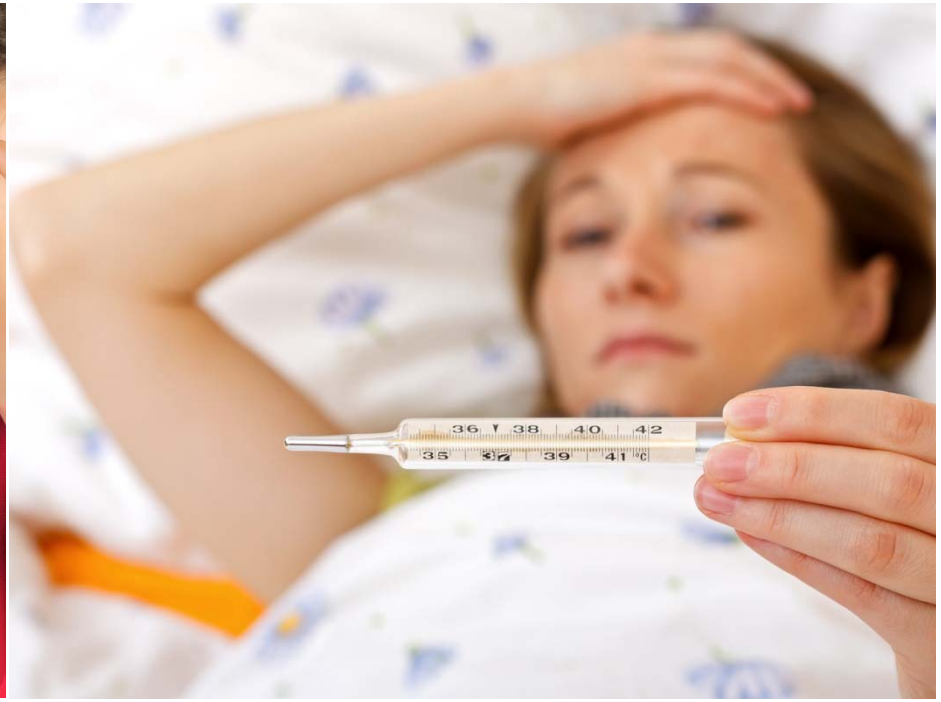
KCE REPORT 204Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SEASONAL INFLUENZA VACCINATION: PRIORITIZING CHILDREN OR OTHER TARGET GROUPS?

PART II: COST-EFFECTIVENESS ANALYSIS – SYNTHESIS



Belgian Health Care Knowledge Centre

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HEALTH TECHNOLOGY ASSESSMENT

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PART II: COST-EFFECTIVENESS ANALYSIS – SYNTHESIS

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Part II: cost-effectiveness analysis – Synthesis.

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FOREWORD

Two years ago, the KCE published a study on the prioritization of the target groups that should receive annual vaccination against influenza. The question that prevailed then was which strategy can prevent the largest number of cases and deaths. The answers varied somewhat depending on the selected objective. If we want to prevent a maximum number of ambulatory cases, the priority should be to vaccinate those below 65 years of age, but if we want to reduce the number of hospitalizations, we better focus on those with co-morbidities within that group or on the elderly above 75 years of age (although the vaccination rate is already high in this group).

The Interministerial Conference on Health also asked us advice about which strategies would generate the most health benefit per euro spent. With this cost-effectiveness study, once again conducted in collaboration with the renowned teams of the University of Antwerp and the University of Hasselt, we try to give an answer to that question. As was already clear from the first study, and can only be confirmed today: influenza models inevitably have to be built on shifting grounds. First, there is the unpredictable behavior of the virus itself that modifies its immunological signature from year to year. This in turn has an impact on the epidemic patterns and the virulence across different age groups, and hence the effectiveness of the vaccine as well. In addition it is difficult to distinguish the impact of genuine influenza from the many other types of ‘winter flu’ that circulate during that season. All this makes for a larger number of 'variables' in every sense of the word. And finally - but certainly not the least important - there is the price of the vaccine to be negotiated by the authorities, that will also crucially affect the cost-effectiveness of a vaccination campaign.

Evidence-based health policy rests on a best possible evaluation of the potential options - this is the role of KCE. But then choices must be made. Ideally, these choices should also consider what is happening beyond health care. Besides its medical impact, influenza also has a significant economic impact indeed, given the large number of sick leave days flu causes annually. The generally preferred approach to cost-effectiveness analysis does not include this type of data, though. But in the meantime we hope that policymakers find the material provided in this study clarifying and useful.

Christian LÉONARD
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General director

ABSTRACT

Influenza is a common viral infection, which presents as a mild illness in most healthy adults but is responsible for significant morbidity among vulnerable groups such as the elderly, patients with underlying conditions and children. Vaccination against influenza is one of the most effective tools to protect against the disease and its complications. However, the influenza virus shows a great variability from one season to another and is continuously evolving. This has two consequences: first, neither natural infection nor vaccination will provide long-lasting immunity, implying that every year, people at risk should be re-vaccinated; second, predictions of future seasons are imprecise and subject to uncertainty.

In Belgium, the influenza vaccine is recommended for people over 50 years, those with chronic diseases, pregnant women and health care workers. Recently, several countries have introduced annual vaccination of children, for two main reasons. The first is that the rate of influenza hospitalizations in young children is as high as that of the elderly. The second is that children play an important role in the transmission of the virus in the population, to the extent that their inclusion in the vaccination programme may provide indirect protection to unvaccinated members of the community, including those at risk.

The analyses in this report were requested by the Interministerial Conference on Health to prioritize the various target groups for seasonal influenza vaccination. They explore the effectiveness and cost-effectiveness of more than 5600 vaccination strategies, including universal vaccination of children and improved vaccination coverage of the current target groups, as well as combinations of children and adult vaccination. We also explored scenarios in which coverage would be reduced in healthy adults while coverage in other (recommended) target groups would be increased. To account for the impact of vaccination on virus transmission, a transmission dynamic model was developed. The parameters used in the analyses are mainly based on Belgian data, collected from specific studies, and analyses of hospital data, while the remainder was extracted from literature reviews. To account for the variability of the virus and the uncertainty around a number of parameters, the model is based on a large number of past seasons and the uncertainty around most parameters was included as an integral part of the analyses.

This study shows that childhood immunization can provide some level of indirect protection to others, but its impact would not be sufficient to replace the vaccination of adults at risk, even if a high coverage rate can be attained. The cost-effectiveness of universal childhood vaccination is in the same range as for other vaccinations recently introduced in the vaccination calendar, providing that vaccination costs are reduced by at least 25 %. This reduction could be achieved if the vaccine is administered for example by school health services and if pooled procurement (e.g. by a tender procedure) can reduce the cost of the vaccine. Although the UK will implement this vaccination intervention in school age children on the basis of a very favorable cost-effectiveness ratio, their estimate is based on much more optimistic assumptions (including much lower vaccination costs) than the ones used in most analyses of our study.

Vaccination of pregnant women, health care workers and persons with chronic diseases, appears as cost-effective as recently introduced vaccines, certainly if the vaccine can be administered at no extra-cost. Even if the vaccine administration would require an extra visit, these options could be attractive if we assume more protection from mother to newborn and from health care workers to patient. The most cost-effective adult vaccination options involve stopping vaccination in healthy young adults (18-49 years), but this will have a detrimental effect on this group. The increase in coverage of the elderly ≥75 years while maintaining the current coverage in other age groups ranks as a very attractive strategy.

