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Cost-effectiveness of seasonal influenza vaccination in pregnant women, health care workers and persons with underlying illnesses in Belgium

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Abstract

Risk groups with increased vulnerability for influenza complications such as pregnant women, persons with underlying illnesses as well as persons who contact them, such as health care workers, are currently given priority (along with other classic target groups) to receive seasonal influenza vaccination in Belgium. We aimed to evaluate the efficiency of this policy by performing cost-effectiveness analysis of increased vaccine uptake in the three specific target groups above, while accounting for effects beyond the target group. Increased influenza vaccine coverage is likely to be cost-effective for pregnant women (median €6,589 per Quality-Adjusted Life-Year (QALY) gained [€4,073-€ 10,249]) and health care workers (median €24,096/QALY gained [16,442-€36,342]), if this can be achieved without incurring additional administration costs. Assuming an additional physician's consult is charged to administer each additional vaccination, the cost-effectiveness of vaccinating pregnant women depends strongly on the extent of its impact on the neonate's health. For health care workers, the assumed number of preventable secondary infections has a strong influence on the cost-effectiveness. Vaccinating people with underlying illnesses is likely highly cost-effective above 50 years of age and borderline cost-effective for younger persons, depending on how this risk group's life expectancy compares to that of the general population. The case-fatality ratios of the target group, of the secondary affected groups and vaccine efficacy are key sources of uncertainty.

Keywords

flu; vaccination; risk groups; cost-utility; pregnancy; immuno-compromised; elderly

Introduction

Seasonal influenza causes a substantial number of symptomatic infections, hospitalisations and fatalities, especially in young children, the elderly and people with underlying illnesses [1]. The Superior Health Council of Belgium recommends giving priority to immunizing people at increased risk of influenza complications, namely people living in institutions, people with underlying illnesses and the elderly (>65 years). Furthermore, health care workers (HCWs), pregnant women in the 2nd and 3rd trimester of pregnancy, the general population between 50 and 64, and poultry and pig farmers and their household members, have priority over the general population [2]. Prioritization is important, because the demand for influenza vaccines has surpassed supply in recent years [3]. Although these recommendations were based on the medical literature, their potential cost-effectiveness was largely unknown. Also, doubts have been expressed about the usefulness of influenza vaccination in view of uncertainties related to season-specific effectiveness in at-risk groups [4]. Therefore, up to date information on the cost-effectiveness of vaccinating these risk groups, may improve the prioritisation and acceptability of seasonal influenza vaccines. In this paper, we evaluate the cost-effectiveness of increasing seasonal influenza vaccine uptake in (1) pregnant women in their 2nd and 3rd trimester, (2) HCWs and (3) people with underlying illnesses. Currently these groups have relatively low vaccine uptake [3], despite the above recommendations. Cost-effectiveness analyses of influenza vaccination of the elderly are presented elsewhere in combination with childhood vaccination options using a dynamic transmission model [3]. We did not consider here the specific risk group of poultry and pig farmers, because the rationale for their vaccination (recombination of viruses in their work environment with potential risk to the general population) requires a different modelling approach.

The cost-effectiveness of vaccinating pregnant women [5-7], HCWs [8-11] and people with underlying illnesses [12-16] has been evaluated before in other countries, but the results depended strongly on assumed vaccine efficacy. In this study, we use the most up to date estimates [17], and consider the potential impact of influenza vaccination beyond the target group. Vaccination during pregnancy has the potential to reduce foetal death through avoided maternal mortality, and confers vaccine-induced immunity to the neonate [18]. In previous cost-effectiveness analyses, these potential effects were not [5, 7] or only partially [6] accounted for. Vaccinating HCWs was also shown to have an effect on the patients they contact [19, 20]. This could be of particular importance for institutionalised or hospitalised patients and the elderly in general, and is therefore also considered in our analyses.

Material and methods

Decision analytic model

Since the groups of pregnant women, HCWs and people with underlying illness are relatively small in Belgium and are not core transmitter groups for the influenza virus, the cost-effectiveness of their vaccination can be analysed using a static model [21]. For each risk group, a decision tree model was developed in the R software. (R development Core Team, 2012, http://www.R-project.org). The general structure is displayed in Figure 1 and model parameters are listed in Table 1. The model assumes that susceptible individuals (unvaccinated or vaccinated without being protected) experience an age dependent rate of acquiring a symptomatic influenza infection for which they seek medical care. This rate is based on estimates from a dynamic model for influenza like illness (ILI) fitted to ILI surveillance data [3], combined with laboratory confirmed influenza proportions on these ILI data. We obtained the total number of symptomatic cases and thence the age-specific number of cases who do and do not seek medical care (i.e. do not consult a physician). Thus we obtained the number of cases not receiving medical care, ambulatory cases, hospitalisations and fatalities.

Direct medical costs and QALY losses associated with these outcome categories were included in order to compare the costs and QALYs of current with increased vaccine uptake scenarios (up to 50% (40% for persons with underlying illnesses)) [1]. A health care payer perspective was used. Costs and non-fatal health outcomes were not discounted because of the short analytical time horizon (one year). Future life-years lost due to influenza-attributable mortality were discounted at an annual rate of 1.5%, in accordance with Belgian guidelines [22].

