42] To account for the increase of life expectancy over time, we used predictions of the year 2024 (halfway through the time horizon).[43]

Cost-effectiveness

The base-case estimate per vaccination scenario was obtained by averaging the clinical and economic results across simulations. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in costs by the difference in QALYs. Results are also presented as net health benefits (NHB), in which monetary outcomes are converted into QALYs using a cost-effectiveness threshold (λ). We used a threshold of €20 000 per QALY gained that is often applied for prevention programs in The Netherlands.[44] We also draw cost-effectiveness acceptability curves to present the probability of being cost-effective over a range of cost-effectiveness thresholds. Because for some cost-effectiveness thresholds the policy with the highest probability of being cost-effective might not correspond to the one with the highest NHB,[45] the probability of the optimal policy (highest NHB) over a range of cost-effectiveness thresholds was shown in a cost-effectiveness acceptability frontier.

Univariate sensitivity analysis

Univariate sensitivity analyses were performed to test for structural uncertainty, including variation of the pediatric vaccine uptake to 20% and 80%, a higher vaccine efficacy of LAIV according to clinical trial data,[46] and the vaccine price.

Results

Calibration

During the calibration stage, 7198 simulations were selected as a close enough fit to the Dutch data. The resulting updated distributions are plotted in the in Supplemental Materials (Appendix 2: Figure 2.1-Figure 2.7 and Table 2.1-Table 2.3 found at https://doi.org/10.1016/j.jval.2020.10.011), as are comparisons of the model incidence to the GP regression data (Appendix 2: Figure 2.8-Figure 2.11 found at https://doi.org/10.1016/j.jval.2020.10.011). Sampling from uniform input distributions and keeping the samples that met the calibration criteria produced clearly defined unimodal distributions for the basic reproduction number; these distributions were clearly updated from their initial

Table 2. Model simulations on 20-year average annual numbers of clinical outcomes in The Netherlands.

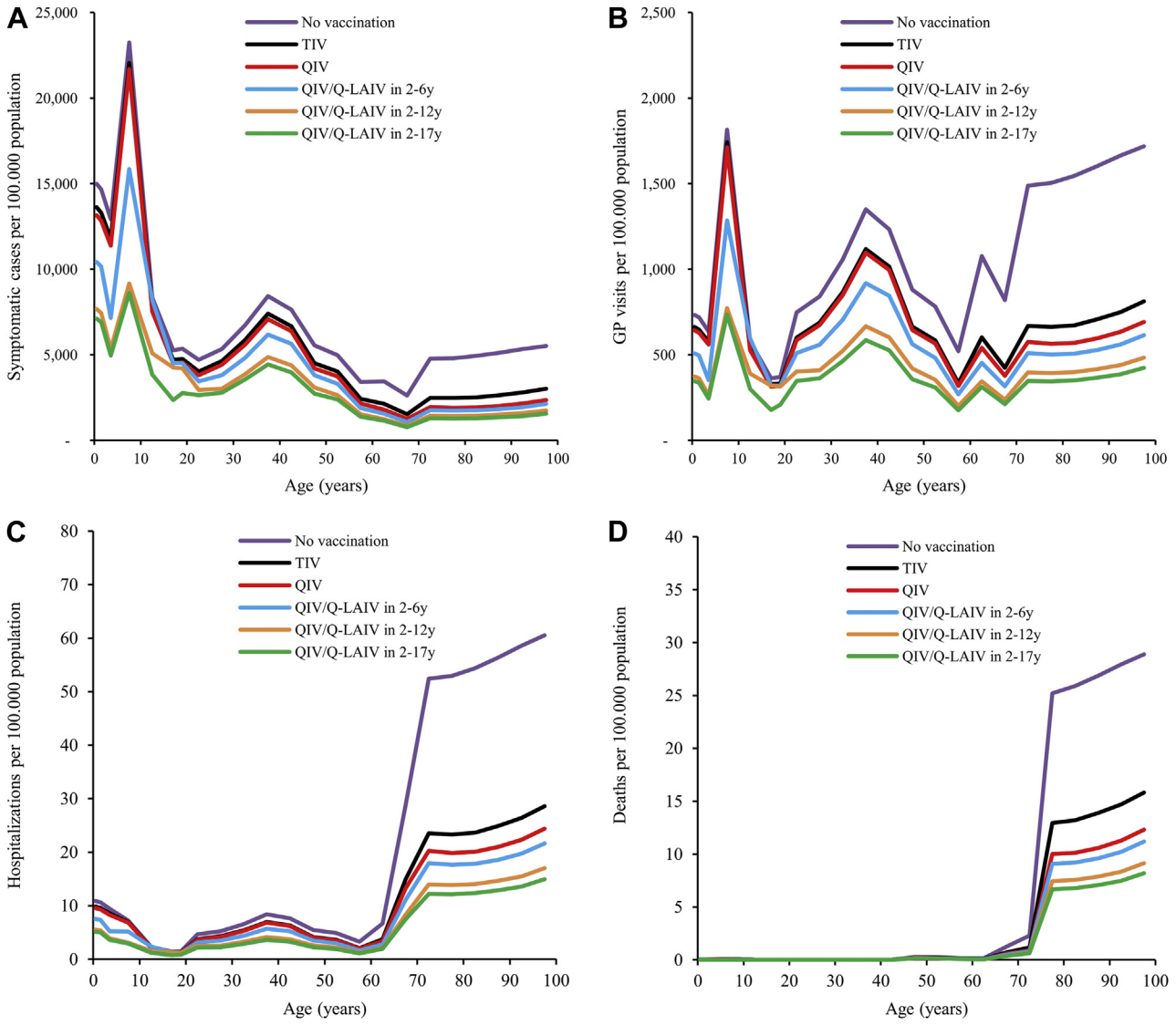
Vaccination strategy	Symptomatic infections			GP visits			Hospitalizations			Deaths		
(Current/pediatric)	Exp	(95% range)*	Rate†	Exp	(95% range)*	Rate†	Exp	(95% range)*	Rate†	Exp	(95% range)*	Rate†
No vaccination	1 157 285	(510 878-4 186 700)	6755	172 603	(85 867-425 223)	1007	2560	(1073-7295)	14.9	523	(153-2377)	3.05
TIV	954 353	(462 235-2 960 578)	5570	120 906	(71 688-212 412)	706	1426	(700-2961)	8.32	274	(76-1152)	1.60
QIV	898 133	(445 978-2 848 591)	5242	114 729	(68 743-201 573)	670	1292	(638-2451)	7.54	213	(57-941)	1.24
TIV/TIV in 2-6 y	853 115	(362 641-2 706 864)	4979	106 125	(46 046-192 326)	619	1274	(582-2730)	7.44	264	(74-1129)	1.54
TIV/Q-LAIV in 2-6 y	817 610	(341 554-2 691 753)	4772	103 417	(43 180-178 955)	604	1235	(494-2412)	7.21	251	(61-1104)	1.47
QIV/Q-LAIV in 2-6 y	761 137	(309 280-2 567 393)	4442	97 261	(39 245-168 471)	568	1105	(444-2149)	6.45	193	(51-880)	1.12
TIV/TIV in 2-12 y	734 350	(225 422-2 505 900)	4286	86 626	(23 822-187 957)	506	1086	(302-2767)	6.34	250	(60-1091)	1.46
TIV/TIV in 2-17 y	691 051	(203 290-2 351 643)	4033	79 320	(23 797-183 698)	463	1006	(272-2721)	5.87	240	(56-1070)	1.40
TIV/Q-LAIV in 2-12 y	619 176	(112 083-2 388 111)	3614	76 943	(12 305-167 081)	449	952	(166-2586)	5.56	211	(27-903)	1.23
QIV/Q-LAIV in 2-12 y	565 024	(53 577-2 286 728)	3298	71 267	(6163-139 189)	416	835	(67-1792)	4.87	157	(11-841)	0.92
TIV/Q-LAIV in 2-17 y	548 084	(74 821-2 200 169)	3199	67 308	(7856-134 861)	393	843	(108-1979)	4.92	191	(19-878)	1.12
QIV/Q-LAIV in 2-17 y	496 313	(26 593-2 075 552)	2897	61 972	(3188-126 244)	362	733	(35-1695)	4.28	141	(5-814)	0.82

