Seasonal influenza vaccination: priority target groups – Part I

KCE reports 162C

Belgian Health Care Knowledge Centre
Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Title: Seasonal influenza vaccination: priority target groups – Part I

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FOREWORD

Who is now afraid of the flu? In lay language, this usually stands for a big cold. A few days of discomfort and you are back at work. But in the meantime, we have learned more. Every winter, the flu epidemic is claiming many lives, in particular among elderly and debilitated persons.

A difficulty with flu is that the virus is taking a different form every year, so that you never become really immune to the disease. The vaccine producers, however, responded to the challenge, and produce each year a tailor-made vaccine. But they cannot do it in unlimited amounts, and a choice must be made on who will get the vaccine.

The question that policymakers have asked to the KCE is then as follows: for which groups will a better vaccine coverage lead to the largest drop in the number of cases and deaths? And which groups should therefore be given priority when the amount of available vaccines will be insufficient?

Making predictions for such a fickle virus is a challenge, especially as the estimates of the problem magnitude and the effectiveness of the vaccine itself are also surrounded by uncertainty. With the help of many experts, we have responded to the challenge, and the first part of our research is presented here. In a second part, which will be published next year, we will go deeper into the health economics. But meanwhile, here are useful insights for a well-targeted protection of the most vulnerable populations.

Jean Pierre CLOSON
Vice Director general

Raf MERTENS
Director general

Executive summary

INTRODUCTION

Influenza viruses are responsible for a considerable burden of disease, occurring mostly as seasonal epidemics during the winter months. Influenza can cause disease at any age, but some vulnerable groups, such as the elderly and persons with underlying diseases, are more likely to develop severe illness or die as a consequence of influenza. Influenza vaccines are considered to be effective tools to protect against influenza disease and its complications.

A difficulty in influenza research is that cases and deaths due to influenza are not easily identified, as the clinical picture is not specific and only a minority of cases is confirmed by laboratory testing. This implies that the burden of influenza is difficult to quantify and is frequently underestimated. It is commonly estimated as a proportion of non specific syndromes, such as influenza–like illnesses (ILI), acute respiratory infections and pneumonia, all of which may also be caused by other pathogens.

Different types of influenza viruses cause human disease, which may differ in virulence, affected groups and timing. New variants of influenza viruses emerge as a result of frequent and minor changes, while antibodies against one influenza virus type confer limited protection against another type of influenza virus. This has three major consequences:

- continuous changes in the circulating virus strains may allow the virus to partially escape the immune response and thus spread more rapidly among the population;
- 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 the most likely to cause illness in the coming season.

More dramatic changes in influenza viruses may also result in new strains that never circulated before, and have the potential to cause an influenza pandemic. This study is, however, limited to seasonal influenza.

In Belgium, influenza epidemics mostly occur between November and April, but the beginning of the epidemic, its peak and duration vary from year to year.

Vaccines against seasonal influenza are trivalent inactivated vaccines or TIV (containing two components from influenza A and one component from influenza B); they are administered in the period October-December. The Belgian Health Council has established an order of priority among the target groups to be immunized, to be considered if vaccine shortage occurs. Their immunization strategy has so far given priority to persons at higher risk of influenza complications: the elderly, persons living in institutions and all patients with underlying chronic disease. Other groups for which influenza vaccination is recommended are, by order of priority, healthcare workers, pregnant women in the second or third trimester at the time of vaccination, persons aged 50 to 64 years, and poultry and pork farmers, as well as their household members. Vaccines are partially reimbursed for all these groups.

THE RESEARCH QUESTION

During recent years, the demand for seasonal influenza vaccines has usually exceeded its supply, resulting in scarcity of vaccines. As egg-based production is currently the most widely used technology for TIV vaccines, the amounts available at national level are limited, or cannot be easily increased.

In 2009, the Belgian inter-ministerial conference on health commissioned the KCE to undertake a study that would allow establishing priorities to prevent seasonal influenza, aiming to optimize the use of available vaccines.

The objective of this study is to determine, based on scientific evidence, which of the defined target groups should receive higher priority for seasonal influenza vaccination, based on the number of prevented outcomes in these groups. Six outcomes have been considered: outpatient cases of ILI, outpatient cases of confirmed influenza, admissions for influenza, admissions for pneumonia, deaths from influenza and deaths from pneumonia. We limited our study to the direct protection conferred by the classical TIV vaccines. Also, life years gained and quality of life have not been considered as outcome. These other outcomes will be included in a cost-effectiveness study, conducted in part II of this KCE study, which will also address the indirect effects and the impact of other vaccines (such as live attenuated vaccines).

METHODS

The vaccination scenarios (Table 1) that were simulated in this study involve the classical target groups for influenza vaccination, with the exception of persons living in institutions and those working in poultry and pork farms due to lack of data. Each scenario is considered as a change in vaccine uptake compared to the current (2008) situation. These scenarios have been determined in consultation with stakeholders and experts, taking into account their feasibility in terms of organization of the vaccination. In addition, a scenario of not vaccinating the healthy adults aged 15-49 years – that are not targeted by the recommendations – has been considered, though this may be difficult to implement in real life.

Outside the influenza season, ILI and pneumonia are probably caused by other pathogens and thus unlikely to be prevented by influenza vaccination. There are two ways of defining seasons. The *classical influenza season* is defined in Europe as the period between week 40 to week 20 of the next year. However, the period during which the influenza virus is effectively circulating, or *activity season*, is systematically shorter and varies from year to year. As late complications from influenza may occur later, after the activity season, all analyses are performed for the two types of seasons.

Table 1: Vaccination scenarios and target groups selected

Target groups	Scenario In terms of uptake change	Current situation	
		Population 2008	Estimated number vaccinated (%uptake)[1]
1-64 years with co-morbidities	+10% +20%	845,758	169,152 (20%)
Healthy 15-49 years	-11% (reach 0%)	4,624,646	499,462 (11%)
Healthy 50-64 years	+10% +20%	1,658,785	414,696 (25%)
Elderly 65-74 years	+ 25% (reach 75%)[2]	919,531	456,087 (50%)
Elderly 75 years +	+4% (reach 75%)[2]	895,366	634,814 (71%)
Health care workers active (HCW)	+15%	239,740	84,868 (35%)
Pregnant women	+50%	121,362	0 (0%)

1: Estimates based on uptake from HIS 2008 (J. Tafforeau, La vaccination) and the 2008 population. 2: According to the WHO 2010 target of vaccinating 75% of the elderly.

Two other influenza season characteristics were taken into account in this study, as they have an impact on influenza vaccine effectiveness and vary from year to year: the degree of matching between circulating and vaccine influenza strains, and the intensity of influenza seasons.

Because the burden of influenza and the way to measure it are influenced by variations in health care system, contact patterns and vaccination policies, we used Belgian data to the largest extent possible:

- Data on outpatient influenza and ILI cases were based on the Belgian sentinel system of general practitioners (GPs). This system does, however, not cover cases seen by paediatricians and in emergency rooms.
- Data on hospitalizations due to influenza and pneumonia are based on Minimal Clinical Data (MCD) representing discharge data from all Belgian hospitals.
- Data on deaths were based on death certificates, provided by the three Communities, and on hospital deaths from the MCD dataset.
- As no specific data were available on pregnant women, health care workers and persons with co-morbidities (with the exception of hospitalizations), we searched the literature to assess outcomes in these groups.

We restricted data to the period from January 2000 to April 2009, as the intensity of influenza seasons was much higher before 2000, and as we did not wish to include the 2009 pandemic strain A(H1N1) – that appeared in Belgium in May 2009.

We selected influenza vaccine effectiveness (IVE) parameters based on a systematic literature review. As observational studies involve serious methodological problems (especially when using non specific outcomes), we only included randomized controlled trials and observational prospective studies that controlled for the major confounding factors. We limited our search to the period 2000-09, similar settings (i.e. the EU, US or Canada) and TIV vaccines.