We assumed the vaccine is offered to pregnant women, on average in calendar week 47 (i.e. mid-November). We assumed also a 4-week delay before vaccinees benefit from vaccine protection. Hence, costs and QALY losses were included for infections occurring between calendar week 51 and 25 (assumed end of the influenza season), by using a partial attack rate in the model (84% of the yearly ILI cases occurs in that time window). According to the Belgian guidelines, pregnant women should receive an influenza vaccine during the second or third trimester of their pregnancy, implying the average delivery date of pregnant vaccine recipients is in calendar week 7 (assuming uniformly distributed deliveries over the year and vaccination in calendar week 47). It is assumed that when the pregnant mother dies due to influenza, so does the foetus. Therefore, to account for fatalities in the period leading up to calendar week 7, the discounted expected life years lost of both the mother and her unborn child are summed to calculate the associated cost-effectiveness ratios. From calendar week 7 until week 25, infants can be assumed to be exposed to an autonomous risk of acquiring an influenza infection (one third of the annual attack rate in the infant (<1 year) age category). Within that period we foresee potential transferred vaccine-induced immunity from mother to child. Since the extent to which an immune response may translate into clinical protection is not yet demonstrated for our setting [23], we vary the factor by which vaccine efficacy is transferred from mother to child from 0% over 50% to 100% in sensitivity analysis. We ignore any separate health or cost consequences for the infants due to influenza-related deaths in mothers in the period after birth. Furthermore, we assume identical probabilities for influenza-related hospitalisation and death of the mother before and after giving birth.

Finally the occurrence of multiple pregnancies has not been accounted for, since they only make up a small part of the total number of pregnancies.

The health outcomes for secondary symptomatic influenza infections amongst patients in contact with health care workers are calculated in the same manner as those for primary infections.

Data sources and input parameters

Table 1 contains all input parameters by risk group. In this subsection, we provide some background and clarification for these parameters.

The choice of age groups of people with underlying illnesses and patients in contact with HCWs is based on the available input data and on plausible options for vaccination. Patients in contact with HCWs are conservatively assumed to have the same characteristics (hospitalisation costs, hospitalisation and death rates, etc.) as the general population of the same age class. We limited the analysis to 50 year olds.

The number of yearly influenza-related hospitalisations and fatalities were estimated by applying an attributable fraction for influenza to reported influenza and pneumonia hospitalisations and fatalities. This attributable fraction was obtained by regressing weekly counts of influenza and pneumonia admissions and deaths on the weekly numbers of laboratory confirmed cases of respiratory pathogens that may cause influenza-like-illness or pneumonia (influenza (A and B), *S. pneumoniae*, adenovirus, respiratory syncytial virus, *m. pneumoniae*, parainfluenza, and *haemophilus*), population size, holiday and school term indicators. Details of this regression analysis are described elsewhere [3].

Cost-effectiveness was only assessed for increased uptake of the trivalent inactivated influenza vaccine (TIV), up to 2013 the only influenza vaccine type available in Belgium, and reimbursed for pregnant women, HCWs and people with underlying illnesses (amongst other risk groups). TIV provides moderate protection against outpatient virologically confirmed influenza with a pooled vaccine efficacy of 59% [95% CI 51%–67%] [17]. This estimate was used irrespective of age or risk class, because there is currently no evidence suggesting differences according to such characteristics [1, 3, 17].

Uncertainty, variable importance and sensitivity analysis

Where appropriate, uncertainty around the input parameters was specified as probability distributions (Table 1, [24]). For the hospitalisation and case-fatality ratios, the number of successes and the number of failures from the beta distribution are based on the predictions obtained from different selected "best" regression models (see above). Model uncertainty was taken into account by randomizing with equal probability between selected regression models for the different outcome measures. To assess the uncertainty of the cost-effectiveness results, we conducted Monte-Carlo sampling with 10,000 draws taken from the joint input distribution, assuming independence of the uncertain input variables (i.e. probabilistic sensitivity analysis).

The relative influence of each of the uncertain parameters was investigated by fitting multiple linear regression models with as covariates all standardized uncertain input variables and as response the incremental costs, the incremental QALYs gained and the net benefits. The net benefit was calculated by

subtracting the incremental costs from the QALYs gained valued at €35,000 per QALY. In Belgium there is no official willingness to pay threshold to obtain gains in (quality-adjusted) life years, but €35,000 is about the Gross Domestic Product per capita. The amount of GDP per capita has been put forward by the World Health Organization as representing the costs per QALY gained of a 'very cost-effective' strategy [25]. The larger the absolute value of the regression coefficients, the more important the uncertain parameter is in determining the response (incremental costs, QALYs and net benefits).

Probabilistic sensitivity analysis was repeated for different key model assumptions regarding clinical protection against influenza transferred from mother to child, the number of influenza cases caused in patients through contacts with health care workers, and life expectancy of people with underlying illnesses relative to that of the general population. An important question regarding implementation is whether we can assume zero marginal administration costs for vaccinating pregnant women or HCWs, or whether an additional GP visit will be charged for these acts. Since this was unknown to the Belgian program managers, both these options were evaluated.

Results

Pregnant women

The cost-effectiveness of increasing vaccine uptake in 2nd or 3rd term pregnant women depends on the assumed vaccine administration cost and the degree of vaccine protection indirectly inferred to the new-born child. Increasing vaccine uptake is very likely to be cost-effective when there are no marginal administration costs, or when these remain substantially lower than the current price for a GP consultation. At marginal administration costs of 1 GP consult (€23.32), seasonal influenza vaccination of pregnant women would only be cost-effective, if indirectly transferred vaccine protection to the child is high (i.e. 100% in Figure 2). Figure S1 (in supplementary material) shows the variable importance, indicating that the case-fatality ratio of the mother, vaccine efficacy and QALY loss are all influential. Ignoring the life years lost due to the death of a foetus only has a minor impact on the cost-effectiveness (median ICER of €6,706 instead of €6,616 per QALY gained). With a per-season median of 26 versus 3 hospitalisations prevented, the incremental health gains of the program are larger for the neonates than for the pregnant women, respectively (see Table 2). The larger scope for prevented hospitalisations and deaths in neonates is due to the high risks for neonates afflicted by ILI (mean proportion hospitalised 2.92%, based on the 0-4 year old age group).