Note. Current practice concerns the invitation of all adults aged ≥60 years and individuals aged <60 with certain chronic illnesses with overall uptake rates of approximately 3% in <18 years, 8% in 18-59 years and 65% in >60 years. Pediatric vaccination strategies assume a vaccination uptake of 50% in the indicated age group. GP indicates general practitioner; QIV, quadrivalent inactivated vaccine; Q-LAIV: quadrivalent live-attenuated influenza vaccine; TIV, trivalent inactivated vaccine; y, years of age.

*Exp: expectation (average over 7198 simulations) with range in which 95% of simulations fall.

†Rate per 100 000 person-years.

Figure 1. 20-year average clinical outcome rates by age in The Netherlands as estimated by the model. The different panels show outcomes of (A) symptomatic cases, (B) GP visits, (C) hospitalizations, and (D) deaths. Current practice concerns the invitation of all adults aged ≥60 years and individuals aged <60 with certain chronic illnesses with overall uptake rates of approximately 3% in <18 years, 8% in 18-59 years and 65% in >60 years. Pediatric vaccination strategies assume a vaccination uptake of 50% in the indicated age-group. To improve the readability of the figure, we selected pediatric vaccination strategies with Q-LAIV that were added to vaccination of elderly and high-risk groups with QIV.



GP indicates general practitioner; QIV, quadrivalent inactivated vaccine; Q-LAIV, quadrivalent live-attenuated influenza vaccine; TIV, trivalent inactivated vaccine.

inputs by the acceptance-rejection sampling according to the calibration heuristic (Appendix 2: Figure 2.2 and Table 2.1 found at https://doi.org/10.1016/j.jval.2020.10.011). The estimated basic reproduction numbers are also in line with values for seasonal influenza reported in the literature.[47]

Clinical Impact

Clinical outcomes predicted by the model were averaged across simulations to give the expected average annual clinical burden of influenza in The Netherlands over the 20-year time horizon, along with ranges in which 95% of the 7198 simulations fell (Table 2). On average, the historic vaccination program for elderly and high-risk groups with TIV prevented 202 931 (95% range: 69 058-522 523) symptomatic cases and 274 (76-1152) deaths per year compared to no vaccination. Replacing TIV with QIV prevented an additional 56 216 (95% range: 12 612-138 093) symptomatic cases and 61 (19-150) deaths per year. Figure 1 shows 20-year average annual clinical events rates per 100 000 population by age, indicating that the prevented clinical events were mainly in adults.