The health benefit of each vaccination scenario was estimated separately for each target group, because influenza burden, IVE and uptake differ in each group. The predicted impact is computed by a simple model, based on the baseline number of outcomes, the change in uptake and the vaccine effectiveness in the respective groups.

Because of uncertainty around future influenza season characteristics, the true influenza burden and some IVE parameters, the KCE was requested to estimate vaccination benefits for each of the following three cases: (1) a mean case (according to a distribution of recent influenza seasons), (2) a best case for vaccination benefits (good matching, high virus intensity, highest IVE parameter estimates), and (3) a worst case (poor matching, low intensity, lowest IVE parameter). In addition, we performed a probabilistic sensitivity analysis, to take into account the uncertainties around the IVE estimates and the number of ILI cases.

INFLUENZA BURDEN IN 2000-09

The 9 recent Belgian seasons showed high variability across seasons in terms of timing, circulating strains and number of outcomes. None of the 2000-09 seasons presented a high intensity, but matching was good in most (6/9) seasons.

Table 2: Influenza-related outcomes, by age group (mean of 2000-2009 seasons)*

Mean number of outcomes	ILI	Influenza	Admissions		Deaths	
			influenza	pneumonia	influenza	pneumonia
Age groups (healthy and with co-morbidities)						
0-4 years	45,472	21,824	498	4,986	0	2
5-14 years	95,266	60,534	293	1,635	0	1
15-49 years	260,087	138,320	376	2,641	1	30
50-64 years	99,651	46,938	96	2,375	1	94
65-74 years	21,052	10,313	73	3,167	9	257
75 years +	19,361	8,022	148	8,693	92	2,319
Total	540,890	285,951	1,484	23,498	103	2,704
Specific groups						
HCW	12,467	6,425	17	176	4.4	
Pregnant	6,106	3,243	73 (low) to 103 (high)**		0.8 (low) to 144 (high)**	
Co-morbidities <65 years	46,382	24,099	148	2,992	18 (low) to 99 (high)**	

HCW: Health care workers. ILI: Influenza like illness. *: As these numbers have been rounded to the nearest unit, totals may not sum due to rounding. **: Scenario considered in the absence of appropriate data.

Table 2 shows large variations across age groups in the mean numbers of outcomes reported in an influenza season. Overall, 5% of the total population consulted a GP for an influenza-like illness and influenza was found in 3% of the population during a GP visit, but this may vary from 1% in the elderly (≥65 years of age) to 5% in the school age children (5-14 years of age).

The number of admissions coded as influenza was relatively small, and 53% of them were found in children <15 years of age. Pneumonia admissions were much more frequent, especially in the elderly (≥65 years) who accounted for half of all admissions, followed by young children (21% in <5 years). Persons with co-morbidities showed a 8-fold higher risk to be admitted for influenza and pneumonia compared to healthy persons, which explains that 53% of hospitalizations are in this group (24% of those <65 years and 84% of the elderly). Health care workers (HCW) and pregnant women accounted for a relatively small number of admissions, even when considering a high case scenario.

Most deaths reported to be caused by influenza and pneumonia are found in persons with co-morbidities of all ages (86% of all influenza and pneumonia deaths), especially in the elderly ≥65 years (95% of all influenza and pneumonia deaths). However, we do not have sound data on the number of deaths that are truly caused by influenza, because they may not be recognized and coded as such. As no data could be found on mortality in pregnant women, we selected 2 scenarios: a low case with the same mortality as in persons from the same age (which is supported by most studies) and a maximum scenario corresponding to the H1N1 mortality in the US (with a high prevalence of obesity, which appeared to be a risk factor for H1N1 mortality).

INFLUENZA VACCINE EFFECTIVENESS (IVE)

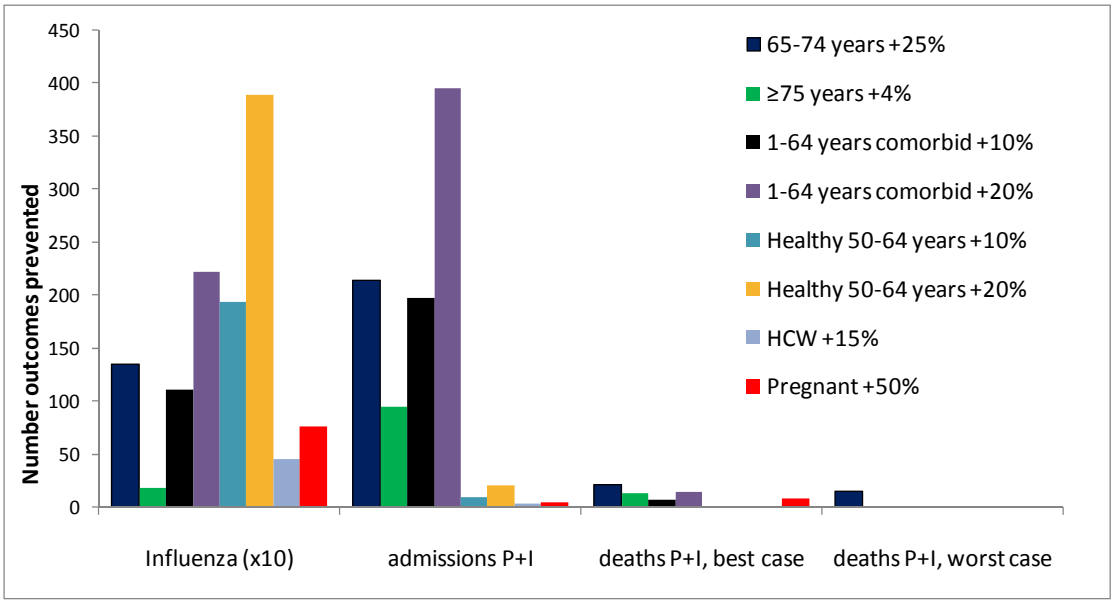
IVE of TIV vaccines showed relatively low values: even for the most specific outcome (laboratory confirmed influenza), IVE ranged from 62% in the best case (seasons with good matching and high intensity) to 22% (non significant) in the worst case (poor matching and low intensity). IVE against a less specific outcome, such as admission for pneumonia or influenza (or P+I), was lower as expected: it ranged 12-29% (depending on the age group), with a higher 63% in persons 15-64 years of age with co-morbidities.

IVE against influenza and pneumonia deaths was only measured in all elderly, at 12%, with a higher 29% IVE in the 65-74 years old with co-morbidities. The effectiveness of TIV to prevent deaths in the ≥75 years old is still subject to debate. It was classically considered as high and a Cochrane review concluded in a 50% reduction in all-cause winter deaths. But this has been challenged by recent and low bias studies, which suggest that IVE in this group is likely to be low due to poor immune function that deteriorates with aging. In our search, IVE was unclear and non-significant in this group, and we used a best and a worst case scenario for IVE. IVE in HCW and pregnant women were similar to those in adults of the same age.

IMPACT OF VACCINATION STRATEGIES

As expected, the type and number of prevented outcomes differ substantially between the various vaccination scenarios (Figure 1). Most results in the section below represent the impact in an average influenza season.

Figure 1: Average numbers of prevented outcomes per influenza season, by vaccination scenario



P+I: Pneumonia and influenza. HCW: Health Care Workers.

Table 3 shows the impact of selected combinations of scenario, called vaccination strategies, in a mean influenza season.