Health care workers

Also for HCWs, vaccine administration costs have a large influence on the cost-effectiveness of influenza vaccination, as well as the extent of indirect protection conferred to patients. That is, the assumed number of secondary symptomatic influenza infections among patients caused by an influenza case in the HCWs is influential. At zero marginal administration costs (i.e. vaccination during a routine medical visit or through occupational health doctor), increased influenza vaccination of active HCWs is likely to be cost-effective, even without accounting for secondary influenza cases (median ICER: €24,103 per QALY gained; 95% ICER range: €16,421-€36,355; see Table S1 in Supplementary material). If we assume

at least one secondary symptomatic influenza infection in the elderly patients above 75 years of age per symptomatic infection in the HCWs the program becomes even cost-saving.

At marginal administration costs of one GP visit (€23.32), increased influenza vaccine uptake in HCWs can be considered cost-effective, only if at least one secondary symptomatic influenza infection in patients older than 64 is assumed per 3 primary symptomatic infections in the HCWs. Alternatively, at least one secondary influenza case in persons aged 50-64 per primary case in HCWs can compensate for these marginal administration costs (see Figure 3, Table S1 in Supplementary material).

Probabilistic sensitivity analysis, assuming one secondary symptomatic influenza infection per symptomatic infection in the target group, reveals that the uncertainties around the case-fatality ratio for secondary cases and the vaccine efficacy exert the highest relative influence on QALYs gained and consequently on the net benefits (see Figure S2 in supplementary material). This finding holds for the different age groups of secondary cases.

We additionally investigated splitting up the group of HCWs according to age. Observed changes in ICER values are minor, since differences in input variables between HCW age groups are small.

Persons with underlying illnesses

Increasing vaccine uptake in people with underlying illnesses is cost-effective for persons aged 50 and older, for all life expectancies considered (Figure 4, Table 2). Also for younger persons, it is likely to be cost-effective for most combinations of uncertain parameters and life expectancies. The ICERs become less favourable when life expectancy of younger persons with underlying diseases is assumed to be only 30% of that of the general population of the same age group, and for small values of case-fatality ratios. Indeed, the uncertainty around the case-fatality ratio and to a lesser extent around vaccine efficacy are the most influential for all age groups, with the case fatality ratio being more influential in younger age groups. (Figure S3 in Supplementary material)

For these youngest age groups (<50 years), we calculated the maximum marginal vaccination costs (vaccine price and administration costs) such that the 95th percentile of the ICER distributions falls below €35,000. For children with underlying illness below 15 years of age, these maximum costs would be €20.44 and €7.57, assuming their life expectancy was 50% and 30%, respectively, of that of an average child below 15 years of age. For the age group 15-49, such a maximum amount cannot be found using the same assumptions for life expectancy (i.e. at zero marginal costs the 95th percentile is above €35,000).

Discussion

For pregnant women, we found increased influenza vaccine uptake to be particularly cost-effective (median ICER < €10,000 per QALY gained). This result is similar to that of Jit et al. [6], when assuming identical administration costs. Jit et al did not attribute life years lost to fetal death, but used a higher overall vaccine efficacy estimate.

Also for elderly with underlying illness (65+), increased vaccine uptake yielded generally acceptable cost-effectiveness. This contrasts with the few other studies for this target group (summarized in de Waere et al. [26]), mainly because we used a more favorable rapport between vaccine efficacy and occurrence of preventable disease. Cost-effectiveness fundamentally depends on relating vaccine efficacy on appropriate outcomes to reliable estimates of the occurrence of such outcomes in the context of the envisaged target group, for which we used the most specific, soundest and latest evidence [17, 27].

Ours is one of the few studies to evaluate the cost-effectiveness of influenza vaccination in HCWs [27]. We demonstrated that the cost-effectiveness of vaccinating HCWs depends strongly on the assumed number of secondary symptomatic influenza infections prevented in patients they contact, as well as these patients' ages and vulnerability to influenza. Up to now only Chicaiza-Becerra et al. [11] included such patient benefits. They found vaccination of Colombian HCWs who care for cancer patients, to be cost saving. Some of the studies not accounting for patient benefits, also reported favourable results [8, 10, 28]. Furthermore, there is empirical evidence to show that vaccination of HCWs might be more effective in preventing disease and death in the elderly in long-term care, than vaccinating these elderly patients directly [19, 20]. These results are likely to be generalizable to HCWs making contact with other vulnerable groups such as people living in institutions and persons with severe underlying illnesses.

Our findings are based on the currently available evidence on vaccine efficacy and disease burden in the specific risk groups, combined with plausible assumptions inferred from the literature. For instance, vaccine efficacy was assumed constant over the different age and risk groups considered here since the most recent authoritative trial review found no age difference (in <65 years of age, [17]) and more recent observational studies found similar efficacy across risk groups [29-32]. Clearly, if future research would show vaccine efficacy to be lower in elderly with underlying illnesses, the cost-effectiveness of their vaccination would become less attractive. Better knowledge of vaccine efficacy would strongly reduce uncertainty in all presented cost-effectiveness results, because it remains a main source of uncertainty (see large impact of vaccine efficacy on the net benefit in Figure S1 in supplementary material), together with the case-fatality and hospitalisation ratios.