Introducing pediatric vaccination was estimated to prevent a substantial additional number of clinical events, and its impact increases by targeting a broader age group or by using Q-LAIV instead of TIV or both. Inclusion of Q-LAIV for 2- to 17-year-olds at 50% coverage in the vaccination program for elderly and high-risk groups with QIV prevented, on average, 136 996 (95% range: 57 788-284 623) symptomatic cases and 20 (2-52) deaths per year, and this

Table 3. Model simulations on 20-year cumulative costs, QALY losses, incremental cost-effectiveness ratios, and net health benefits in The Netherlands.

Vaccination strategy (Current/pediatric)	Total QALYs lost (thousands)	Total costs (€, millions)	QALYs gained (thousands)	ΔCosts (millions)	ICER (€/QALY gained)*	NHB (QALYs, thousands)†
Societal perspective						
No vaccination	125.4	6687	-	0		
TIV	89.8	6750	35.6	63	Dominated	32.5
TIV/ TIV in 2-6 y	81.4	6293	44.0	–394	Dominated	63.6
QIV	80.9	6659	44.5	–28	Dominated	45.9
TIV/Q-LAIV in 2-6 y	77.8	6142	47.6	–545	Dominated	74.9
TIV/TIV in 2-12 y	71.6	5788	53.8	–899	Dominated	98.8
QIV/Q-LAIV in 2-6 y	69.1	6041	56.3	–646	Dominated	88.6
TIV/TIV in 2-17 y	67.7	5658	57.7	–1029	Dominated	109.1
TIV/Q-LAIV in 2-12 y	59.9	5298	65.5	–1389	Dominated	134.9
TIV/Q-LAIV in 2-17 y	53.4	5070	72.0	–1617	Dominated	152.9
QIV/Q-LAIV in 2-12 y	51.9	5195	73.5	–1492	Dominated	148.1
QIV/Q-LAIV in 2-17 y	45.8	4972	79.6	–1715	Cost-saving	165.4
HC payer's perspective						
No vaccination	125.4	324				
TIV	89.8	1493	35.6	1168	Dominated	–22.8
TIV/TIV in 2-6 y	81.4	1604	44.0	1279	Dominated	–20.0
QIV	80.9	1682	44.5	1358	Dominated	–23.4
TIV/Q-LAIV in 2-6 y	77.8	1637	47.6	1313	Dominated	–18.0
TIV/TIV in 2-12 y	71.6	1756	53.8	1432	Dominated	–17.8
QIV/Q-LAIV in 2-6 y	69.1	1822	56.3	1498	Dominated	–18.5
TIV/TIV in 2-17 y	67.7	1854	57.7	1529	Dominated	–18.8
TIV/Q-LAIV in 2-12 y	59.9	1848	65.5	1524	Dominated	–10.7
TIV/Q-LAIV in 2-17 y	53.4	1971	72.0	1646	Dominated	–10.3
QIV/Q-LAIV in 2-12 y	51.9	2023	73.5	1699	Dominated	–11.4
QIV/Q-LAIV in 2-17 y	45.8	2140	79.6	1815	22,807	–11.2