Table 3: Prevented outcomes for a combination of vaccination scenarios (total number and by 10,000 vaccine doses) in an influenza season, and in a mean case, best and worst case for deaths

Strategies	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
Target groups	All elderly reach 75%; co-morbidities 1-64 yrs +20%	Healthy 50-64 yrs +20%; HCW and pregnant	All groups, higher uptake*	All groups, lower uptake**	Healthy 50-64 yrs +20%; co-morbidities 1-64 yrs +20%
N vaccines needed	434,849	428,399	863,248	612,794	500,909
Number of outcomes prevented by influenza season					
Influenza	3,757	5,125	8,882	5,825	6,113
Admissions P+I	705	29	734	526	416
Deaths P+I, best case	49	10	59	51	15
Deaths P+I, worst case	15	0	15	15	1
Number of outcomes prevented by 10,000 vaccine doses, by influenza season					
Influenza	86	120	103	95	122
Admissions P+I	16.2	0.7	8.5	8.6	8.3
Deaths P+I, best case	1.1	0.2	0.7	0.8	0.3
Deaths P+I, worst case	0.4	0.0	0.2	0.2	0.0

P+I: Pneumonia and influenza. HCW: Health care worker.
*: 10% uptake for elderly 65-74 years of age and persons with co-morbidities 1-64 years of age.
**: 20% uptake for elderly 65-74 years of age and persons with co-morbidities 1-64 years of age.

IMPACT BY TYPE OF OUTCOME

Outpatient cases

The strategies that prevent the most outpatient cases are those targeting the <65 years of age. For instance, in an average influenza season, a 20% higher vaccine uptake in the healthy 50-64 year-old adults would prevent around 4,000 outpatient influenza cases. However, this strategy would cost more than 300,000 vaccines (19% of vaccines reimbursed in 2008) and only prevent 20 admissions and zero deaths. Yet, the benefit on outpatient cases could not be estimated in a worst case scenario (poor match, low intensity), due to non significant IVE, and exceeded 6,000 cases in a best case scenario (good match, high intensity).

Admissions

Vaccinating the persons with co-morbidities is the most efficient option to prevent admissions, with the highest number of admissions avoided per vaccine dose (23/10,000). The uptake in this group is currently low (20% in those <65 years in 2008) and increasing it by an additional 20% would prevent 396 admissions in an influenza season, at a cost of 167,000 vaccines. Targeting the elderly ≥75 years would prevent a similar number of admissions per dose, but would not bring a high absolute benefit (95 prevented admissions only) as 71% of this group is already vaccinated while we aim at reaching the WHO target of 75%. Exceeding this high target may be difficult to implement.

Deaths

The optimal strategy to prevent influenza and pneumonia deaths is difficult to establish: targeting the elderly ≥75 years would prevent the highest number of deaths per vaccine dose in a best case (4/10,000), but the proposed scenario would only prevent 13 deaths per influenza season. Other scenarios would prevent a lower number of deaths per dose (<1/10,000), with the exception of pregnant women in the most extreme scenario (mortality from 2009 pandemic H1N1). Vaccinating 50% of them would prevent 9 deaths. Even a maximum strategy (Strategy 3 in Table 3), aiming at a high uptake in all target groups, would only prevent 59 deaths in an influenza season in a best case. These estimations are also limited by the lack of sound data on the number deaths due to influenza.

WHICH STRATEGIES WOULD BE THE MOST EFFECTIVE?

Strategy 1, targeting the highest risk groups (reach 75% in all elderly and increase by 20% in persons with co-morbidities) is the most efficient strategy to prevent severe disease (Table 3): it would prevent 3,757 outpatient influenza cases, 705 admissions and 15-49 deaths in an average influenza season, at a cost of 434,000 vaccines. A "maximum" strategy, aiming at a high uptake in all target groups (Strategy 3) is expected to attain the best impact. It would prevent more than the double of outpatient cases compared to Strategy 1, but only a similar number of admissions and deaths while requiring the double of vaccines (863,000 doses or 51% of vaccines reimbursed in 2008). Strategy 2, that involves the target groups with lower risk (healthy adults 50-64 years old, HCW and pregnant women) would prevent more than 5,000 outpatient cases but is the least effective in preventing admissions and deaths, at a cost of 430,000 vaccines. Strategy 5, which is limited to adults <65 years of age (with or without co-morbidities), is effective in preventing outpatient cases and admissions, but not deaths.

The young healthy adults (15-49 years) are currently not targeted by the Health Council recommendations, but 11% of them are vaccinated. If this group would not be vaccinated, around 6,000 additional influenza cases are expected to occur in an influenza season, but only 28 additional admissions and zero deaths. Though this scenario is difficult to implement, it would make 500,000 vaccines available to increase the uptake of more vulnerable groups.

As the 65-74-years old have only a 50% uptake, a significant rise (25%, 230,000 doses) is required to reach the WHO target, for a relatively small decrease in outpatient cases (1346), admissions (214) and deaths (14 under the best case).

The increased vaccination of HCWs and pregnant women shows a limited impact in terms of prevented outcomes (<1000 influenza cases and <6 admissions each), even when using parameters of the H1N1 pandemic. This is partly due to the low number of persons involved, but also because our model does not account for indirect effect (protecting patients of HCW and infants of mother vaccinated while pregnant).

A surprising finding is that, whatever the scenario, the number of prevented outcomes is small compared to the total influenza burden: the maximum strategy would only prevent 3% of all outpatient cases and 1.4% of all pneumonia and influenza deaths (best case). Though we underestimate the real benefit of influenza vaccination because our study is restricted to pre-specified outcomes, the use of more effective influenza vaccines (e.g. adjuvanted vaccines) may provide a more effective strategy.

VARIABILITY AND UNCERTAINTY

The value of the vaccination benefit estimates from our model is affected by two main sources of uncertainty.

Firstly, the outspoken variability of influenza strains, season intensity and matching with vaccine strains makes predictions on future vaccination benefits highly uncertain, especially for outpatient cases. The benefits on admissions are more stable from season to season – even for those only coded as influenza. Future influenza seasons are unpredictable, and we based most of our results on the epidemiology of the last 9 seasons. For instance, we did not take into account that the 2009 H1N1 strain would circulate in the next influenza seasons (as this was unknown when this study was initiated), and our predictions may not fully apply to this strain – that show lower attack rates in the elderly.

Second, there is additional uncertainty on the parameters fed into our model, mostly due to the difficulty to identify outcomes that are related to influenza. We could not validate coding of hospital discharge data; it is for instance unclear whether influenza admissions outside the influenza period are correctly diagnosed. And our study underestimates the outcomes due to influenza because we could not include outpatient cases seen at emergency wards and by paediatricians, nor admissions and deaths that result from a complication of influenza other than pneumonia. We thus had to make a number of assumptions and extrapolations for missing parameters. The uncertainty analysis, featuring best and worst case scenarios for each outcome, shows a wide interval around the mean estimates of prevented outpatient influenza cases. Similarly, estimates of prevented deaths in the <65 years old show a high level of uncertainty, even in a best case scenario. The only results with a relatively low level of uncertainty are the estimates of prevented outpatient influenza in a best case and admissions and deaths in the elderly.

The sensitivity analysis showed that adjusting the baseline burden for the number of vaccinated elderly, i.e. including in the baseline the outcomes prevented by the current vaccination in the elderly - would improve the impact of the additional vaccination in this group in an average season by preventing 463 outpatient influenza cases, 47 P+I hospitalizations and an unknown number of deaths due to too many uncertainties around the vaccine protection against deaths in this group. Similarly, adjusting the baseline burden for the institutionalized elderly (who have a higher burden and should be removed from the baseline because they are not included in the scenario) would only decrease the impact by 28 prevented admissions; this could not be estimated for the prevented deaths.