The basic structure of our decision-analytic model is rather conservative. Firstly, for pregnant women and people with underlying illnesses, herd immunity was not accounted for. Indeed, for these target groups herd immunity is likely to be negligible, because they are not core transmitter groups in the general population or in specific settings. Secondly, we assumed the vaccine would only protect for one season against the circulating strains. However, it seems plausible that some vaccine recipients would enjoy some residual protection into the next season, and that therefore this is also a conservative

assumption. Thirdly, we opted for a mean approach for the relative timings of vaccination of pregnant women in relation to the onset of the influenza season and gestational age, based on previous seasons. However, previous studies found assumptions regarding these relative timings to be influential for the cost-effectiveness [6, 7]. Clearly, vaccination of second or third term pregnant women is more effective and cost-effective, if it can take place before or as early as possible in the flu season.

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Author contributions

PB conceived the study. AB developed and implemented the model. GH, YV, JB and PB provided input data. AB performed and interpreted the analyses, with revisions by PB, JB and GH. AB, PB and JB wrote the manuscript, which GH, JV and NH critically revised. All authors approved the final version of the manuscript

Conflicts of interest

The authors have no conflicts of interest to declare.

Tables and captions

Table 1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses.

	Value or distribution			
Parameter	**Pregnant women**[a]	**Health Care Workers** [a]	**People with underlying illnesses**	**Source**
Vaccination program and vaccine characteristics				
Size target group	121,363	239,740	117,473 (0-14 years of age) 407,613 (15-49 years of age) 320,672 (50-64 years of age) 559,788 (over 65 years of age)	[1]
Vaccine uptake (P_{vac})	0.50 increased uptake scenario 0 current uptake scenario (assumed)	0.50 increased uptake scenario 0.35 current uptake scenario	0.40 increased uptake scenario 0.20 current uptake scenario	[1]
Fixed marginal cost vaccination programme	€ 0			
Variable vaccination costs: TIV per dose	€ 11.81			[33]
Variable administration cost per dose (GP visit in Belgium)	€ 0 or € 23.32	€ 0 or € 23.32	€ 23.32	[33]
Vaccine efficacy of the TIV vaccine (ε)	Gaussian(mean=0.59; sd=0.04)			[17]
Epidemiological parameters				
Yearly attack rate of influenza like illness (ILI) seeking medical care (λ_{ILI})	Weighted average over the age distribution			The yearly attack rate for patients with ILI seeking medical care was obtained by dividing the predicted number of ILI infections, under current vaccination coverage, from a dynamic transmission model [3] by the population size in that age cohort.
The proportion of influenza within the ILI cases seeking medical care (P_{influ})	• Beta(2,070; 2,075) for pregnant women • Beta(132; 2,075) for neonates	Beta(2,070; 2,075)	• Beta(751; 593) (0-14 years of age) • Beta(2,070; 2,075) (15-49 years of age)	[3]

			• Beta(2,070; 2,075) (50-64 years of age) • Beta(142; 202) (over 65 years of age)	
The proportion of symptomatic influenza cases who do not seek medical care: no GP visit, not hospitalised. (P_{nomed})	Beta(1,107; 1,143)			[3]
The hospitalisation rate of influenza cases seeking medical care (τ)	We randomize with equal probability between 3 scenarios: • Beta(7, DENOM[b]-7) • Beta(11, DENOM[b] -11) • Beta(15, DENOM[b] -15)	We randomize with equal probability between 2 scenarios: • Beta(18, DENOM[b]-18) • Beta(55, DENOM[b]-1.3)	• Beta(76, DENOM[b]-76) (0-14 years of age) • Beta(127, DENOM[b]-127) (15-49 years of age) • Beta(160, DENOM[b]-160) (50-64 years of age) For the age group over 65 years, we randomize with equal probability from the hospitalisation rates of the general population of that age (see reference)	[3]
The case fatality ratio of influenza cases seeking medical care (μ)	For pregnant women we randomize between 2 scenarios Beta(0.1, DENOM[c]-0.1) Beta(0.2, DENOM[c] -0.2) For neonates we randomize between model predictions of the general (hospitalised) population between 0-5 years of age[d]	For HCW, we randomize between 2 scenarios: • Beta(0.6, DENOM[b]-0.6) • Beta(1.3, DENOM[b]-1.3) We randomize between models for the elderly (hospitalised) population[c]	• Beta(2, DENOM[b]-2) (0-14 years of age) • Beta(8, DENOM[b]-8) (15-49 years of age) • Beta(30, DENOM[b]-30) (50-64 years of age) For the age group over 65 years we randomize from the case fatality ratios of the general (hospitalised) population of that age[c]	[3]
Outcomes: quality of life and life expectancy				
QALY loss for an ambulatory patient	0.0071 (sampling from 8 Gaussian distributions: 7 days for which VAS scores were measured + number of days with symptoms)			[34], [3]