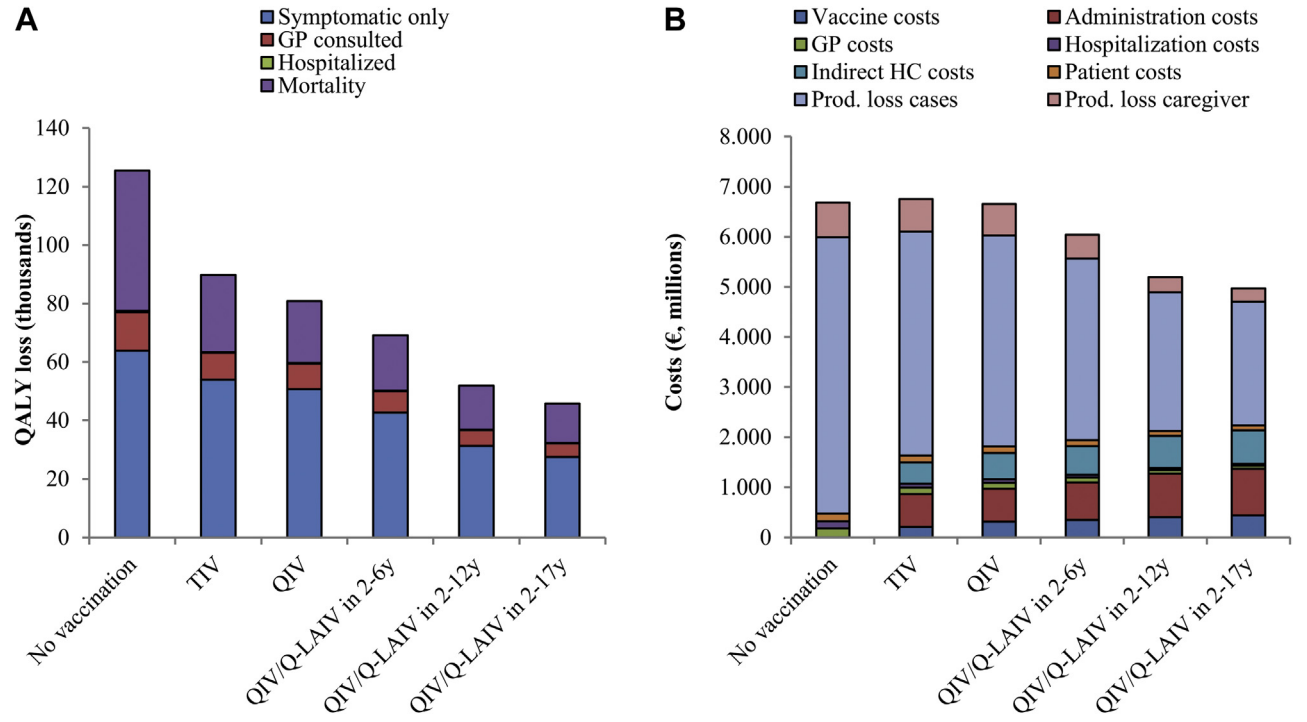
Note. Current practice concerns the invitation of all adults aged ≥60 years and individuals aged <60 with certain chronic illnesses with overall uptake rates of approximately 3% in <18 years, 8% in 18-59 years and 65% in >60 years. Pediatric vaccination strategies assume a vaccination uptake of 50% in the indicated age-group. Results include an annual discount rate of 4% for costs and 1.5% for QALYs and can therefore not be averaged across seasons.
ICER indicates incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life-year; QIV, quadrivalent inactivated vaccine; Q-LAIV, quadrivalent live-attenuated influenza vaccine; TIV, trivalent inactivated vaccine; y, years of age.
*Vaccination policies were listed as dominated when there was another policy with a QALY gain against lower costs (strict dominance) or a QALY gain against a lower ICER (extended dominance).
†Calculated as: QALYs gained – (ΔCost / λ)), with λ = €20 000/QALY.

number increased to 333 109 (179 110-648 441) symptomatic cases and 56 (19-124) deaths per year for targeting 2- to 12-year-olds, and to 401 820 (224 125-760 152) symptomatic cases and 72 (30-155) deaths per year for targeting 2- to 17-year-olds. The pediatric vaccination program offered substantial herd immunity (Fig. 1); approximately half of prevented symptomatic cases and 99% of prevented deaths were in other age groups than 2- to 17-year-olds. Another indirect effect of pediatric vaccination was an age shift of influenza cases to older age-groups. For instance, vaccination for 2- to 6-year-olds increased the number of influenza cases among 10- to 17-years-olds compared with no pediatric vaccination (Fig. 1).

Cost-Effectiveness

The 20-year cumulative discounted total costs and QALY losses, calculated as the average across all simulations run, are summarized in Table 3. From a societal perspective, inclusion of pediatric vaccination into the vaccination program for elderly and high-risk groups was estimated to result in lower costs and fewer QALYs lost—that is, adding pediatric vaccination is dominant—and each extension of the targeted pediatric age group or a switch from TIV to Q-LAIV dominated the preceding scenario. Considering all strategies, vaccination of 2- to 17-year-olds with Q-LAIV and vaccination of elderly and high-risk groups with QIV dominated all other scenarios. The discounted 20-year cumulative savings of this strategy were 35 068 QALYs and €1687 million (NHB: 119 430 QALYs) compared to QIV for elderly and high-risk groups. The majority of the QALYs gained were due to prevention of influenza illness rather than prevention of influenza deaths (Figure 2A), and the majority of costs saved were due to the reduction of productivity losses among influenza cases or caregivers of sick children (Figure 2B). All strategies were expected to be cost-saving compared to no vaccination, with the exception of vaccination program for elderly and high-risk groups with TIV, which is likely

Figure 2. Estimated average impact of a selection of influenza vaccination strategies on discounted influenza-related (A) QALY loss and (B) costs over a period of 20 years. Current practice concerns the invitation of all adults aged ≥60 years and individuals aged <60 with certain chronic illnesses with overall uptake rates of approximately 3% in <18 years, 8% in 18-59 years and 65% in >60 years. Pediatric vaccination strategies assume a vaccination uptake of 50% in the indicated age group. Future costs were annually discounted at 4% and QALY loss at 1.5%.



GP indicates general practitioner; QIV, quadrivalent inactivated vaccine; Q-LAIV, quadrivalent live-attenuated influenza vaccine; TIV, trivalent inactivated vaccine; y, years of age.

to be cost-effective (€1776 per QALY gained, calculated from Table 3).