The most clinically effective intervention, i.e. to vaccinate 80% of children and increase the coverage in all adults ≥50 years, could prevent around 40% of the current number of influenza hospitalisations and deaths. However, from a cost-effectiveness point of view, this intervention would only be attractive if we assume immunity wanes more slowly and/or vaccination costs decrease compared to our baseline assumption (non-tendered price, and the cost of a general practitioner consultation per dose).

These conclusions are equally valid for the upcoming quadrivalent vaccines, as the expected improvement in efficacy would only slightly impact on the cost-effectiveness ratio of the vaccination strategies.

SYNTHESIS

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1. INFLUENZA DISEASE AND VACCINES

1.1. Influenza, a common disease but a complex virus

Influenza is one of the most frequently acquired infectious diseases in humans, affecting around 10% of the global population each year. This viral infection is transmitted through the respiratory tract, occurs mostly as seasonal epidemics during the winter months in the Northern hemisphere and is responsible for a considerable burden of disease. Although in healthy individuals it usually presents as a self-limited respiratory illness, in vulnerable groups it causes a large number of hospital admissions and is a major cause of winter deaths amongst the elderly. Influenza viruses can cause disease at any age, but the groups the most likely to develop severe illness are the children, the elderly and persons with underlying illness.

The evolutionary changes in influenza viruses are largely unpredictable. Different types and subtypes of influenza viruses cause disease in humans but they differ in virulence, affected groups and timing. Frequent and small mutations in the virus result in slight changes in viral antigens (called antigenic drifts) and their accumulation causes the emergence of new variants of influenza viruses. Because these changes may affect the immune response, antibodies against the previously circulating influenza virus will confer limited protection against the new strain. This has three major consequences: continuous changes in the circulating virus strains allow the virus to spread more rapidly among the population as it partially escapes the immune response; influenza seasons show different patterns from year to year in terms of timing, affected groups and severity; the components included in influenza vaccines are adapted every year, based on forecasts about which viruses are most likely to cause illness in the coming season. More dramatic changes in influenza viruses may also result in new strains that have never been circulating before, and have the potential to cause an influenza pandemic. The current report, however, focuses only on seasonal influenza, which manifests itself mostly between November and April in Belgium.

1.2. Influenza vaccines and policies in Belgium

Influenza vaccines are generally considered to be effective tools to protect against influenza disease and its complications. Two main types of seasonal influenza vaccines are currently registered in Europe:

1. The live attenuated influenza vaccine (LAIV), which is given as a nasal spray and has been approved by the European Medicines Agency for use in the 2-17 years of age.
2. The trivalent inactivated influenza vaccine (TIV), which is injectable and indicated for all ages over 6 months.

These “trivalent” vaccines contain two components from influenza type A and one component from influenza type B, which are recommended by the World Health Organization (WHO) and are reconsidered on an annual basis. The first LAIV vaccine (Fluenz, from MedImmune LLC) has been authorized in the European Union in 2011 but is not yet on the Belgian market; its manufacturer has announced it could be available in our country around 2014-15. Therefore, in Belgium only TIV has been used so far. It is reimbursed by the National Health Insurance (INAMI/RIZIV) for the risk groups defined by the Superior Health Council.[a]

In recent years, the demand for seasonal influenza vaccines has regularly exceeded its supply, resulting in some years in scarcity of vaccines. As the cumbersome egg-based production is still the most widely used technology for influenza vaccines, doses at the national level are scarce and the production cannot be easily increased. The Superior Health Council has thus defined an order of priority for the vaccination of the risk groups, to be considered in the event of vaccine shortage. The first priority is given to persons at higher risk of influenza complications: the 2012-13 advice recommends vaccination of pregnant women who are in the second or third trimester at the time of vaccination, patients with underlying chronic disease, the elderly ≥65 years, persons living in institutions and children (6 months to 18 years) under long-term aspirin therapy. The next priority is given to healthcare workers, followed by household members of persons at high risk of complications and of children <6 months of age.

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[a] Conseil Supérieur de la Santé (CSS) or Hoge GezondheidsRaad (HGR), http://www.health.belgium.be/eportal/Aboutus/relatedinstitutions/SuperiorHealthCouncil/19080808_FR?ie2Term=influenza&ie2section=9744

1.3. Why vaccinating children against seasonal influenza?

The strategy of vaccinating children annually against seasonal influenza is receiving increasing attention in recent years. In the US, annual vaccination of children is recommended since 2004 and has been progressively expanded to older age groups up to all persons aged ≥6 months in 2010. In 2012, WHO also advised that all children aged <5 years should be considered as a risk group for influenza vaccination, because of a high burden of severe disease in this group.[1] In Europe, as of April 2013, only seven countries (Austria, Estonia, Finland, Latvia, Poland, Slovakia and Slovenia) recommend universal seasonal influenza vaccination for different age groups <18 years, but Finland is the only country that has introduced it into the routine childhood vaccination programme (in children from 6 months to 3 years of age).[2-4] The United Kingdom (UK) has announced in 2012 that it will introduce influenza vaccination of all children aged 5-17 years from 2014 onwards.[5, 6]

There are two main rationales for introducing universal childhood vaccination: the direct effect and the indirect effect of influenza vaccination.

The direct effect is the expected reduction in influenza-related disease in vaccinated children. In the US, the more than 150 paediatric influenza-associated deaths reported during the 2003-04 season played a role in the decision to introduce universal influenza vaccination of children.[7, 8] In that season, a new influenza drift variant circulated and showed a high virulence among children. The rationale for US vaccination decision is that the risk of influenza-associated hospitalization in healthy children <2 years of age was found to be equal to or greater than the risk in previously recognized high-risk groups. The extension to other age groups was justified by the increased risk for influenza-associated outpatient and emergency department visits observed in those age groups as well.

The indirect effect is the expected reduction of influenza-related disease in unvaccinated people due to a reduced circulation of influenza virus, i.e. the so-called herd immunity. Indeed, children not only experience the greatest incidence of influenza infection, they also shed relatively more virus, and have intensive contacts with other children and other members of their families. They are the key group that drives transmission in the entire population, and their vaccination has thus the potential to provide protection to other age groups by reducing virus transmission.[9, 10] A number of trials and observational studies in the US, Canada and Italy have shown a significant reduction in the rates of influenza-related illness and hospitalizations in the communities or families of vaccinated subjects, even in seasons with very poor match between circulating and vaccine viruses.[11-16] This evidence of indirect protection, added to the low vaccine effectiveness in the very old, encouraged a number of countries to consider childhood influenza vaccination as an efficient option to reduce the disease burden of influenza. In particular, the recent UK decision to introduce vaccination in school age children was made on the basis that the additional herd immunity conferred by this strategy would make it a highly cost-effective intervention as shown by mathematical modelling studies undertaken to support policy making.[5]

1.4. Research questions

In 2009, the Belgian Interministerial Conference on Health commissioned the KCE to undertake a study to prioritise target groups for influenza vaccination in order to optimize the use of available vaccines. A first study within this project (KCE report 162, 2011)[17] estimated the morbidity and mortality impact of different adult vaccination scenarios. This second study is addressing the cost-effectiveness of a wider range of influenza vaccination options, including any indirect effect. In a first step, we explore the addition of a range of universal vaccination options for children to the current adult vaccination programme. In a second step, we explore an extensive range of options for vaccination, combining changes to current adult vaccination with the addition of childhood vaccination options to the programme.