CONCLUSIONS ON PRIORITY SETTING

The priority setting in targeting groups for influenza vaccination would depend on the programme objective:

- If the programme objective is to prevent **outpatient cases**, children and adults <65 years of age, with or without co-morbidities, should be targeted. However, increasing influenza uptake in healthy adults would only prevent a few admissions in a best case scenario. The prediction of prevented outpatient cases also involves the highest level of uncertainty and variability, mostly due to unpredictable seasons and changing influenza strains.
- If the vaccination programme aims at reducing **severe disease, such as admissions**, the most effective strategy would target the persons 1-64 years old with co-morbidities. Current uptake in this group is only 20%, and a 20% increase in uptake would prevent on average around 400 admissions and 1-15 deaths. Another possible strategy is to increase the uptake in elderly ≥75 years, but this has a low feasibility and, hence, a low potential impact as the current uptake in this group is already high.
- None of the strategies seem able to substantially decrease **deaths from influenza and pneumonia**. Most of these deaths are found in the elderly ≥75 years, and it is not clear whether increasing influenza vaccination in this group could really prevent (or delay) additional influenza-related deaths. We can only conclude that, based on current knowledge, influenza vaccination is not very effective in reducing deaths – at least deaths coded as caused by pneumonia and influenza. This conclusion could be revised if we would be able to better estimate the number of deaths that are attributable to influenza.

We did not assess strategies to decrease the epidemic curve by reducing influenza transmission. Several studies have predicted a large impact of vaccinating school age children in reducing influenza transmission, and therefore reducing the exposure of most vulnerable groups. This aspect will be addressed in the second part of this study.

The 65-74-years old, who have a 50% uptake (to be compared to the WHO target of 75%) and are not yet affected by immune senescence, were considered as a potentially important target group by stakeholders. However, our study showed that around 230,000 vaccines would be required to achieve only a moderate impact in this group. This is explained by the lower impact on outpatient cases than the vaccination of younger subjects, as well as the lower impact on admissions than the vaccination of elderly ≥75 years or the adults with co-morbidities.

If the young healthy adults would not be vaccinated, the 500,000 vaccines currently used to cover them could target groups at high risk.

All strategies involving persons with co-morbidities present the advantage of having a high impact on admissions, due to the high admission burden and high vaccine effectiveness in this group, while also having a high effect on outpatient cases and some effect on deaths

Targeting the HCWs and pregnant women does not yield an important benefit in terms of prevented outcomes, but this result may be due to the inability of our model to account for the indirect vaccination effect.

RECOMMENDATIONS[a]

The target groups that should receive higher priority for seasonal influenza vaccination depend on the programme objective:

- **If the objective is to prevent more outpatient cases, persons <65 years of age, with or without co-morbidities, should be targeted. However, the predicted impact on outpatient cases involves a high level of uncertainty.**
- **If the objective is to reduce hospital admissions, persons 1-64 years old with co-morbidities should be targeted. Additionally, further increasing the uptake in the elderly ≥75 years would also be effective, but has a low feasibility and, hence, a low potential impact as the current uptake in this group is already high. It is recommended to maintain the effort to keep this uptake high.**
- **None of the proposed strategies can be recommended to substantially decrease deaths from influenza and pneumonia.**

All results show that targeting persons with co-morbidities, who are mostly unvaccinated, has the double advantage of preventing a large number of outpatient cases as well as a substantial number of admissions.

These recommendations may be revised when more effective vaccines become available.

a The KCE is the only responsible for the recommendations given to the public authorities

Scientific summary

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GLOSSARY

ABBREVIATION	DEFINITION
AIM/IMA	Inter-mutuality agency
CI	Confidence interval
CVD	Cerebro-vascular disease
GP	General Practitioner
H	Haemagglutinin
HCW	Health care worker
HIS	Health Interview Survey
HR	Hazard ratio
ILI	Influenza like illness
ILI +	ILI with influenza positive swab
INAMI/RIZIV	Institut national d'assurance maladie-invalidité / Rijksinstituut voor ziekte- en invaliditeitsverzekering
INS	Institut National de Statistique
IPH	Scientific Institute of Public health
IR	Incidence rate
ITT	Intention to treat analysis
IVE	Influenza vaccine effectiveness or efficacy
LAIV	Live attenuated influenza vaccine
MA	Meta-analyse
MCD	Minimal Clinical Data
N	Neuraminidase
NIC	National Influenza Centre
NS	Non significant (statistically)
OP	Outpatient
OR	Odd ratio
P+I	Pneumonia and/or influenza
PCR	Polymerase chain reaction
PPA	Per protocol analysis
RCT	Randomized clinical trial
RR	Risk ratio
RSV	Respiratory syncitial virus
RTI	Respiratory tract infection
SPMA	Standardized Procedures for Mortality Analysis
SR	Systematic review
TIV	Trivalent inactivated vaccine
VE	Vaccine effectiveness or efficacy

1 INTRODUCTION

1.1 INFLUENZA DISEASE

Influenza viruses are responsible for a considerable burden of disease. Though influenza can cause disease at any age, some groups, defined by age and underlying disease, are more likely to develop severe illness or die as a consequence of influenza. While influenza infection and morbidity is most frequent among children, severe disease and mortality mostly affects the elderly and the persons with co-morbidities.[1]

The clinical and economic burden of seasonal influenza is frequently underestimated, as cases and deaths caused by influenza are rarely identified or coded as influenza outcomes, and only a minority of cases is confirmed by laboratory testing. The most common influenza-related outcomes are non specific syndromes, which may also be caused by other infections (viral or bacterial), or even have non-infectious causes. These outcomes are influenza–like illnesses (ILI), acute respiratory infections, pneumonia and all-cause deaths.

Two types of influenza viruses cause epidemic human disease: influenza type A and B. Influenza A viruses are divided into subtypes on the basis of the combination of 2 surface antigens (H for haemagglutinin and N for neuraminidase). Influenza A and B viruses can be further broken down into different strains. In recent decades, influenza A (H1N1) and A (H3N2) viruses, as well as influenza B viruses, have circulated among humans in Europe.[1] An important characteristic of influenza viruses is their ability to evolve continuously to escape the immune response. New variants of influenza viruses emerge frequently as a result of frequent and minor antigenic change (point mutations in the H and N genes), called drifts. More dramatic changes, or antigenic shifts (re-assortment between different influenza viruses), occur less frequently and only with influenza A viruses. But shifts may result in new strains that have never been circulating before, and therefore have the potential to cause a pandemic when they are able to cause human illness and human-to-human transmission.[2] In addition, antibodies against one influenza virus type confers limited protection against another type of influenza virus, or against infection with a new antigenic variant of the same type. This allows the virus to spread more rapidly among the population.

In Europe and in Belgium, annual epidemics of influenza occur mostly during the winter months, usually between week 40 and week 20 of the following year. However the patterns of these epidemics are highly variable from year to year in terms of the beginning of the epidemic, its duration, intensity, and influenza strains that circulate. For instance, the epidemic peak may occur as early as late fall or only appear in February-March. As a result, numbers of cases and deaths from influenza, as well as the most affected age groups, varies each season.

1.2 VACCINES FOR SEASONAL INFLUENZA

Influenza vaccines are considered as the most effective preventive tools to reduce disease burden and severe disease due to influenza in individuals. The predominant seasonal vaccines are the trivalent inactivated vaccines or TIV; most of them are split vaccines (virus particles are disrupted using detergents) or subunit vaccines that only contain the purified antigens.[3] Trivalent vaccines typically contain two components from type A influenza (subtypes H3N2 and H1N1) and a third component from type B viruses, according to the WHO recommendations. These recommendations are adapted every year, based on surveillance-based forecasts about what viruses are most likely to cause illness in the coming season. Seasonal influenza vaccines are administered before the influenza season, usually in the period October-December in the Northern hemisphere.