From a payer's perspective, inclusion of pediatric vaccination into the vaccination for elderly and high-risk groups was expected to result in higher total costs but remained cost-effective to a threshold of €20 000 per QALY. For instance, the inclusion of Q-LAIV for 2- to 17-year-olds with Q-LAIV into the vaccination program for elderly and high-risk groups with QIV resulted in a discounted 20-year cumulative cost of €458 million, and the ICER was €13 004 per QALY gained (calculated from Table 3). Considering all strategies, vaccination of 2- to 17-year-olds with Q-LAIV and elderly and high-risk groups with QIV dominated all other vaccination strategies due to fewer QALY lost and a lower ICER. Compared with no vaccination, the ICER of this strategy was €22 807 per QALY gained.

Probabilistic Sensitivity Analysis

The multivariate PSA demonstrated that the uncertainty around the economic impact of pediatric vaccination was considerable, but the trend of the average values is clear (Fig. 3A). The 95% ranges of adding Q-LAIV for 2- to 17-year-olds to QIV for elderly and high-risk groups were 19 187-69 567 QALYs and €693 million-€3722 million saved, resulting in a 95% range of the NHB of 54 723-252 097 QALYs. The cost-effectiveness acceptability curve and the cost-effectiveness acceptability frontier, in which individual simulations are compared, indicate that the strategy of QIV for elderly and high-risk groups and Q-LAIV for 2- to 17-year-olds had the highest probability of being cost-effective and the highest probability of being the optimum policy at any willingness-to-pay threshold considered (Fig. 1B and C).

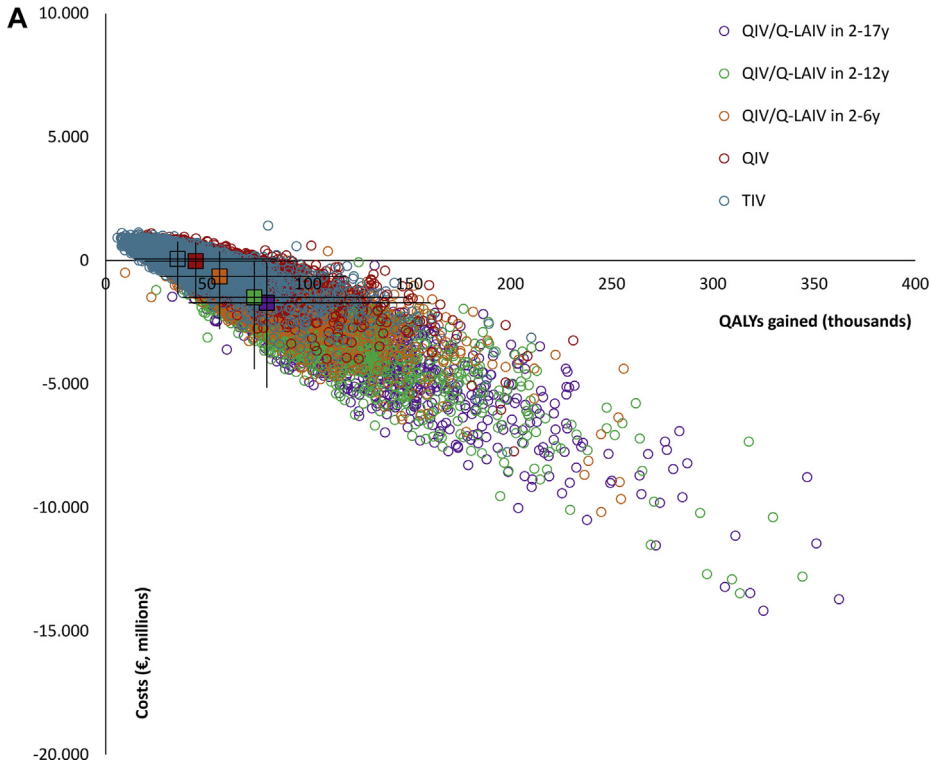
Univariate Sensitivity Analysis

Figure 3D shows the univariate sensitivity analysis of adding QIV for elderly and high-risk groups with Q-LAIV for 2- to 17-year-olds. Varying the vaccination coverage in children between 20% and 80% indicated a nonlinear relationship between the coverage and the NHB, with increasing coverage resulting in relatively lower returns. Nevertheless, pediatric vaccination strategies at 80% coverage dominated strategies at 20% or 50% coverage from a societal perspective (Appendix 2: Table 2.5-Table 2.6 found at https://doi.org/10.1016/j.jval.2020.10.011). A higher vaccine efficacy of Q-LAIV increased the average prevented number of symptomatic infections from 401 820 to 561 710 (Appendix 2: Table 2.4 found at https://doi.org/10.1016/j.jval.2020.10.011) and the NHB from 119 430 to 175 263 QALYs (Appendix 2: Table 2.7 found at https://doi.org/10.1016/j.jval.2020.10.011). Pediatric vaccination remained also cost-saving when a considerably higher Q-LAIV price was used.