Duration of symptoms for an ambulatory patient	Gaussian (mean=6.43; sd=0.14)			[3]
Duration of symptoms for a hospitalised patient	Gaussian (mean=8.5; sd=1.04)			[3]
Duration of symptoms for a person not seeking medical care	Gaussian (mean=5.51; sd=0.14)			[3]
QALY loss for a hospitalised patient	QALY loss ambulatory patient * ratio duration of symptoms hospitalised patient and duration of symptoms ambulatory patient			Assuming average QALY loss for a day with influenza does not differ between ambulatory patients, hospitalised patients and persons not seeking medical care [34], [3]
QALY loss for a person not seeking medical care	QALY loss ambulatory patient * ratio duration symptoms person not seeking medical care and duration of symptoms ambulatory patient			
Life expectancy	as a function of age	as a function of age	as a function of age multiplied with a factor 1 or 0.5 or 0.3 to investigate the influence of shorter life expectancy due to underlying illnesses	[3]
Outcomes: Costs: We use a single randomization parameter for the following 3 cost categories, to randomize between the highest and lowest costs with equal probability				
Out-of-hospital costs for a hospitalised patient	lowest unit costs: Gaussian(mean=€119.65, sd=€17.69)			[3]
	highest unit costs: Gaussian(mean=€139.94, sd=€20.19)			[3]
Cost for an ambulatory patient (i.e. consulting GP) (no difference between ILI and influenza)	lowest unit costs: Gaussian(mean=€51.04, sd=€1.18)			[3]
	highest unit costs: Gaussian(mean=€63.8, sd=€1.34)			[3]
Cost for a person with ILI not seeking medical care	lowest unit costs: Gaussian (mean=€3.39, sd=€0.21)			[3]

	highest unit costs: Gaussian (mean=€7.17, sd=€0.37)			[3]
In-hospital cost for a hospitalised patient[d]	For pregnant women, we randomize between two options: • weighted average of primary influenza hospitalisation costs, for women with primary diagnosis influenza (€ 1838.16) and • cost of women with primary diagnosis influenza and secondary diagnosis pregnancy complication (€ 1,481); For neonates we use the average hospitalisation cost of primary diagnosis influenza (€ 2,572)	Depending on the age group: • €2,513 (HCW, 20-65 years of age) • €1,653 (HCW, 20-29 years of age) • €2,300 (HCW, 30-49 years of age) • €3,660 (HCW, 50-65 years of age) • €3,660 (elderly, 50-64 years of age) • €4,825 (elderly 65-74 years of age) • €5,664 (elderly, over 75 years of age)	We calculate the cost per age of admission[b]: • €3,437 (0-14 years of age) • €4,576 (15-49 years of age) • €6,293 (50-64 years of age) • €7,507 (65+ years of age)	[3]
Discount rates				
Discount rate for costs	0.03			[22]
Discount rate for health effects	0.015			[22]
Specific factors for the pregnancy model				
Proportion of attack rate (λ_{ILI}) exposure during pregnancy and during the period of vaccine protection for the	0.84	-	-	See attack rate (λ_{ILI})

cohort giving birth, on average, on 15th February. This period is defined as week 51-week 25				
In mothers who acquire influenza and die during pregnancy, the proportion of neonates who are not yet born. (Cases week 51-week 7 of the mother/ cases week 51-25 for women)	0.58	-	-	See attack rate (λ_{ILI})
Proportion of the attack rate (λ_{ILI}) applicable to neonates after they are born. (week 8-25)	0.33	-	-	See attack rate (λ_{ILI})

[a] *Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.*

[b] *DENOM refers to the denominator of the case fatality ratio and hospital rate, and has the meaning of the number of Influenza cases seeking medical care sampled from a run of the static model (see Figure 1) with the current uptake scenario vaccination coverage. Working with model based versus observed denominators had an ignorable impact on the cost-effectiveness.*

[b] *Hospitalisation rates and case fatality ratios of an age class of the general population were calculated by applying the attributable fraction of influenza derived from regression models to the observed number of influenza and pneumonia per observed influenza cases in the target group.*

[d] *People with underlying illnesses were identified by looking for following underlying ICD-9 diagnostic codes (http://icd9.chrisendres.com): asthma (493; V17.5), cardiovascular disease (989.1, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 413, 412, 410, 411, 414, 420, 422), chronic obstructive pulmonary disorder (490-492), diabetes (249, 250, V18.0, V77.1, 253.5, 588.1), HIV (042), hypertension (401-405, 997.91, 459.3) and stroke (430-438, 342).*

[e] *Direct costs for a deceased person are implicitly accounted for in the costs for medication, GP visit and hospitalisation, as the sum of these 3 relates to the total number of influenza cases (including those who die from influenza)*

TIV: Trivalent Inactivated Influenza Vaccine; HCW: health care workers; CFR: case-fatality ratio; ILI: Influenza like illness

Age specific parameters such as the attack rate, hospitalisation costs and life expectancy were summarized by taking averages, weighted by the age distribution in the general population in 2011. For pregnant women, the weights were based on the frequency of live births by age of the mother.

Table 2: Incremental direct costs, Quality-Adjusted Life-years (QALYs) and cost-effectiveness ratio (ICER) of increased seasonal influenza vaccination uptake in different target groups. Results of 10,000 simulations, presented as median (mean) [95% range] (price level 2011)