The immunization strategy for seasonal influenza in most EU countries has focused on protecting the high-risk groups rather than trying to achieve herd immunity[a] and reduce transmission in the community.[4, 5]

These "risk groups" targeted for influenza vaccination generally include:

- **The elderly**. Older people are at higher risk of severe illness, hospitalisation and death if they are infected with influenza, compared to younger adults.
- **Persons with co-morbidities**. Persons of all ages with specific chronic medical conditions are at higher risk for severe disease.
- **Health care workers (HCW) and staff working in nursing care**. HCW are considered to be exposed to higher level of influenza transmission while providing care, and they may also transmit the disease to patients at risk.[6]
- **Pregnant women**. If infected, this group is considered to be at higher risk of severe outcome compared to non pregnant women of the same age.
- **Children**. Children are the major pathway by which influenza infections are spread within a community. In several EU countries (6 countries in 2007), the US and Canada, routine immunization of young children is recommended from a public health perspective, with the age limits varying from 6 months to 18 years.[4, 7, 8] Such recommendations mainly aim to reduce the transmission of influenza infections.

Several randomized controlled clinical trials (RCT) and observational studies have shown that vaccinating these groups reduces the risk of disease and severe outcome.[9-14] In addition, several studies showed substantial indirect effects of vaccinating young children by reducing transmission.[15-17]

However, several issues are still debated due to conflicting findings, leading to diverging recommendations across EU countries. For instance, the protection afforded in the elderly ≥ 85 years, especially against mortality, as well as the age 'cut-off' above which vaccination should be recommended to all persons, are unclear.[18] Whether pregnant women should be vaccinated is also a matter of debate. In addition to protecting themselves, immunization of pregnant women may provide some passive protection to the child they are carrying, which may last for the first few months after birth.[19] In 2007, 8 EU countries offered the vaccine to healthy pregnant women.[4] However, the increased risk of complication is not clearly documented, outside pandemic influenza, and has to be weighed against safety concerns and limited evidence on vaccine effectiveness.[20, 21]

a Herd immunity is an indirect effect of vaccination, i.e. an effect in the non-vaccinated groups, due to the reduced circulation of pathogens following widespread vaccination of children.

1.3 SEASONAL INFLUENZA VACCINATION IN BELGIUM

In Belgium, seasonal influenza vaccination is currently recommended for the prevention of influenza in persons at higher risk of influenza complications. The Health Council recommends to limit vaccination to these risk groups, and an order of priority has been established among them and should be considered in the event of vaccine shortage (Table 1).[22]

Table 1: Target groups for which influenza vaccination is recommended by the Belgian Health Council[22]

Group	Definition
Group 1: Persons at high risk of complications	All persons aged 65 years and above Persons living in institutions All patient above 6 months of age with a underlying chronic disease, even stabilized, involving lungs, heart, kidney, liver or metabolic and immune disorders Children from 6 to 18 months under long term therapy with aspirin
Group 2: Health care workers	All staff working in the health sector that are in direct contact with the persons from group 1
Group 3: Pregnant women	Pregnant women that will be in the second or third trimester at the time of vaccination
Group 4: Adults 50-64 years of age	Persons aged 50 to 64 years, even those not having underlying disease, and particularly those smoking, having a drinking problem, and obese persons
Group 5: Poultry and pork farmers	Poultry and pork farmers, as well as their family members sharing the household and other persons that have occupational contacts with live poultry or pork

Regarding the universal vaccination of young healthy children, the Health Council considered that available evidence is currently not sufficient to propose this strategy.

Seasonal influenza vaccines are reimbursed by the INAMI/RIZIV for the groups at risk defined by the Health Council. In 2011, six vaccines were available:[b] Agrippal (Novartis), Fluad (Novartis), Influvac S (Abbott), Vaxigrip (Sanofi Pasteur MSD) α-Rix (GSK) and Intanza (Sanofi Pasteur MSD). The first three are sub-unit vaccines and the next three are split vaccines. Their cost ranged from 10 to 12€ per dose. One dose is advised, except for children aged 6 months - 7 years who have never been vaccinated earlier: these will need 2 doses at 1 month interval. The vaccine is administered before the influenza season, i.e. in October or November.

[b] http://www.cbip.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_1.cfm

2 RESEARCH QUESTIONS

During recent years, the demand for influenza vaccines has usually been greater that its supply. This has resulted in scarcity of seasonal influenza vaccines. For instance, temporary shortages have been reported in Belgium during the 2005 H5N1 pandemic risk, as this has increased the vaccine use. As egg-based production is currently the most widely used technology for TIV vaccines, the amounts available at national level are limited, or cannot be easily increased.[c23]

Considering this recurrent risk of shortage, the prioritization of groups to vaccinate is an important issue to address at a public health level. In 2009, the Belgian inter-ministerial conference on health commissioned the KCE to undertake a study that would allow establishing priorities to prevent seasonal influenza, aiming to optimize the use of available vaccines, in a public health perspective.

The objective of this study is to determine which of the defined target groups should receive higher priority for seasonal influenza vaccination, taking into account the limited availability of influenza vaccines. This prioritization, using scientific evidence, will be based on the number of prevented outcomes in these groups. Six outcomes have been considered:

- outpatient cases of influenza-like-illness (ILI)
- outpatient cases of confirmed influenza
- admissions for influenza
- admissions for pneumonia
- deaths from influenza
- deaths from pneumonia.

We only included the clinical benefits conferred by the direct effect of the classical TIV vaccines. Life years gained and quality of life have not been considered as outcome in this part of the study. These other outcomes and benefits will be included in a cost-effectiveness study, conducted in part II of this KCE study. We also did not address the organizational issues of prioritizing specific groups, nor the barriers to vaccination.

c Each component of the TIV is grown separately in embryonated chicken eggs. On average, approximately one egg is required to produce one dose of one vaccine strain. The supply of eggs from a certified source is thus critical, and a lead-time of several months is required to establish a reliable supply of fertilized eggs of suitable quality to meet the requirements of seasonal flu-vaccine production.

3 METHODS

Several meetings with stakeholders and experts have allowed to refine the research questions and the methodology, and more specifically to determine vaccination scenarios, outcomes, basic model and selection of data sources for parameters.

3.1 TARGET GROUPS AND VACCINATION SCENARIOS

The vaccination scenarios (Table 2) that were simulated in this study have been determined in consultation with stakeholders and experts, taking into account the needs in decision-making and practical aspects of vaccination. The classical target groups for influenza vaccination in Belgium are included, with the exception of the persons living in institutions, and those working in poultry and pork farms (Table 2). We did not include them for two main reasons: data on their total numbers and influenza burden are not available in Belgium – with the exception of institutionalized elderly persons. These elderly living in institutions showed very high uptakes in recent surveys (78-81% in 2006-07),[24] which rank higher than the WHO target of 75% by the year 2010 - and thus higher than the uptake considered in the scenarios.

The scenario also considered separately the 65-74 years and the ≥75 years of age. The main reason is the difference between these 2 groups: in the older elderly, influenza mortality is substantially higher, influenza vaccine effectiveness is more difficult to measure and is probably lower due to immune senescence.[18] Additionally, we included the healthy young adults (15-49 years) because a small proportion of this large group (around 11%) is already vaccinated by occupational health services.

The selection of target group in each scenario is also taking into account the feasibility in terms of organization of the vaccination: for instance, groups that are vaccinated in the same time by the same vaccinators (e.g. different co-morbidities or different categories of health care workers) are not divided into specific categories, but considered all together.

We defined the vaccination scenario based on the 2008 vaccine uptake (used as baseline), as the most robust uptake data were available from the 2008 Health Interview Survey (HIS) conducted by the Scientific Institute of Public health (IPH). Data from the Inter-mutuality Agency (AIM/IMA) and the INAMI/RIZIV, based on reimbursed doses, were also consulted, as well as specific surveys in health care workers (see details in Appendix 1). No data are available on the uptake in pregnant women, which was assumed to be negligible.

Each vaccination scenario is considered as the change in vaccine uptake from the 2008 situation (Table 2), as our objective is to estimate the impact of a change in intervention. For the healthy adults aged 15-49 years, the objective was to estimate the impact of not vaccinating this group (though this may not be fully realistic in real life settings).