2. METHODS

2.1. Vaccination options

The vaccination scenarios (Table 1) involving the current target groups for influenza vaccination have been determined in consultation with stakeholders and experts. In children, no specific scenario could be put forward and we therefore considered coverage varying from 10% to 90% in 10% steps for a number of different age groups. Each scenario is considered as a change in vaccine uptake compared to the 2008 situation. In addition, we explored options of not vaccinating healthy 18-49 year-old adults (not targeted by the recommendations) which may be difficult to implement in real life.

Table 1 – Target groups and vaccine coverage change (see Part I, KCE report 162)[17]

Target groups	2008 vaccination coverage[a]	Change in vaccine uptake	Proposed vaccination coverage
Children 6 months-17 years (4 age subgroups)	<0.1%	10 to 90%	10 to 90%
Healthy 18-49 years	11%	-11%	0%
Healthy 50-64 years	28%	+10% +20%	38% 48%
Elderly 65-74 years	50%	+25%	75% (WHO target)
Elderly ≥75 years	71%	+4%	75% (WHO target)
Persons 1-64 years with co-morbidities	20%	+20%	40%
Pregnant women	NA (~0%)	+50%	50%
Health care workers	35%	+15%	50%

a: Based on the 2008 Health Interview Survey conducted by the Institute of Public Health.

In children <8 years of age, we assumed that two doses of TIV or LAIV are required for the first vaccination, whereas one dose is required for those aged over 8 years. Subsequent vaccinations are given under a single dose schedule. In line with respective vaccine indications, LAIV options are only explored in age groups 2-17 years of age, and TIV options in age groups above 6 months. The options for children and adult vaccination are separately compared to the current situation as well as combined. Based on the described combinations of target ages, vaccine uptake and the two available vaccines, we modelled a total of 5667 different vaccination options targeting healthy children and/or adults. Additionally we undertook separate analyses for three special target groups (people with comorbidities, pregnant women and health care workers).

2.2. Models

The cost-effectiveness is explored through two types of state transition models, according to the target group:

- A dynamic transmission model for vaccination of the major age groups of the general population: children (<18 years), adults (18-64 years) and the elderly (≥65 years).
- Three static (fixed risk) models for vaccination of the following target groups: pregnant women, persons with comorbidities and health care workers (HCW).

The dynamic model can account for changes in the transmission dynamics of influenza that would occur when large groups in the population are vaccinated. The costs and effects occurring in specific risk groups, such as pregnant women, are addressed by static models as the vaccination of these smaller groups is not expected to influence the population transmission dynamics.

2.2.1. *Dynamic model*

We used a "SEIRS" model with vaccination, which includes compartments of Susceptible, Exposed, Infectious, Recovered and Vaccinated individuals. We built on the model developed by Vynnycky et al in the UK and made two main adaptations to this model.[18] First, we estimated model parameters that are less certain and about which there is no general consensus, from Belgian influenza-like-illness (ILI) cases, instead of using pre-specified values. Second, we assumed one generic influenza strain instead of modelling different influenza strains, on which we had insufficient Belgian surveillance data. However, we used age and season-specific parameters to capture part of the influenza season heterogeneity.

The model assumes an "all-or-none" vaccine effect, which means that the vaccine effectively provides complete protection against infection in a fixed proportion of these individuals, while it completely fails in the remaining part. The model also assumes that vaccinated individuals with influenza disease are as infectious to others as unvaccinated infected individuals (i.e. no vaccine effect on infectiousness).

2.2.2. *Static model*

For the estimation of the costs and benefits of vaccination options in risk groups through static models, we considered cases not requiring hospitalization (including cases consulting a physician and cases not consulting a physician), those requiring hospitalization and deaths. Although these models may lead to small underestimates of the benefits of vaccination (as indirect effect is ignored), the most important aspects of indirect protection are explored as well. In particular, we included in some options the indirect protection provided to patients when HCW are vaccinated, and the indirect protection of the newborn whose mother was vaccinated while pregnant. As no robust data was found on these indirect effects, we made assumptions and attributed a proportionate decrease in the risk of infection of these secondary target groups. Since these assumptions are largely unknown and likely influential, the impact of changing them is explored in sensitivity analysis.

2.3. Economic analysis

The analysis is performed from the perspective of the health care payers (i.e. considering payments out of the federal government's and the communities' health care budget as well as patients' co-payments), in line with KCE guidelines. Results are presented in terms of incremental direct costs, incremental health outcomes and incremental cost-effectiveness ratios (ICERs) of an option for intervention versus the current situation, as well as versus the next best alternative. The next best alternative for a vaccination option is identified through application of the concepts of dominance and extended dominance to the incremental direct costs and quality-adjusted life-years (QALY). Probabilistic sensitivity analysis is carried out for many analyses, based on 10 000 simulations for each vaccination option considered. ICERs presented in the results section refer to those against the current situation, unless otherwise stated.

3. MODEL PARAMETERS AND ASSUMPTIONS

We used Belgian data to the largest extent possible because the influenza burden and how it is measured depend largely on country-specific health care systems, contact patterns and vaccination policies. In particular, we conducted a survey on the costs of treating influenza cases, analyzed Belgian datasets to estimate the influenza burden and used Belgian social contact pattern data. Several transmission parameters were estimated by fitting the dynamic model to Belgian ILI cases. Other parameters were based on literature reviews. Due to its very specific nature, the pandemic season 2009-2010 was excluded from data analysis. The variability of influenza seasons was taken into account in a range of parameters, for which this is relevant. The uncertainty around virtually all parameters that were estimated from data, and not through model fitting, was taken into account by different forms of sensitivity analyses.

3.1. Disease burden and transmission

We estimated age-specific ILI and influenza cases consulting a general practitioner from the national influenza surveillance conducted by the Scientific Institute of Public Health. Although this system does not cover cases seen by paediatricians and in emergency rooms, it allowed us to derive the age-specific number of influenza infections (symptomatic or not) and influenza cases not seeking health care, based on model fitting and survey data. As admissions and deaths due to influenza are rarely laboratory confirmed or coded as influenza, we conducted a regression analysis based on data from the Minimal Clinical Dataset (MCD), death certificates and counts of respiratory pathogens to estimate influenza-attributable hospitalizations and deaths. The estimates found are likely to underestimate the true burden of severe influenza because the 2004-08 seasons were milder, but they were close to those found in other studies using similar parameters during similar seasons. As no data were available on influenza outcomes among pregnant women, HCW and persons with co-morbidities, we used the same age-specific rates as for the general population and adjusted them for the increased risk of these groups when relevant, based on the literature or Belgian data. Influenza-related outcomes among neonates were based on rates for the <5 years.

Costs of treatment in ambulatory care or self-care were estimated by our survey among 2250 ILI cases in the general population (2011-2012 season). Influenza inpatient costs were estimated from nationwide hospital databases (Hospital Billing Data and MCD). The health-related quality of life (QoL) impact was estimated based on the best study identified through a systematic search. The estimates on QoL impact in ambulatory patients were extrapolated to hospitalised influenza cases, conservatively assuming that the average QALY loss for a day with influenza does not differ between persons with ambulatory care and hospitalisation.

Table 2 shows mean values of influenza outcomes by target group and highlights the high burden of severe disease in young children and the elderly. The high observed variability of these outcomes is also propagated in the various model projections.

We assumed age-dependent influenza transmission rates to be proportional to the rates of making (conversational) contact involving skin-to-skin touching and taking longer than 15 minutes from an extensive Belgian social contact study. Transmission parameters on which there is evidence were extracted from the literature and others were estimated by fitting the model to Belgian ILI cases.