Effects Among Children

If only the effects of pediatric vaccination on those aged 2-17 years were considered (Appendix 2: Table 2.11 found at https://doi.org/10.1016/j.jval.2020.10.011), the estimated QALY losses of pediatric vaccination significantly reduce and the net costs

Figure 3. Sensitivity analyses of the cost-effectiveness of pediatric influenza vaccination in The Netherlands from a societal perspective over a period of 20 years. Current practice concerns the invitation of all adults aged ≥60 years and individuals aged <60 with certain chronic illnesses with overall uptake rates of approximately 3% in <18 years, 8% in 18-59 years and 65% in >60 years. Added pediatric vaccination strategies assume a vaccination uptake of 50% in the indicated age group. (A-C) Results of the multivariate probabilistic sensitivity analysis (PSA), taking into account uncertainty in the transmission, clinical, and economic parameters. A set of key transmission parameters was repeatedly sampled from input distributions, and 7198 simulations were retained as they fitted observed influenza epidemiology in The Netherlands. Results of these simulations (incidence of infection) served as an input for the economic PSA in which clinical and economic parameters were sampled from input distributions, and outcomes were compared for a range of vaccination policies. (A) The cost-effectiveness plane shows discounted incremental costs from the societal perspective and incremental QALYs accumulated over 20 years compared to no vaccination of 7198 simulations. A square represents the average across simulations, and bars represent the range in which 95% of the simulations fell. To improve the readability of the table, we only show results of the adding pediatric strategies with Q-LAIV to the current practice with QIV. (B) The cost-effectiveness acceptability curve, showing the probability of probability of being cost-effective over a range of cost-effectiveness thresholds. (C) The cost-effectiveness acceptability frontier, showing the probability of being the optimal policy (highest net health benefit). (D): Scenario analysis of the inclusion of pediatric influenza vaccination of 2- to 17-year-olds with Q-LAIV in the current vaccination program for elderly and clinical high-risk groups with QIV. (a) efficacy of 48% in base case; (b) 50% uptake in base case; (c) 0.10 QALYs lost for nonhospitalized and 0.217 QALYs lost for hospitalized[71]; (d) 4% for costs and 1.5% for QALYs in base case; (e) human capital method includes lifelong productivity losses for premature deaths. Base friction method in base case, (f) Q-LAIV price of €5.38 in base case.



LE indicates life expectancy; QALY, quality-adjusted life-year; QIV, quadrivalent inactivated vaccine; Q-LAIV, quadrivalent live-attenuated vaccine; RCT randomized clinical trial; TIV, trivalent inactivated vaccine; y, years of age.

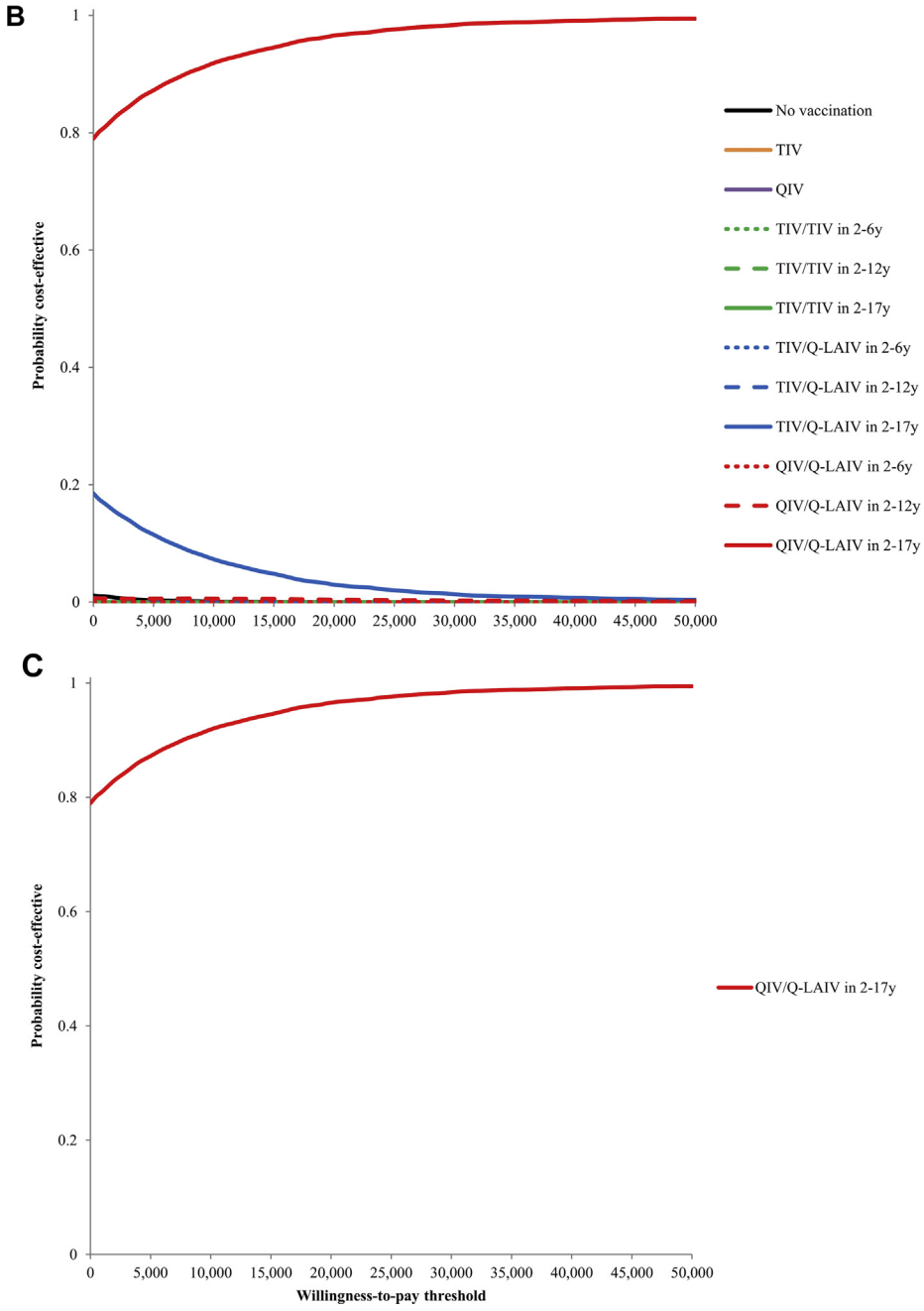
increase. However, the inclusion of pediatric vaccination in the vaccination program for elderly and high-risk groups remained cost-saving or cost-effective.