Table 2: Vaccination scenarios and target groups selected

Target groups	Population 2008	2008 uptake[1]	Estimated number vaccinated[3]	Scenario (in terms of uptake change)
1-64 years with co-morbidities	845,758	20%	169,152	+10% +20%
Healthy 15-49 years	4,624,646	11%	499,462	-11% (reach 0%)
Healthy 50-64 years	1,658,785	25%	414,696	+10% +20%
Elderly 65-74 years	919,531	50%	456,087	+ 25% (reach 75%)[2]
Elderly 75 years +	895,366	71%	634,814	+4% (reach 75%)[2]
Health care workers (active)	239,740	35%	84868	+15%
Pregnant women	121,362	~ 0%	0	+50%

1: From the 2008 Health Interview Survey, J. Tafforeau, La vaccination.[25]
2: According to the WHO 2010 target of vaccinating 75% of the elderly.
3: Estimate based on uptake from HIS 2008 and 2008 population; HCW may be also included in healthy adults and in persons with co-morbidities, but no data were available to extract them.

3.2 DENOMINATORS

Mid-year population figures by age group were retrieved from the SPMA website (http://www.wiv-isp.be/epidemio/spma/). We use the number of live births as approximation for the number of pregnant women. For the number persons with co-morbidities, the IPH provided age-specific proportions of self-reported co-morbidities from the 2008 HIS, as these are defined in the Belgian influenza vaccine recommendations. We applied these proportions to the corresponding age-specific population figures on the last 3 influenza seasons.

Numbers of HCWs were retrieved from the INAMI/RIZIV databases, updated in February 2009. As not all registered HCWs are involved in health care services, we estimated the number of "active" HCWs by applying the proportion of GPs that were active in 2008 (82.4%) to all HCWs, assuming that this proportion is similar for non-GP HCWs (INAMI 2008).

Further details on sources and methods are provided in Appendix 1.

3.3 PARAMETERS FOR INFLUENZA SEASONS

Outside the period of influenza virus circulation (or seasons), non-specific outcomes such as ILI and pneumonia are likely to be caused by other pathogens – which may also vary in frequency. Disease burden occurring outside the influenza season is thus not likely to be prevented by influenza vaccination, first because it is probably not due to influenza, but also because vaccinees may lose some degree of protection from the season vaccine due to accumulating drifts in circulating influenza strains.

3.3.1 Influenza seasons and viral activity seasons

The *influenza season* is classically defined in Europe as the period between week 40 to week 20 of the next year. However, the period during which the influenza virus is effectively circulating each year is systematically shorter than the conventional influenza season (10-20 weeks vs. 32 weeks). This period, called here *viral activity season*, varies from year to year and across countries; the criteria to determine this period also differ across countries, but is usually based on the incidence of ILI and/or the number of positive ILI samples (see Appendix 1).

As we use mostly non-specific outcomes in this study, we restricted the estimation of disease burden to influenza seasons, and estimated the health benefit of vaccination in both types of seasons, influenza season and activity season. Activity seasons are more specific but are defined based on ambulant ILI cases, thus not necessarily reflecting the occurrence of severe (admitted) cases.

We thus cannot exclude that complications and deaths due to influenza may occur outside the activity season, when the virus does not longer circulate. We defined the periods of activity seasons in Belgium using criteria described in the vaccine effectiveness studies that were used to derive estimates (Table 3 and Appendix 1).

3.3.2 Matching and season intensity

Besides duration and timing of influenza season, another factor to take into account is the degree of antigenic match between circulating and vaccine strains. This degree of matching varies significantly across seasons, due to frequent drifts in the circulating strains. In addition, influenza seasons vary in intensity, mostly due to variations in circulating strains and pre-existing immunity in population groups. The intensity is classically related to the peak levels of clinical and virological activity, but no clear definition could be found in the literature.[26]

Because vaccine effectiveness values vary with the level of matching and season intensity, we collected data on these characteristics for the 9 Belgian seasons in 2000-09 (Table 3). This information was found in annual influenza reports on Belgium (IPH and European Influenza Surveillance Scheme or EISS) or requested to the Belgian National Influenza Centre for missing seasons.[27-34]

These variations of influenza seasons results in substantially differences in incidence, severity, and affected target groups across seasons. For this reason, we used data from the most recent 6-7 influenza Belgian seasons for each outcome (2000-07 for admissions and 2003-09 for outpatient influenza), broken down by week or month of onset, to take seasonal variability into account.

Table 3: Definitions of influenza season characteristics

Season characteristic	Definition and criteria	Data source
Influenza season	Week 40 to week 20	None
Activity season	- Beginning: the first week of the 2 weeks in which the first 2 laboratory confirmed ILI cases are reported. - End: the last week of the last 2 weeks in which the last 2 laboratory confirmed ILI cases of the season are reported.	Sentinel GP network and Virology results from the national Influenza centre, IPH
Matching between vaccine and circulating strains	Good, relative and poor: as defined in annual reports and/or by the National Influenza centre.	IPH or EISS annual reports
Season intensity (viral activity)	High, medium and low: as defined in annual reports and/or by the National Influenza centre.	IPH or EISS annual reports

3.4 MODEL

As influenza vaccination may reduce viral transmission, a dynamic transmission model would be more suitable to account for the indirect effect of vaccinating specific groups. However, indirect effect on influenza infection has only been clearly demonstrated following vaccination of children. Vaccinating other age groups, comparatively small in size (see Table 2) or/and at low uptake (as in our scenarios) is not expected to confer indirect protection.[35] Therefore, this study is based on a simple static model. The health benefit of vaccinating children is estimated by a dynamic transmission model in part II.

The health benefit of each vaccination scenario is estimated by using the following formula, for each of the 7 target groups above. It is thus based on the baseline number of outcomes in this group, the change in uptake and the vaccine effectiveness in this group. The number of outcomes prevented is calculated for each of the 6 outcomes separately, and is summed over all groups, as follows.

$$\text{N outcome prevented} = \sum_g O_g * VE_g * U_g$$

g: target group considered
O: group-specific number of outcomes (outpatient cases, inpatient cases or deaths)
VE: group-specific vaccine effectiveness
U: group-specific change in uptake

The parameters used for influenza outcomes are described in section 4.3 and 4.4, and those for vaccine effectiveness in section 4.5.

We faced two main areas of uncertainty to predict the outcomes that could be prevented by vaccination: which type of influenza season should be expected in the future (knowing that the type of season partly determines the number of prevented outcomes), and we could not find influenza vaccine effectiveness (IVE) parameters for all target groups and outcomes. We thus computed the results in three cases:

1. Mean case: mean of results related to a distribution of recent influenza seasons (according to matching and intensity) and/or using a single IVE for all seasons.
2. Best / high case: results from a season with good matching with the vaccine strain and high viral intensity; and/or highest IVE parameter selected from the literature.
3. Worst / low case: results from a season with poor matching with the vaccine strain and low viral intensity; and/or lowest IVE parameter selected from the literature.

For a few IVE parameters that are not clearly defined, we did not define a "mean" baseline case but only a best and worst case. The outcomes for which vaccine effectiveness parameters differ with the type of season are also shown for the 6-8 recent seasons (depending on availability of burden data).

3.5 PARAMETERS FOR INFLUENZA OUTCOMES

Sources and methods to estimate the baseline data are described in detail in Appendix 1 and are summarized below.

Influenza outcomes are difficult to quantify because influenza infections are rarely confirmed by laboratory, and outcomes coded as influenza underestimate the true burden of influenza.[36, 37] Therefore, this study also includes more broadly defined conditions that may be caused by influenza infections, such as ILI and pneumonia.