Table 2 – Current influenza burden and cost estimates by age group (mean values by season)

Age or target groups	Influenza cases	GP visits (2003–09)	Hospitalizations[a] (2004–08)	Deaths[a] (2004–08)	Cost of ambulatory care (2011–12)	Cost of inpatient[b] (2004–07)
<5 years	29 362	21 824	540–661	0–2	Lowest: mean €51.04 Highest: mean €63.81 (shown to be statistically similar across ages)	€2237
5-14 years	72 223	60 534	287–348	0		€1656
15-49 years	191 834	138 320	309–462	5–8		€1802[c]
50-64 years	82 176	46 938	201–356	11–30		€3660[d]
65-74 years	25 925	10 313	234–386	24–51		€4825
≥75 years	10 749	8022	568–1043	204–266		€5664
Total	412 269	285 951	2140–3256	244–356		€2599
Pregnant women	-	3243	Base: 7–11 High: 54	Base: 0.1–0.2 High: 2–20		€1481–1838[e]
Health care workers	-	6425	18–55	0.6–1.3		Range €1653–3660 according to age
Persons 1-64 years with co-morbidities	-	24 099	363	39		Range €3437–7507 according to age

a: Influenza-attributable admissions and deaths based on regression analyses on hospital discharge data and death certificates, respectively. For specific age-groups and health care workers: lower values are based on the analysis of admissions coded as pneumonia and/or influenza (P+I) as main cause (model 1 for admissions, see Scientific Report); higher values based on admissions coded P+I as any diagnosis. For pregnant women, a very high case was estimated based on H1N1 2009 pandemic US data. b: Costs for admissions with influenza as main diagnosis. c: For age group 16-35 years. d: For age group 56-69 years. e: Lower value is costs of influenza admission as primary diagnosis and pregnancy complication as secondary diagnosis; higher value is costs in 15-49 years of age admitted with influenza as primary diagnosis.

3.2. Influenza vaccines, safety and immunity

Influenza vaccine effectiveness (IVE) parameters were based on a systematic literature review, restricted to randomized controlled trials with the exception of the current target groups in which RCTs are no longer conducted for ethical reasons; we thus included observational prospective studies controlling for the major confounding factors for these groups. As TIV efficacy estimates are highly influenced by the degree of matching between vaccine and circulating strains and the influenza intensity, we pooled IVE values by type of season and age groups across studies and extrapolated for seasons with no studies (Table 3). Conversely for LAIV, given the demonstrated stability of efficacy estimates across different types of season, we used single IVE estimates for all seasons and pooled study estimates by number of doses (Table 4). Clinical trials on LAIV have only explored IVE in children 6-71 months of age but estimates were stable across age. We used similar IVE estimates in children 6-17 years of age, as IVE measured in observational studies did not show significant differences in children above 6 years of age.

Table 3 – TIV efficacy/effectiveness against confirmed cases of influenza per age group and type of season

Season	High-medium intensity		Low intensity	
Age group	Good-relative match	Poor match	Good-relative match	Poor match
6 months - 17 years	65%	48%	30%	16%
18-64 years (healthy)	65%	60%	45%	22%
≥65 years	60%	55%	42%	20%

Table 4 – LAIV efficacy in children 6-71 months of age, pooled estimates per schedule

LAIV dose schedule	Efficacy (95%CI)
VE 2 doses	81% (69–89%)
VE 1 dose	75% (8–93%)
VE 2 doses year 1, 1 dose year 2	81% (64–90%)

The immunity conferred by vaccination is assumed to be similar to that conferred by infection. As immunity against one influenza strain wanes over time and confers limited protection against new strains, we estimated the immunity to "wane" at a rate of 1/1.68 year based on model fitting and assumed a similar rate for both types of immunity. This means that the immunity acquired against influenza through vaccination or infection would wane by 60% (1/1.68) every year or last on average 1.68 years. This value is in line with recent effectiveness studies. As a number of other modelling studies assumed a slower waning at 1/6 years for the circulating strain, we explored that assumption in sensitivity analyses.

Seasonal influenza vaccination of children would entail vaccinating complete age cohorts each year between September and December. In the absence of specific information and in agreement with experts guiding this study, we assumed in the first place that all vaccines are administered by GPs and, in the absence of LAIV price information, that LAIV and TIV were purchased at identical costs. Additionally, many alternative values were projected using lower cost estimates, which could be achieved by vaccination through school system or well baby clinics and through tender process preceding bulk purchase to lower the price of the vaccines. For each of the specific adult target groups we also calculated the cost-effectiveness assuming no additional administration costs (e.g. during regular prenatal visits for pregnant women, or during regular occupational or medical visits for HCW and people with comorbidities), or assuming an additional administration cost of a GP visit.

The literature on safety only revealed minor adverse events related to TIV and LAIV (above 2 years). In summary, no important safety issues have been published for the large-scale use of seasonal vaccines in children. Although Guillain-Barré disease was found associated to influenza vaccination in the seventies, further studies found no evidence of an increased risk after vaccines but the risk was increased after influenza like illness. Narcolepsy has been temporally associated with H1N1 AS03 adjuvanted vaccine in some countries but this was not observed in other countries. More research is required to understand these observations. Costs of vaccine-associated adverse events were not included in the models since they were considered to be negligible compared to the other vaccination costs (certainly in view of the large uncertainty related to the latter).

Table 5 – Other parameter values and sources

Outcome	Parameter	Estimate	Source (Section where it is described in scientific report)
Dynamic model			
ILI	No medical care fraction	0.492	BE survey ILI (section 4.2.1)
Influenza	Fraction of ILI that are influenza	By season and age group, range 15–67%	Laboratory results from GP sentinel surveillance
Influenza / ILI *	Out-of-hospital costs for a hospitalized patient	Lowest: mean €119.65 Highest: mean €139.94	BE cost survey ILI (section 4.2.1.5)
ILI	Cost for an ILI not seeking medical care	Lowest: mean €3.39 Highest: mean €7.17	BE cost survey ILI (section 4.2.1.4)
NA	Fixed marginal cost vaccination programme	€0	Assumption
NA	Vaccine costs: TIV and LAIV per dose	€11.81	BE official price TIV (BCFI/CBIP), assume price parity for LAIV
NA	Administration cost per dose	€23.32	BE official price of one GP visit
ILI	QALY loss for an ambulatory or hospitalized patient	0.0070	O'Brien et al, adapted to the number of days with symptoms
ILI	Duration of symptoms for ambulatory patient	Mean 6.43 days	BE cost survey ILI
ILI	Duration of symptoms for a hospitalized patient	Mean 8.5 days	BE cost survey ILI
ILI	Duration of symptoms for ILI without medical care	Mean 5.51 days	BE cost survey ILI
NA	Discount rate for costs	0.03	BE, Belgian guidelines[19]
NA	Discount rate for health effects	0.015	BE, Belgian guidelines[19]
Influenza	Mean reproductive number (R_0)	Vary by season, range 1.7–2.5	Best fitting model based on ILI BE cases by season