Discussion

The inclusion of childhood influenza vaccination in the Dutch national vaccination program for elderly and high-risk groups was estimated to prevent substantial morbidity and mortality on the population level, to be cost-saving from a societal perspective, and to be cost-effective from a payer's perspective. Indirect protection made a pronounced contribution to the cost-effectiveness of pediatric vaccination, given that half of the prevented symptomatic cases and nearly all prevented deaths were among adults. Vaccination of 2- to 17-year-olds with Q-LAIV and elderly and high-risk groups with QIV was the optimum policy at any willingness-to-pay threshold considered. Pediatric vaccination was also estimated to be cost-effective when only effects of pediatric vaccination among children were considered.

There was a nonlinear relationship between vaccine uptake in children and effects of vaccination. This is explained by the concept that once a critical uptake rate has been achieved, further increase yields diminishing returns.[48] Nonetheless, the economic returns of pediatric vaccination were estimated to be such that the NHB kept increasing with increasing coverage. Pediatric vaccination is also likely to shift the average of influenza infections to an older age, because the probability of becoming infected is lower and the long-term naturally acquired immunity is replaced by short-term vaccine-acquired immunity. However, this age shift did

Figure 3. (continued)

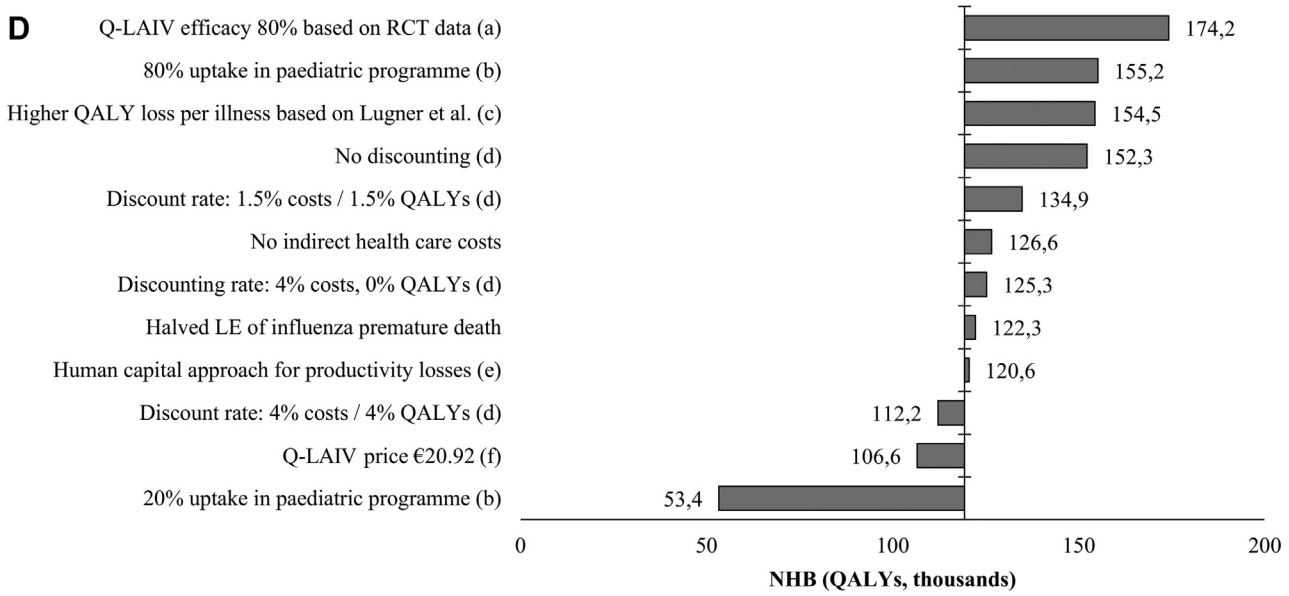


not outweigh the benefits of pediatric vaccination as a whole, and it could also be considered a good thing, because there is a lowering of the likelihood of infection in the very young.