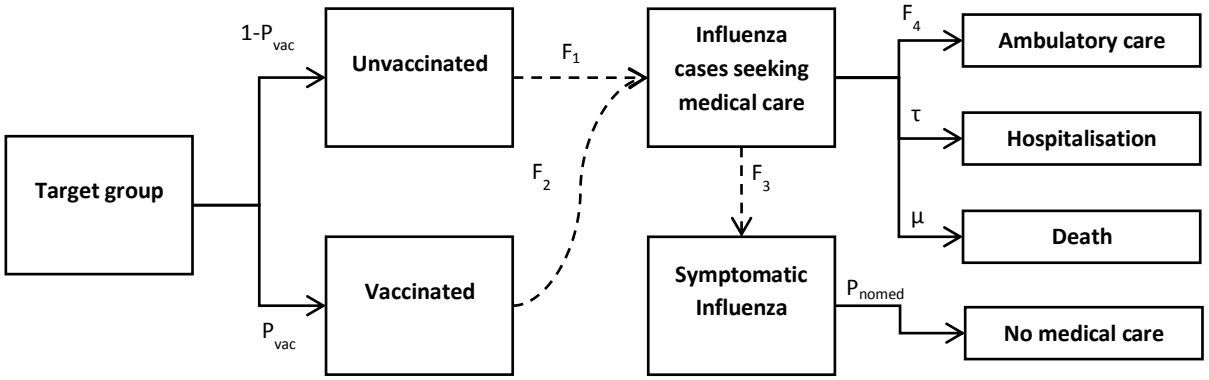
	Pregnant women[a] (121,363 persons)	**Health care workers[b] (239,740 persons)**	**People with underlying illnesses[c]**			
			0-14 years of age (117,473 persons)	**15-49 years of age (407,613 persons)**	**50-64 years of age (320,672 persons)**	**Over 65 years of age (559,788 persons)**
Program coverage	**From 0% to 50%**	**From 35% to 50%**	**From 20% to 40%**	**From 20% to 40%**	**From 20% to 40%**	**From 20% to 40%**
Assumed marginal administration costs	**€0**	**€0**	**€23.32**	**€23.32**	**€23.32**	**€23.32**
hospitalisations prevented - neonate	26 (26) [20-33]	-	-	-	-	-
hospitalisations prevented – target group	3 (3) [1-5]	3 (4) [1-8]	10 (10) [8-13]	17 (17) [13-21]	21 (21) [17-26]	156 (166) [99-249]
Deaths prevented - neonate	0.07 (0.09) [0.04-0.33]	-	-	-	-	-
Deaths prevented – target group	0.00 (0.04) [0.00-0.33]	0.07 (0.10) [0.00-0.42]	0.23 (0.27) [0.03-0.77]	1.02 (1.06) [0.45-1.93]	3.96 (4.02) [2.63-5.77]	42.41 (43.53) [31.10-58.71]
Incremental direct costs	€385,978 (€383,962) [€309,787-€450,365]	€709,703 (€709,133) [€673,983-€740,952]	€689,687 (€689,189) [€658,694-€716,877]	€2,476,027 (€2,473,748) [€2,388,545-€2,552,104]	€1,902,263 (€1,901,102) [€1,830,151-€1,967,352]	€2,587,383 (€2,513,987) [€1,857,678-€3,044,346]
Incremental QALYs	58 (59) [40-85]	29 (30) [20-43]	31 (33) [20-56]	100 (101) [70-139]	132 (133) [97-176]	518 (529) [382-708]
ICER	€6,616 (€6,763) [€4,097-€10,345]	€24,096 (€24,595) [€16,442-€36,342]	€22,008 (€22,596) [€12,180-€36,574]	€24,768 (€25,278) [€17,623-€35,725]	€14,378 (€14,610) [€10,627-€20,005]	€4,784 (€4,932) [€2,797-€7,607]

[a] *Assuming 100% vaccine efficacy transfer, leading to clinical protection, from mother to child trough maternal antibodies*

[b] *Assuming no secondary influenza infections in the patients they contact*

[c] *Assuming the same life expectancy as the general population of the same age*

303 **Figure 1: Basic structure of the static model**



304

305 Full arrows indicate the causal structure of the model. Dashed arrows indicate how the group sizes were calculated, when it is different from the causal
306 structure, and how the sizes of the different groups were calculated using the input data available in Table 1. $F_1 = \lambda_{ILI} * P_{influ}$; $F_2 = F_1*(1-\varepsilon)$; $F_3 = 1/(1-P_{nomed})$; $F_4 =$
307 $1-\mu-\tau$; P_{vac} is the vaccination coverage of the target group; λ_{ILI} is the yearly attack rate of influenza like illness (ILI) for which medical care is sought; P_{influ} is the
308 proportion of influenza relative to the ILI cases seeking medical care; ε is the vaccine efficacy against influenza; τ is the influenza hospitalisation rate, μ the
309 influenza death rate and P_{nomed} is the proportion of symptomatic influenza cases not seeking medical care (see also Table 1).

310

Figure 2: Cost-effectiveness acceptability curves for vaccinating 50% versus 0% of 2nd or 3rd term pregnant women while varying the administration cost from €0 to €23.32 and the percentage of transferred vaccine efficacy from mother to child after birth form 0% over 50% to 100%. The vertical bar indicates a willingness to pay for a Quality-Adjusted Life-Year (QALY) of €35,000.