Outcome	Parameter	Estimate	Source (Section where it is described in scientific report)
Static models **			
NA	Size target group pregnant women	121 363	BE, SPMA (Report Part I)
NA	Size target group HCW	239 740 aged 20–65 years	BE, INAMI and proportion of active HCW (Report Part I)
NA	Size target group co-morbid patients	1 405 546 (all ages)	BE, Health Interview Survey 2008
Influenza	In-hospital cost for a hospitalised newborn	€2572 (newborn with influenza)	BE, HBD-MCD cost analysis (section 4.2.2)
NA	Cost of administration	Pregnant women: €0 HCW: €0 or €23.32 Persons with co-morbidities: €23.32	Assumed to be administered during prenatal visits Two assumptions (by occupational health or new GP visit). BE official price of one GP visit
Influenza	TIV efficacy	59% (95%CI 51–67%)	Osterholm et al, meta-analysis for adults (section 5.5.2.2)
NA	Life expectancy in persons with co-morbidities	As a function of age multiplied by a factor 1, 0.5 or 0.3	BE, Eurostat. Factor applied to investigate the influence of shorter life expectancy due to co-morbidities

BE: Specific source for Belgium. HCW: Health care workers. ILI: Influenza-like-illness. SPMA: Standardized Procedures for Mortality Analysis. BCFI / CBIP: Belgisch Centrum voor Farmacotherapeutische Informatie / Centre Belge d'Information Pharmacothérapeutique. HBD-MCD: Hospital Billing Data – Minimal Clinical Data. NA: Not applicable.
** Assuming cost of ILI = cost of influenza.*
*** Parameters that differ from those of the dynamic model.*

4. COST-EFFECTIVENESS OF SEASONAL INFLUENZA VACCINATION

4.1. Vaccinating children only

Among the 19 options considered for childhood vaccination, the most *clinically effective* scenario i.e. TIV in the 6-23 months and LAIV in the 2-17 years at a high 80% coverage would prevent an average of 1000 hospital admissions (including ~400 admissions in children <5 years and ~300 admissions in elderly above 64 years) and an average of 75 deaths (including ~60 deaths in elderly above 64 years) (Table 6).

Table 6 – Mean number of influenza outcomes in all ages under selected vaccination options at a 80% coverage

Vaccination option	Mean influenza cases (ILI+)	Mean GP visits	Mean hospital admissions (95% CI)	Mean QALYs lost	Mean life-years lost	Mean deaths (95% CI)
Current situation[a]	412 269	205 313	4002 (2703–5575)	5814	3279	470 (297–676)
TIV <2 years and LAIV in 2-17 years	314 000	156 454	2965 (1909–4331)	4663	2734	395 (245–580)
TIV in <2 years	403 884	201 233	3825 (2587–5340)	5707	3225	463 (293–666)
LAIV 2-17 years	321 710	160 224	3110 (2016–4504)	4770	2793	403 (250–591)
LAIV 5-17 years	355 965	177 362	3366 (2213–4800)	5186	2997	432 (271–626)
LAIV 12-17 years	380 277	189 293	3778 (2536–5296)	5454	3116	448 (647–282)

a: Current situation as predicted by the model. Values differ from Table 2 because the seasons simulated by the model differ from the seasons used to produce the averages in Table 2. CI: Confidence interval.

Table 7 presents the three first most *cost-effective* options followed by the most clinically effective option, at a more realistic 50% coverage (i.e. coverage achieved in the US). The most cost-effective option compared to the current situation is the LAIV vaccination of children 12-17 years of age, followed by vaccinating the 5-17 and the 2-17 year olds. However, under the base case assumptions, i.e. rapid waning, vaccine administration through GP visits and retail price for vaccines, these three options have a median incremental cost-effectiveness ratio (ICER) between €40 000 and €45 000 per QALY gained. This ICER is less favourable (i.e. higher) than some and more favourable (i.e. lower) than other previous estimates from KCE studies for recently implemented vaccinations in Belgium. For instance, the introduction of universal childhood pneumococcal conjugate vaccination was estimated at €10 000/QALY gained for 2+1 doses assuming no replacement disease.[20] Human Papillomavirus (HPV) vaccination of 12 year-old girls was estimated at €33 000/QALY gained for 3 doses at €0 marginal administration costs, and a booster dose every 10 years administered by GPs.[21] On the other hand, the ICER of childhood pneumococcal vaccination assuming replacement disease is worse (€45 000/QALY gained for 2+1 doses),[20] and so is the ICER of rotavirus vaccination in children, at least in the manner in which it was implemented in Belgium, i.e. partially reimbursed as a prescription drug but included in the vaccination calendar, ICER estimated at €50 000–68 000/QALY gained depending on the vaccine used.[22] The ICER of a specific option in the current influenza report remains relatively stable when vaccination coverage increases, mainly because of the high vaccination costs in the base case. However, reductions in vaccination costs for childhood options would substantially improve the cost-effectiveness ratio as a 25% and a 50% reduction will reduce these median ICERs to around €30 000 and €20 000/QALY gained respectively, making them attractive options from a cost-effectiveness point of view.

Further incremental analyses, comparing each option incrementally to the next best option, suggest that it is more efficient to first increase coverage in older age groups, and then progressively expand and increase it among younger age groups. Indeed, the short duration of immunity among young children assumed in our base case (average duration of 1.68 years) limits the expansion of the herd immunity effects compared to older children (who also have more social contacts) and hence also the relative advantage of vaccinating younger children over older ones. In all options, TIV vaccination was less cost-effective than LAIV vaccination (except in <2 years in which LAIV is not indicated).

If we assume a slower waning of immunity (average duration of 6 years), all options become more cost-effective and the best option is now the TIV vaccination of young children <2 years at an ICER around €20 000 per QALY gained. Incremental analyses show that, when only low vaccination coverage can be achieved, it is more efficient to restrict the programme to younger age groups (under 2 or 5 years). Various sensitivity analyses were conducted, besides those varying waning immunity and vaccination costs described above. All results were reported based on probabilistic sensitivity analyses on all variables except for the parameters of the dynamic model, i.e. both fixed and flexible model parameters. The most influential parameters for the costs, QALYs and ICERs for most childhood vaccination options are hospitalisation rates or case-fatality ratios, LAIV efficacy (in particular for single dose as it concerns most children and the 95%CI is wider), the proportion of ILI that are influenza, as well as QALY for non hospitalized patients.

Table 7 – Cost-effectiveness of the best children vaccination options compared to the current situation at 50% coverage

Vaccination option	Median QALYs gained	Median life-years gained	Median incremental cost	Median incremental cost at 25% reduction in vaccination costs <18y	Median ICER (per QALY gained)	Median ICER at 25% reduction in vaccination costs <18y
LAIV in 12-17 years	3589	1532	€150 972 404	€109 179 464	€42 046	€30 411
LAIV in 5-17 years	8274	3537	€366 140 326	€264 834 626	€44 260	€32 014
LAIV in 2-17 years	10 336	4557	€458 330 418	€330 819 568	€44 280	€32 009
TIV <2 years and LAIV 2-17 years	11 381	5098	€505 420 856	€364 562 469	€44 415	€32 058

4.2. Modifying vaccination coverage in adults only

4.2.1. *By age group*

Among the 23 options exploring changes in vaccine coverage in adults (Table 1), the most *clinically effective* option is the largest increase per age group in vaccination coverage in all groups ≥50 years of age. This option would prevent around 350 hospital admissions and around 60 deaths on average per year, but its ICER is higher than those estimated for the introduction of the pneumococcal and HPV vaccines (Table 8). The most *cost-effective* options compared to the current situation involve increasing the coverage in adults 50-64 years of age and/or in the ≥65 years while decreasing it in the young healthy adults below 50 years, which are not a current target group. These scenarios would be attractive from a cost-effectiveness approach (ICER below €25 000/QALY gained or even saving health care costs to the health care payers) but at the expense of an increased morbidity in the 18-49 years. An attractive option is to keep the current coverage in young adults and increase the coverage of all elderly ≥75 years up to 75%, for an ICER around €24 000/QALY gained. Options involving an increase in coverage among elderly ≥65 years while keeping current coverage in young adults result in an ICER around €30 000/QALY gained. In the incremental analysis, the most attractive options also involve a decrease in the coverage among young adults and an increase in coverage among older adults (mostly 50-74 years).