The reduced mortality in elderly people occurred despite the already high vaccination coverages with either TIV or QIV. Also, other "enhanced" influenza vaccines for elderly people have recently become available on the international market, including high-dose influenza vaccine, MF-59 adjuvanted vaccine, and recombinant influenza vaccine, each expected to have higher efficacy than standard IVs. However, modeling studies estimated that the absolute gains of enhanced vaccines are limited (for instance, replacing QIV with high-dose TIV in US elderly would reduce the influenza-related QALY loss by 4%[49]), indicating that pediatric vaccination is expected to be also cost-saving with the use of an enhanced vaccine in elderly people.

As recommended by international guidelines,[50,51] a dynamic transmission model was used that accounts for herd immunity and gains and losses of immunity over time. The calibration procedure resulted in a reasonable number of parameter sample sets, so that we arrived at a model that provides a good caricature of influenza epidemiology in The Netherlands. The multi-strain model structure allowed the modeling of cross-reactivity

Figure 3. (continued)



between viruses, although this feature was not used in the current analysis, because it was complex to include in the calibration process using epidemiological data of 4 influenza viruses. In reality, however, such mechanisms may exist, as, for instance, vaccination with TIV is estimated to offer also partial protection against the nonincluded influenza B lineage.[25,52] If true, the current study overestimates the additional impact of Q-LAIV compared to TIV.

The vaccine efficacy and duration of immunity were assumed to be constant between seasons, but in reality these parameters may vary over time because of variation in vaccine match and irregular antigenic drift. A modeling study that accounted for seasonal variation in vaccine efficacy and duration of immunity indicated that pediatric vaccination would increase the variability in epidemic size; that is, seasons with small epidemics are occasionally alternated with seasons with large epidemics due to a build-up of the pool of susceptibles.[53] Increased variability in epidemic size may reduce the impact of the pediatric vaccination program[53] and was associated with a small risk of an overall QALY loss.[54]

There is ongoing debate about the vaccine effectiveness of LAIV. Clinical trials found that the efficacy of LAIV was superior to that of IVs,[25] whereas effectiveness studies found the effectiveness of LAIV to be superior, similar, or inferior to IV.[29-31] Use of vaccine efficacy data of LAIV in accordance with clinical trial data in the analysis resulted in a substantial higher NHB. Moreover, we assumed no difference in duration of protection between LAIV and IV, while IVs already wane through the season and LAIV may protect in a second season.[55-57] However, using a longer duration of protection of LAIV is expected to have limited impact on the outcomes, because influenza vaccination is given annually.

The analysis was not risk-stratified, although vaccination coverage and clinical and economic burden of influenza is relatively higher in high-risk groups.[58] However, we expect that use of a risk-stratified model would have limited impact on the cost-effectiveness of pediatric influenza vaccination, because the presence of comorbidities in children is low and evidence that herd immunity is unequally distributed across risk groups is absent.

We used influenza-associated mortality rates that were regressed against respiratory diagnoses, while an ecological study that used all-cause mortality data found substantially higher influenza mortality rates.[59] However, the use of all-cause mortality data could also result in an overestimation of the number of deaths attributed to influenza, and the use of respiratory diagnoses reflects a conservative approach.

Furthermore, assumptions had to be made for the vaccine prices of Q-LAIV and QIV, as tendered prices for the Dutch setting are unavailable. However, our sensitivity analyses demonstrate that pediatric vaccination remained to be cost-saving at substantially higher vaccine prices.

We found a higher impact of pediatric influenza vaccination on the overall infection attack rate compared with another modeling study from The Netherlands (28% for TIV in 50% of 2- to 17-year-olds vs 15% for Q-LAIV in 40% of 2- to-16-year-olds).[53] This difference may be explained by differences in the model structure and a higher proportion of children effectively vaccinated in the current study. This also explains why pediatric influenza vaccination was found to be cost-saving in our study, while the other study found pediatric vaccination to be cost-effective.[54] Studies from surrounding European countries estimated pediatric vaccination to be cost-saving from a societal perspective and cost-effective from a payer's perspective.[60-62]

Results of this study are relevant for policy makers deciding whether to include pediatric influenza vaccination in the national influenza program of The Netherlands or elsewhere, even though cost-effectiveness is not the only criterion involved in this decision.[18] For instance, acceptability of the vaccination program is also important, because most of the benefits were among adults via herd immunity. However, such a nonuniform distribution of advantages a vaccination program may well be acceptable when adverse events of vaccination are mild and public health in general is substantially improved.[18]

Finally, the impact of routine influenza vaccination in early childhood on the long-term development of immunity against influenza viruses is a matter of debate. Accumulating evidence

suggests that the first influenza infections in life influence the immune response against subsequent infections (imprinting), but the impact of vaccination on imprinting is unknown.[63,64] LAIV is thought to be a more appropriate vaccine candidate than IV for children naïve to influenza infections because it mimics a natural infection in the upper respiratory tract that activates mucosal antibodies and cross-protective T-cell lymphocytes.[65]

Conclusion

Modeling indicates that inclusion of pediatric influenza vaccination in the national vaccination program for elderly and high-risk groups results in a substantial reduction of influenza morbidity and mortality on the population level, and it would be cost-saving from a societal perspective and cost-effective from a payer's perspective.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.10.011.

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