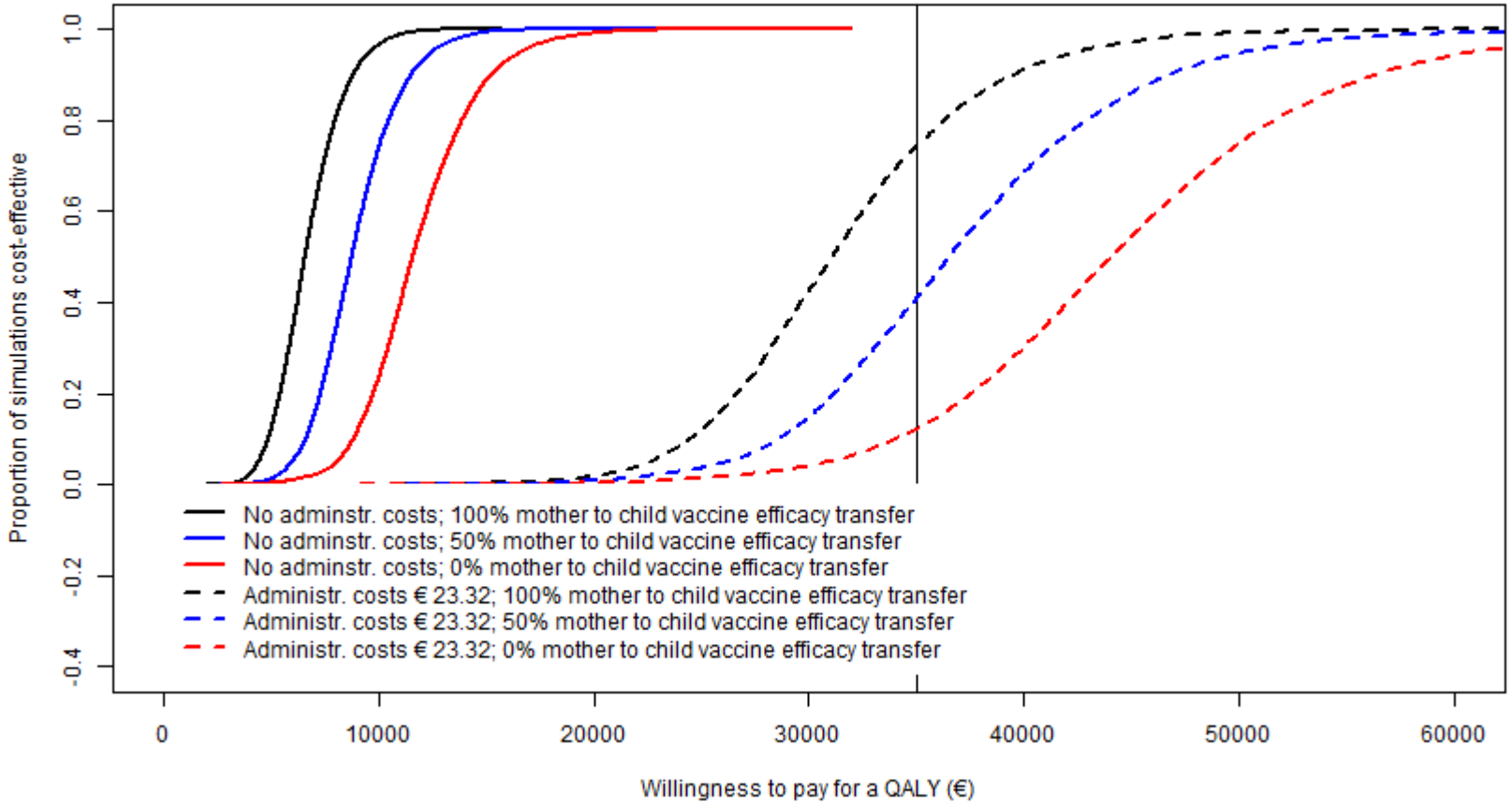


Figure 3: Cost-effectiveness acceptability curves for vaccinating 50% versus 35% of health care workers 20-65 years of age, with varying numbers of secondary infections in elderly patient groups of various ages ("sec. inf. eld." In graph legend), assuming marginal administration costs of €23.32. The vertical bar indicates a willingness to pay for a Quality-Adjusted Life-Year (QALY) of €35,000.