Under the assumption of longer duration of immunity, the most clinically effective option we considered, i.e. maintaining vaccination coverage in 18-49 years and increasing coverage of all adults ≥50 years could still be considered relatively cost-effective compared to other vaccines recently introduced in the calendar with a median ICER at €32 834 (95%CI €19 245–53 630 per QALY gained). If coverage in 18-49 year olds decreases in parallel, then the ICER becomes more attractive (€17 234).

Table 8 – Cost-effectiveness of selected adult vaccination options compared to the current situation*

Vaccination options	Median incremental cost	Median QALYs gained	Median life-years gained	Median ICER (per QALY gained)
0% in 18-49 y, 75% in 65+ y	-€29 694 662	314	1103	Cost-saving (-€44 036)
0% in 18-49 y, +20% in 50-64 y	-€2 727 087	360	557	Cost-saving (-€6815)
0% in 18-49 y, +10% in 50-64 y, 75% in 65-74 y	€21 452 039	1252	1535	€17 234
0% in 18-49 y, +10% in 50-64 y, 75% in 65+ y	€32 976 563	1728	1984	€19 125
75% in 75+ y	€11 482 177	479	450	€23 688
+20% in 50-64 y, 75% in 65+ y	€222 972 076	5716	4047	€39 053

** Selected options are those with best ICER compared to the current situation (< €25 000/QALY gained), with the exception of the option that does not seem operationally feasible (i.e. increasing coverage in all ≥50 years except in the 65-74 years) and the most effective option (last listed). y: Year.*

4.2.2. *In specific target groups*

In separate analyses (static models), we also explored the impact of improving uptake in the other target groups for influenza vaccines, in particular pregnant women, health care workers and persons with comorbidities (Table 9).

Increasing substantially the vaccination in pregnant women during their second or third trimester would only prevent below 30 admissions and nearly no death. But this intervention would be very cost-effective compared to no vaccination, at an ICER <€7000 per QALY gained under the base case of no additional cost for vaccine administration. The impact of adding the costs of a GP visit is large but the ICER (~€30 000/QALY gained) remains relatively attractive compared to other recently introduced vaccines. The case-fatality ratio in pregnant women, which is not documented in Belgium, has a limited impact on ICER estimates compared to the influence of vaccination costs. However if we assume that the case-fatality ratio and hospitalisation rates would be similar to the highest estimates observed in the US during the H1N1 2009 pandemic, the cost-effectiveness would improve substantially (below €2000 per QALY gained), even with an additional GP visit costs. If we assume that mother vaccination would not protect at all her foetus or newborn, vaccinating pregnant women would still be highly cost-effective (ICER around €10 000/QALY gained) without the costs of a GP visit; if we assume the additional costs of a GP visit, then it would be a much less attractive option with an ICER above €40 000 per QALY gained.

Table 9 – Cost-effectiveness of increasing coverage in specific target groups compared to the current situation (median values)

Vaccination options	Prevented hospital admissions	Prevented deaths	Median incremental cost	Median QALYs gained	Median ICER (per QALY gained)
Pregnant women, +50%[a]	28.6	0.07	€384 540	58	€6589
Health care workers, +15%					
- **Assuming no secondary case**	3.5	0.07	€709 674	29	€24 102
- **Assuming 0.4 secondary case**[b]	7.7–88.4	0.3–25.0	€640 327–188 271	49–245	€13 114–732
Persons with comorbidities, +20%					
- **In <15 years**	10.1	0.2	€689 687	31	€22 008
- **In 15-49 years**	16.9	1.0	€2 476 027	100	€24 768
- **In 50-64 years**	21.3	4.0	€1 902 263	132	€14 378
- **In ≥65 years**[c]	155.9	42.4	€2 587 383	518	€4784

a: Assuming €0 extra-cost for vaccine administration. Admissions: 26 in women and 2.6 in neonates. Deaths: in women only.
b: First value if secondary patient is 50-64 years of age, second value if secondary patient is ≥75 years.
c: Not considered separately from the other ≥65 years in the scenario but provided for information.

Increasing by 15% the coverage of health care workers (HCW) at no additional vaccine administration costs would be an attractive strategy compared to other recently introduced vaccines, even when we assume that HCW with influenza would not cause any disease among adult patients with whom they are in contact (~€24 000/QALY gained). Moreover, if we assume that each HCW with influenza would infect 0.2 to 1 patient (≥50 years), the ICER would drop to €15 000–5000/QALY gained. However if we assume that vaccine administration to HCW would cost a GP visit, the ICER of increasing their coverage would remain close to the ICER estimated on the introduction of the HPV vaccine in the calendar only if HCW would cause secondary cases in patients (e.g. 0.8 patients 50-64 years or 0.2 patients ≥75 years per season). Besides administration costs and transmission to patients, the case-fatality ratio of the elderly potentially infected by the HCW would be the most influential parameter, followed by vaccine efficacy.

Increasing by 20% the vaccine coverage in persons with co-morbidities is also an attractive option, with an ICER ranging €4800–25 000/QALY gained, even though we assume in the base case that vaccine administration would cost a GP visit (Table 9). The case fatality ratio and vaccine efficacy are the most influential parameters in ICER estimates. We assumed in the base case that, compared to the general population, life expectancy in this group is not reduced. If the life expectancy of the general population is assumed to be reduced by 50% or 70% in persons with co-morbidities, the median ICER would substantially increase but remain close to the ICER estimated on the introduction of the HPV vaccine in the calendar in each age group.

4.3. Vaccinating children and modifying coverage in adults

We also combined the 19 children options and the 23 adult options considered above and explored these 437 combined options. The most clinically effective option, i.e. vaccinating all children and increasing coverage in all adults ≥50 years, would prevent in average around 1500 hospital admissions and around 150 deaths with a 80% coverage in children. This strategy would thus reduce by around 40% the current number of influenza related severe outcomes, but its ICER would be relatively high at around €40 000 per QALY gained. The incremental analysis incorporating variations in the vaccine coverage for children indicates that the most cost-effective options involve the lowest coverage in children (10-20%), no vaccination of young healthy adults and increases in coverage among the 50-64 years, those ≥65 years and those ≥75 years (ICER <€20 000/QALY gained), thus very close to some vaccination options preferred above. If we assume a longer duration of immunity, the ICER would be more favourable (<€20 000/QALY gained) for the most cost-effective options.

We also explored combined children and adult scenarios involving decreases in coverage among adults ≥50 years of age to assess the cost-effectiveness of relaxing adult vaccination when implementing children vaccination. Savings would occur if vaccination of the oldest age groups (≥85 or ≥95 years) and/or young healthy adults is stopped while children ≥5 years of age or all children would be vaccinated. Such vaccination options would yield total net gains in QALYs, although small, but this would be at the expense of life-years being lost e.g. in the elderly, which is detrimental. Although the maximisation of QALYs is at the foundation of cost-utility analysis, the latter consequence could be seen as unethical.