ILI refers to a group of clinically diagnosed symptoms commonly associated with influenza infection. During influenza epidemic periods, ILI have proven to be a reliable indicator of laboratory-confirmed influenza.[38] ILI has a specific definition for surveillance purpose. It is also known that complication from influenza may be recorded under non-specific syndromes such as pneumonia.[37]

However, influenza coding for admissions and deaths is known to underestimate the true influenza burden.[36, 37] This underestimation differs across countries, mainly due to variations in health seeking behaviour, socio-cultural differences and testing habits. Additionally, influenza epidemiology may also differ across countries due to differences in contact patterns, age distribution, and vaccination policies.[26, 39]

The period selected for parameters may also impact on results. The intensity of influenza seasons showed an overall decrease over time, especially after 2000, and most recent seasons showed a moderate to low intensity.[38] The use of older data on burden (<2000) may thus lead to overestimates in the current burden of influenza, and the burden expected in the near future.

3.5.1 Overall methodological approach

Considering the specificities of influenza-related outcomes, we opted for the following methodological approach:

1. Overall, use Belgian data to the largest extent possible. Validate and complement these data by published data from similar settings (Europe or North America), based on a literature review.
2. Include broader conditions that may be caused by influenza infections, such as ILI and pneumonia (admissions and deaths), as explained above. For parameters on outcomes, we used the definitions that are most commonly used in vaccine effectiveness studies, so that different parameters address the same outcomes. For instance, we used as data on admissions and deaths hospital discharge data defined by ICD coding (ICD9 or ICD10).
3. Include data on influenza confirmed cases by extrapolating data from Belgian sentinel systems (considering them as representative samples) to the entire population.
4. Restrict data to the period January 2000 to April 2009. Besides the risk to overestimate the burden by using older data, we did not include data involving the 2009 pandemic strain A(H1N1), except for pregnant women as "best case" estimates for prevention of outcomes.
5. Restrict admissions and deaths to "main" ICD diagnoses of influenza and pneumonia, because we aim to estimate the outcomes that could be prevented if the patient did not suffer from influenza.
6. As no burden data from unvaccinated subjects in Belgium are available, use the current burden as baseline. As a proportion of the target groups is vaccinated, we tend to underestimate the total burden vaccination and thus the vaccination benefits. As this underestimation is greater in the most vaccinated groups (the elderly), we estimated a corrected burden based on literature data and included it in the sensitivity analysis.

Because none of the scenarios involve institutionalized elderly, and influenza burden data on the elderly do not distinguish those who are living in institutions from others, we could not take into account the mode of residence in this study. As the institutionalized elderly suffer a higher burden of severe disease compared to the community-dwelling elderly, we may overestimate the vaccination benefit on admissions and deaths. But this is likely to have a very limited impact in the 65-74 years of age, as those institutionalized represent <10% of all admissions and this group accounts for 5% of P+I hospitalizations in this age. And this is also likely to have a limited impact in those ≥75 years of age because we simulate only a 4% (additional) uptake in this group. We thus simulated a corrected burden in the sensitivity analysis to assess the extent of this overestimation.

The main data sources by outcome and target group are described in Table 4.

Table 4: Summary of sources of data by outcome and target group

Target group	Outpatient cases: ILI and ILI laboratory confirmed	Inpatient cases: admissions for influenza and pneumonia	Deaths from influenza and pneumonia	Current vaccine uptake	Population figures
Age groups	GP network for ILI + National Influenza Centre	MCD database	Deaths from Communities	HIS 2008	SPMA by year
Co-morbidities	Excess morbidity from literature, rates in healthy age groups	MCD in co-morbidities, and excess admissions from literature	Excess mortality based on MCD deaths, applied to deaths from communities	HIS 2008	SPMA and proportion by HIS
Pregnant women	Excess morbidity from literature, rate in 15-49 years	Literature Admissions during the H1N1 2009 pandemic (best/high case) MCD admission rates in 15-49 years (worst/low case)	Literature Mortality during the H1N1 2009 pandemic (best/high case) Death rate in the 15-49 years (worst/low case)	NA (assumed at 0%)	Birth cohort by year
Health care workers	Morbidity from literature, rate in 15-64 years	Excess admissions from literature, MCD admission rate in 25-64 years	Excess deaths from literature, death rates (communities) in 25-64 years	HIS 2008, Belgian surveys	INAMI/RIZIV Proportion active

ILI: influenza like illness. HIS: Health interview survey. MCD: Minimal clinical data. NA: not available. SPMA: Standardized Procedures for Mortality Analysis.

3.5.2 Outpatient cases of ILI and confirmed influenza cases

Parameters on ILI and influenza outpatient cases were collected over the last 6 pre-pandemic influenza seasons (2003-04 to 2008-09) from a sentinel network of GPs coordinated by the IPH. This network, considered to be representative of the Belgian population, has been evaluated and validated by several studies on influenza and other health problems.[26, 40-43] In 2009, it involved around 200 GPs, representing approximately 1.8% of all Belgian GPs, reporting on ILI consultations.[44] In addition, a sample of the ILI patients are swabbed (around 1000 by season), tested for influenza (by antigen, culture and PCR) and typed by the National Influenza Centre (NIC). Patients are selected on an "ad hoc" way (not systematic) but the sample is aimed at being representative of the patients presenting with ILI. Isolates from a subset of positive samples are also sent to the London WHO reference Centre for further typing. Though the network has varied in size, the same methodology has been used over the study period.

It should be noted that the objective of this registration is not to calculate incidence rates but to detect the beginning of an influenza epidemic, monitor its activity and the circulating strains. Additionally, rate calculation is based on a crude estimation of the denominator.[44] However, data from another GP network (Intego), located only in Flanders, showed almost identical curves for ILI rates, though overall ILI rates were slightly higher in Intego (and based on other case definitions).[41]

This system does not cover cases seen by paediatricians and in emergency rooms. As no data are available on these services, this study is limited to ILI cases seen at GP offices and data are thus an under-estimation of the true burden seen as outpatient. The lack of paediatrician data has however a limited impact as only children with co-morbidities are involved in the vaccination scenarios, representing 7% of the <15 years.

We calculated the total number of ILI and laboratory confirmed influenza cases by season by applying, by age group, the weekly ILI incidence and the proportion of positive ILI to the total population.

ILI in specific subgroups (i.e. co-morbidities, pregnant women and HCWs) are not available from this GP database. Therefore, we performed a literature search to assess whether ILI incidence in these groups differs from the general population, and if so, which values can be used.

3.5.3 Inpatient cases of influenza and/or pneumonia

Parameters on hospitalizations due to influenza and pneumonia are based on Minimal Clinical Data (MCD) representing discharge data from all Belgian hospitals over 2000-07 (main diagnosis ICD-9 CM 480-487). Age, presence of co-morbidities (conditions for which influenza vaccine is recommended), outcome and week or month of admission were retrieved on each inpatient case. Further details are given in Appendix 1. As coding of co-morbidity in MCD has never been evaluated, we compared estimates derived from the MCD data to those published from other countries, for validation purpose.

As no data were available on admissions in pregnant women and health care workers (HCW) in Belgium, we searched the literature to estimate the excess (or lack of) risk in these groups. We also searched for data on the nosocomial transmission of influenza from and to health care workers in the literature.

3.5.4 Deaths from influenza and/or pneumonia

Parameters on deaths were based on three sources:

1. Death certificates, provided by the three Communities (Flanders, Wallonia and Brussels), based on ICD-10 CM codes J10-18, by age and season in 2000-07.
2. Hospital deaths from MCD dataset, by age, week or month and presence of co-morbidity, in 2000-07.
3. Literature search to assess excess mortality in pregnant women, persons with co-morbidities and HCWs.

Death certificates are the most complete source of deaths. MCD deaths only refer to patients deceased during an admission for influenza and/or pneumonia. MCD do not include deaths that occurred at home or in nursing homes, and the reason for admission is not necessarily the cause of death. On the death certificates, the potential causes of death are specified, but not all underlying illnesses are necessarily included amongst these. However, more details were available in the MCD dataset, such as the presence of co-morbidity and the week or month of admission. As there was a high level of overlap between the numbers of deaths from both data sources in all age groups <65 years and in all years, we used the MCD data to extrapolate deaths during the influenza seasons and deaths in co-morbidities.