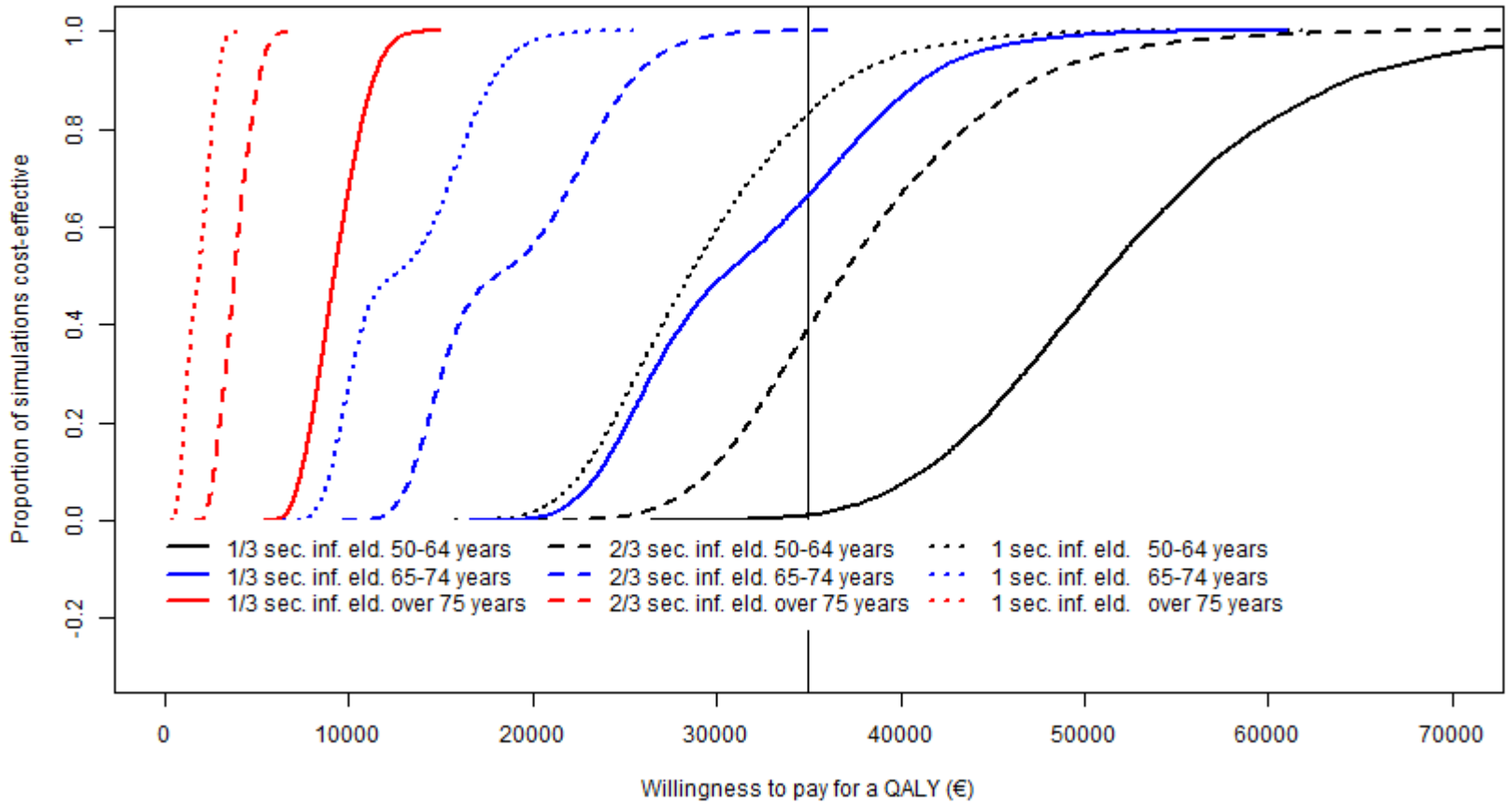
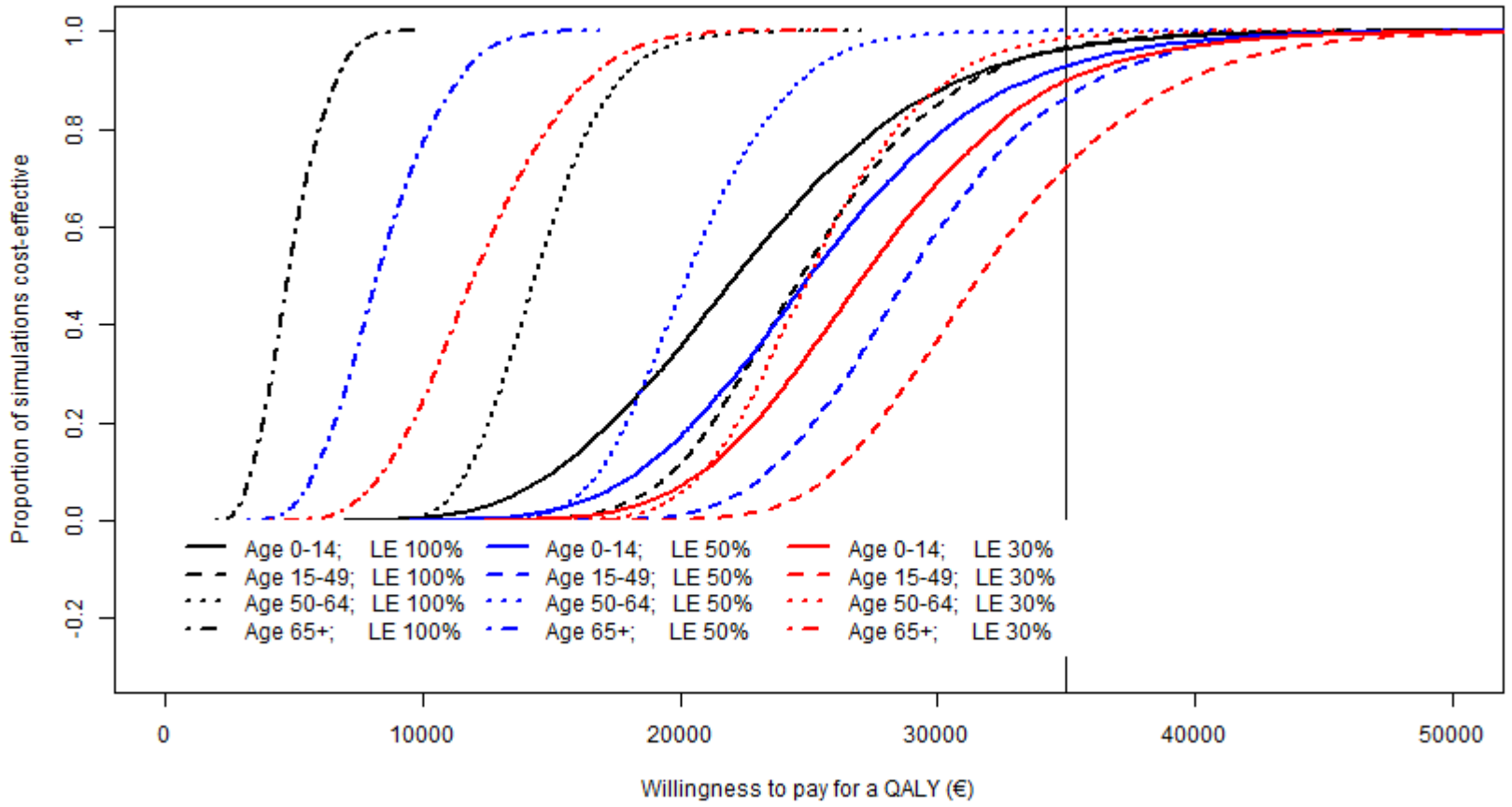


Figure 4: Cost-effectiveness acceptability curves for vaccinating 40% versus 20% of people with underlying illnesses, while varying their life expectancy (LE) from 100% over 50% to 30% of that of the general population of the same age. The vertical bar indicates a willingness to pay for a Quality-Adjusted Life-Year (QALY) of €35,000.



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