5. DISCUSSION

This Belgian study collected and analyzed an extensive range of Belgian data and developed refined modelling tools, which were applied to a very wide range of vaccination options. However, there are several obstacles impeding simple, clear-cut specific advice to policy makers. First as there are a number of possible strategies to organize influenza vaccination of children, we had to model a wide range of age targets and vaccine uptake options (5667 options were considered), which in turn multiplied because these options involved different assumptions on the costs of vaccine administration. Second, there are still many uncertainties on the influenza virus, its interaction with the immune system, and season-to-season variability, which make predictions of the next season uncertain; however over longer time spans these predictions are likely to be more accurate. Third, the clinical picture associated with influenza infection is not very specific, which could lead to misdiagnosis, implying that specific estimates of the disease burden of influenza are subject to substantial uncertainty in terms of health outcomes, health care costs and health-related quality of life. Fourth, the waning of immunity induced by the vaccine or by natural infection is largely unknown. Nonetheless, this thorough study allows drawing a number of general conclusions, which are likely to aid decision-making. Indeed, the findings show that a large variety of influenza vaccination options for children and adults could be considered as relatively cost-effective.

5.1. Vaccinating children

If we assume that vaccines are administered through GPs (base case) and will be purchased at the current retail price, influenza vaccination of children would not be cost-saving and would unlikely be considered highly cost-effective. Indeed, the most cost-effective options show an ICER at about €40 000 per QALY gained, i.e. less favourable than the ICERs estimated on the introduction of pneumococcal and HPV vaccines in the calendar. An interesting finding is that the cost-effectiveness ratio does not depend much on the vaccination coverage achieved.

The attractiveness of the programme however hinges on two pivotal factors: the vaccination costs per dose and the duration of immunity. First, vaccinating children would become a more attractive intervention if vaccination costs can be reduced by 25-75%, which was explored in our analyses, e.g. by vaccinating through school health services and well-baby clinics and by reducing vaccine prices through large purchases. Clearly, all efforts to reduce the vaccination costs would greatly benefit the programme and vaccine programme managers should consider how they could best organize childhood influenza vaccination in Belgium. Second, the waning immunity is important for two reasons. On the one hand, it has a big impact on the incremental cost-effectiveness per se, as the shorter the duration of immunity provided by the vaccine, the worse the cost-effectiveness. On the other hand, it has an impact on the ranking of preferred strategies: the shorter the duration of immunity, the more interesting it is to first vaccinate the “oldest” children, followed sequentially by the other age groups down to the youngest ones. Conversely, when we assume a longer duration of immunity (e.g. 6 years), influenza vaccination of the youngest children would be the most cost-effective option, followed by vaccination of older age groups in children under 18 years. In this study, we adhered to a short duration of immunity in the main analysis because it was estimated (and not assumed) by fitting to Belgian data. It is also more in line with recent vaccine effectiveness findings for any strain, while the immunity of 6 years referred to one circulating strain. Under that assumption, we found that vaccinating older children 5-17 years of age is marginally preferential to vaccinating the younger ones.

Our analyses also systematically show that LAIV is more cost-effective than TIV under our assumption of price parity. This is easily explained by the higher and more stable vaccine effectiveness of LAIV across seasons compared to TIV, for the same age groups. As LAIV is not yet available in Belgium, its future price – and whether prices will be similar for both vaccines – is still unknown. In the UK, the private market (non-tendered) price is however higher for LAIV than for TIV (£14 vs. around £5 for TIV) but the tendered prices are unknown.

A very important finding from this study is that childhood vaccination cannot replace adult vaccination. Although some herd immunity effects can be achieved by childhood vaccination, especially if we assume a long duration of immunity, it would not be sufficient to replace adult vaccination. Even a high coverage scenario of childhood vaccination across a wide age range, i.e. vaccinating all children 6 months - 18 years at 80% coverage, would not prevent more than 300 additional admissions and 70 deaths in the elderly above 64 years. Conversely by increasing vaccine coverage of

all adults ≥50 years of age, a mean of around 350 admissions and around 60 deaths would be prevented. At the same token, a reduction in vaccination coverage in adult age groups (e.g. stopping vaccination at ages 18-49 years and above 85 years while introducing childhood vaccination) could lead to direct net savings at no decrease in QALYs, but this choice would create excess mortality in the elderly and net losses in life years versus current practice, and would thus seem unacceptable for ethical reasons.

The cost-effectiveness study on which the UK decision was based to introduce universal childhood vaccination found that childhood vaccination was a highly cost-effective intervention (<£506/QALY gained), and that vaccinating children 2-4 years of age was even cost-saving.[23] That UK study made use of a similarly structured dynamic transmission model (Vynnycky et al[18]) and it may thus be surprising that our findings are different. Although this discrepancy may be due to health care system and contact pattern differences, we found that many parameters in the UK study were very optimistic while our study ended up with more conservative parameters, while acknowledging as much as possible uncertainties related to model and parameter choices (see below). However, a number of general findings of our study were also reported by other cost-effectiveness or modelling studies. For instance Vynnicky et al also found that the predicted reduction in incidence resulting from vaccination decreased slightly as the assumed duration of protection to the circulating strain decreased.[18] Weycker in the US also found that even relatively low rates of vaccine coverage can yield important public health benefits.[10]

Comparison of key parameters between the UK and our analysis

- All efficacy estimates were assumed to be higher (50-75% for TIV) in the UK, without uncertainty and constant across seasons.
- The quality of life loss due to influenza disease was three times higher in the UK than the one we estimated from the literature.
- The cost of ambulatory care (£80 or €93) was 46% higher in the UK than the highest estimate from our cost survey.
- The cost of vaccine purchase was assumed to be 42% lower in the UK than our base case estimates.
- Immunity was assumed to wane much more slowly, at a rate of 1/6-1/12 years for a circulating strain in the UK.

On the implementation side, the vaccination of age groups that are currently less targeted by other routine vaccines, such as healthy children >2 years of age, is a substantial challenge that would entice organizational changes implying a wide range of actors. First, vaccination of children through private practices implies parental motivation and additional burden. A US study has estimated that 60-80% children aged 5 to 8 years would need 2 unscheduled extra physician visits in the first year to be fully vaccinated, and 20% would need one extra visit, even if every medical visit was used to administer vaccination.[24, 25] Authors stated that school-based vaccination programs might offer the most effective strategy for school-aged children. In Belgium, existing services such as Kind&Gezin, the clinics from the Office National de l'Enfance (ONE) and school health services have shown to be effective in providing vaccination to (pre)school children. However, administering an annual influenza vaccination to entire cohorts of children would add a high burden to their current workload; involve additional costs and organizational challenges.

5.2. Changing coverage in adults with or without childhood vaccination

The most cost-effective strategies for adult vaccination consist in increasing the coverage among various age groups ≥50 years while reducing or even stopping the vaccination of younger healthy adults 15-49 years of age. Although these scenarios result in attractive ICER below €20 000/QALY gained, they are detrimental to the young adults by

inducing an increased morbidity in this group. The next most cost-effective option is to keep the current coverage in young adults and increase it in all elderly over 75 years up to 75% (ICER around €20 000/QALY gained). Savings would occur if the vaccination of the old elderly (≥85-95 years) and/or young healthy adults is stopped and resources are used to vaccinate children. However again, life years would be lost in the elderly which make them detrimental and unethical options.

The most effective intervention would be to vaccinate all children and increase the coverage in all adults ≥50 years. At a 80% coverage in children, this intervention could prevent around 40% of the current number of influenza hospitalisations and deaths, but would only be cost-effective if we assume a slower waning of immunity and/or a substantially lower vaccination price.

We also showed that vaccination of pregnant women, health care workers and persons with comorbidities can all be considered as relatively cost-effective, especially – but not necessarily – if marginal administration costs can be kept low.

5.3. Limitations of the study

Although the use of a model implies that we cannot predict with certainty what would happen in the real world, the models applied here were constructed to deal with uncertainty to the best of our ability.

A main limitation is that the available dataset did not allow us to model influenza A (the most common in our country) separately from influenza B (much rarer in our country). Therefore we modelled all influenza as a single strain. However, we allowed several parameters to vary by season to capture part of the influenza type variability and the impact of this limitation on the results and conclusions should be minor.

Due to the non specific picture of influenza disease, we had to use regression analyses to derive the fractions of hospitalizations and deaths that are attributable to influenza, based on pneumonia and influenza coded hospitalizations. This may lead to underestimating influenza outcomes as some admissions could have been coded as other complications of influenza; although we performed regression on less specific admission codes, the regression results lacked significance. The fractions that we obtained from these analyses were lower than what has been found in a number of other countries, possibly due to differences in database systems, hospitalization practices, and seasonal circulation. However, hospitalization and death rates were close to those found in other studies using similar parameters during similar seasons.

Another limitation is that we had to model a wide range of possible scenarios, leading to an excessive number of options to prioritize, including some that may not be realistic. Clearly, when more specific information will be available on the options towards implementation in Belgium, a more specific analysis can be done using specific estimates for vaccination costs and draw more specific conclusions.

It should be noted that we did not include indirect costs of productivity losses for adult influenza patients and for parents of sick children, as the KCE guidelines recommend a health care payer perspective in the base case. If indirect costs of productivity losses would be considered, it is very likely that all options would become more attractive to the point where they may have shown net savings.

For the analyses related to pregnant women and health care workers, we show the impact of different assumptions regarding secondary infections in newborns or other patients, but there are insufficient data to quantify the uncertainty reliably. We showed though that the main conclusions remained relatively robust under varying assumptions.

5.4. Future perspectives

The analyses in this report, although focusing on the currently licensed trivalent influenza vaccines, are also valid for the upcoming quadrivalent vaccines. The only expected difference is that the quadrivalent vaccines would, on average, be marginally more effective than the trivalent vaccines on all influenza strains. The impact on the selection of optimal strategies and on the estimates of the median ICERs would be very low. For instance, assuming that a quadrivalent LAIV vaccine would be given at the same costs, but would increase the effectiveness by 10% (compared to trivalent LAIV in the current study), the median ICER of vaccinating children 2-17 years versus the current situation would be €38 845 (95%CI €24 882–60 567) per QALY gained versus €44 280 currently (Table 7). This also suggests that the quadrivalent vaccination options should have similar costs as the trivalent options we modelled.

On the research agenda, there is a need for effective vaccines for children <2 years of age. TIV efficacy is lower in children compared to adults, varies

by season. Although LAIV showed a very high efficacy in this age in several trials, it is not indicated in this group (due to excess of wheezing after vaccination observed in clinical trials). However, children <2 years bear the highest burden of disease (together with the elderly) and need to be effectively protected against influenza.

Any decision on vaccination strategies must take into account that influenza viruses are a moving target and that the variability of influenza seasons makes it impossible to predict the future impact of preventive strategies with certainty and accuracy. It is thus essential that the long-term impact of any change in the influenza vaccination of target groups be monitored.

6. CONCLUSIONS

Our study showed that the vaccination of children against seasonal influenza can achieve some level of indirect protection on other age groups but its impact would not be sufficient to replace the vaccination of adults at risk, even if a high coverage can be achieved.

A universal influenza vaccination of children is likely to be considered as cost-effective compared to other interventions if vaccination costs would be reduced by at least 25%. Although the UK will implement this vaccination intervention in school age children, this decision is based on much more optimistic assumptions and parameters than ours. Our parameter choices were based on the best Belgian data we could identify and use, and if these were not available we strived to include the best available estimates from the international literature. When comparing our eventual parameter values with those used in previous studies, it appears our choices were relatively conservative.

The vaccination of pregnant women, HCW and persons with co-morbidities, appears as cost-effective as recently introduced vaccines if the influenza vaccine can be administered at no extra-cost. Even if the vaccine administration would require an extra visit, these options could be attractive if we make more favourable assumptions about indirect protection (from mothers to newborns and from HCW to patients) or case-fatality ratio.

The most cost-effective adult vaccination options involve to stop vaccination in healthy young adults, but this will have a detrimental effect on this group. The increase in coverage of the elderly ≥75 years while keeping coverage in other age groups ranks as a very attractive strategy.

Improving the coverage in all adults ≥50 years old would prevent around 350 hospital admissions and around 60 deaths on average per year, but at a high cost since it is a very large group. This option could be considered as cost-effective if the vaccination of younger healthy adults (18-49 years old) would be reduced in parallel.

The most clinically effective intervention, i.e. to vaccinate 80% of all children and increase the coverage in all adults ≥50 years, could prevent around 40% of the current number of influenza hospitalisations and deaths. However, this intervention would only be cost-effective if we assume a slower immunity waning and/or a substantially lower price.

These recommendations are also by large valid for the upcoming quadrivalent vaccines, as the improvement in efficacy they could provide, would only slightly impact on the cost-effectiveness ratio of the vaccination strategies.

It is essential that the long-term impact of any change in the influenza vaccination of target groups be monitored, through surveillance over several seasons after introducing such changes.

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RECOMMENDATIONS[b]

To the competent authorities:

- **Childhood seasonal influenza vaccination can be as cost-effective as other vaccines recently introduced in the vaccine calendar (i.e. pneumococcal conjugate vaccines and human papillomavirus vaccine) providing that the vaccination costs would be reduced by at least 25%. This means that, if implemented, childhood influenza vaccination should be organized through e.g. school health services and the price of the vaccine should be lowered to an acceptable level.**
- **Childhood influenza vaccination should not replace influenza vaccination of adults at risk, as childhood vaccination would only provide a limited indirect protection to the other age groups.**
- **If childhood influenza vaccination is to be implemented, LAIV should be preferred above TIV, providing that its price is similar to or lower than the price of TIV.**
- **The vaccination of the following target groups should be continued and reinforced as it remains attractive from a cost-effectiveness perspective: persons above 75 years of age, pregnant women, health care workers and persons with co-morbidities.**
- **Improving the coverage in all adults ≥50 years old could reduce substantially the number of influenza-related hospitalizations and deaths but at a high cost since it is a very large group. From a cost-effectiveness point of view, it is advisable to reduce in parallel the vaccination of younger healthy adults (18-49 years old).**
- **The long-term impact of any change in the influenza vaccination of target groups should be monitored as influenza virus is a moving target.**
- **These conclusions are also by and large valid for the upcoming quadrivalent vaccines, as the expected improvement in efficacy would only slightly impact on the cost-effectiveness ratio of the vaccination strategies.**

Research agenda:

- **New influenza vaccines - or new indications of existing vaccines - are needed to protect young children <2 years of age as they show the highest hospitalisation rates and the very effective LAIV is currently not indicated in this age group**.

[b] The KCE has sole responsibility for the recommendations.