3.6 PARAMETERS FOR VACCINE EFFECTIVENESS

The selection method for influenza vaccine effectiveness (IVE) parameters is fully described in Appendix 4. A summary is provided below.

A systematic literature review has been conducted and can be found in Appendix 5. However, not all retrieved studies were relevant for this study and we used the following selection criteria for the determination of IVE parameters:

1. Study design: we preferred randomized controlled trials (RCT), due to the high impact of confounders in observational studies. However, RCTs cannot be performed for ethical reasons in populations for which vaccination already is recommended.[7] We thus also included observational prospective studies that controlled for the major confounding factors (including the presence and severity of underlying diseases).
2. Outcome: we restricted ourselves to studies involving the outcomes of interest, as described above. For laboratory confirmed influenza, we only included studies that confirmed influenza based on culture and/or PCR, not by serology, to fit with the Belgian data. We only considered IVE against all influenza strains, not those limited to the cases that matched to the vaccine strains. We only included studies on ILI if the ILI definition was provided.
3. Period: as for the outcomes, we restricted to data covering the seasons 2000-09, moreover as higher intensity seasons usually result in higher IVE estimates. However, no IVE studies were available after 2000 for some specific outcomes, and we then retrieved studies pooling several seasons in the 1990-2000 period.
4. Setting: we restricted to studies conducted in the EU, US or Canada. The rationale was to limit the discrepancies in the prevalence of other seasonal pathogens causing ILI and pneumonia.
5. Population: we restricted to the selected target groups described above. Studies in the elderly were limited to the community-dwelling elderly, as we did not include nursing home settings in this study.
6. Intervention: we restricted studies to those using an inactivated trivalent vaccine (TIV). Adjuvanted, live attenuated vaccines and pandemic vaccine interventions were excluded. We restricted to studies comparing TIV intervention to a placebo or to no intervention.

We classified the retrieved IVE by season characteristics (matching and intensity), based on study reports, or surveillance reports from the same area when this was not mentioned in the study. When relevant (e.g. by type of season), IVE estimates from RCTs were pooled as risk ratios (RR) and 95% confidence intervals were calculated, using Review Manager 5. We used random-effects models to take into account the between-study variance in our findings, as there are uncontrollable systematic differences between trials regarding the circulating strains and the levels of immunity presented by different population in different settings. Influenza vaccine efficacy (IVE) was expressed as a percentage using the formula (depending on study design):

VE= 1-RR or VE=1-OR or VE=1-HR.

VE: vaccine effectiveness or efficacy
RR: risk ratio
OR: odd ratio
HR: hazard ratio

3.7 SENSITIVITY ANALYSIS

For all input parameters, confidence intervals are derived from the original study values (when these were available) or meta-analyses from these studies. We did not calculate confidence intervals for data covering the entire country (MCD and death certificates), as these represent total counts from the population. We used the normal approximation to the Binomial test to calculate 95% CI around proportions. We calculated the RR and their exact 95% confidence intervals assuming a Poisson distribution. P values were calculated by the Fisher exact test and two-sided p values <0.05 were considered statistically significant.

Uncertainty of the model results was assessed in Excel, using @Risk as an add-in software for probabilistic analyses, to take into account the uncertainties around the vaccine efficacy estimates and the number of ILI cases. With this software, probability distributions were defined for the uncertain variables, based on prior information about their frequency distribution (from the literature or from the datasets). Probability distributions for 5 different outcomes (impact influenza best, impact admissions best, impact deaths best, impact admissions worst, impact deaths worst) were computed by running 1000 Monte-Carlo simulations. With each Monte Carlo simulation, a random value is selected from each distribution and the results are calculated. Based on the results, the distribution of each outcome (mean and 95% confidence interval) can be defined.

The uncertainty for the vaccine efficacies was reflected by a normal distribution on the natural log (whose exponent is taken afterwards). The numbers of ILI cases were fitted with normal distributions (truncated to avoid negative values when needed), or with gamma distributions when the data appeared to be skewed. The type and characteristics of the distributions applied to those input variables are presented in Appendix 6.

In addition, we conducted univariate sensitivity analysis to assess the impact of making two types of corrections:

1. Considering the influenza burden in the community dwelling elderly only (excluding burden from the institutionalized);
2. Considering the influenza burden adjusted to reflect unvaccinated groups only (after extrapolation of for the burden prevented by the current vaccination).

3.8 ASSUMPTIONS USED

The method to estimate disease burden, population figures and IVE is based on certain assumptions. Table 5 describes the major assumptions, how they were verified and to which extent they proved to be correct, based on available data and current knowledge.

Table 5: Main assumptions used for the calculation of parameters and how they were tested

Assumptions	How to test it	Results and conclusion
Extrapolate number of ILI by age group from sentinel data		
Clients from sentinel GPs are representative of all GP clients	As proxy: all GPs have similar practice and profile	Data on sentinel GP: GPs have similar profile, except for a higher proportion of female, an under-representation of younger and older GPs, and higher use of computerized medical files.[45] GP clients had similar vaccination uptakes than general population.[46]
ILI incidence are homogenous within large adult age groups (15-64 years)	Compare to other Belgian data or to European data	Data from adults in UK, Spain and the Netherlands show comparable rates in this age group.[47, 48]
Extrapolate number of influenza by age group from sentinel data		
ILI cases reported and swabbed are similar and representative	Compare distribution for known variables	Similar distributions by region and age group in the 2 datasets (ILI reports and ILI swabbed), except for a lower proportion of swabbed children and elderly.
The proportion of influenza laboratory positive is homogenous within each age group	Compare proportion positive across age groups	Proportions are homogenous except in children: we stratified by <5 and 5-14 years
Extrapolate missing mortality data from Wallonia based on Flanders and Brussels		
The proportion of Belgian influenza and pneumonia deaths occurring in Wallonia remains similar across seasons	Compare these distribution with other mortality data	Numbers of deaths in 2004-06 correspond to the extrapolation; the proportion of deaths from Wallonia was similar in 2003 and 2004 (earlier data not available).
Extrapolate burden in HCW from general population		
Rates of ILI, influenza, admissions and deaths for P+I is comparable between HCW and the general population	Search the literature	Burden is similar, except for a lower occurrence of ILI and ARI in old GPs but a higher occurrence in young GPs
Efficacy and effectiveness		
Efficacy (measured in RCT) is similar to effectiveness in healthy adults[d]	Compare RCT IVE with those from observational studies	Values were similar
IVE estimated in 15-64 years with co-morbidity can be applied to children 1-14 years with co-morbidities	Compare IVE with those from studies in children with co-morbidities	Only one study comparing IVE in the <18 years and those 18-64 (no significant difference)[50]

IVE: Influenza vaccine effectiveness or efficacy. ILI: influenza-like illness.

[d] Using the classical WHO definition for efficacy and effectiveness,[49] and not those from Jefferson et al.[12, 13]

4 DETERMINATION OF PARAMETERS

4.1 DENOMINATORS

The 2008 numbers of persons by age group, with and without co-morbidities, and other target groups are provided in Table 6. Population figures by season were used for the calculation of rates. Data were received from the IPH (SPMA for population and HIS 2008 for the proportion of co-morbidities by age group). HCW data are based on the 2009 data provided by the INAMI/RIZIV, taking into account an estimated 82.4% active GPs from INAMI/RIZIV 2008 data.

Table 6: Population estimates for the different target groups, by co-morbidity status, in 2008

	Total	With co-morbidity*	Healthy*
0-4 years	595,442	45,254	550,188
5-14 years	1,203,650	72,219	1,131,431
15-49 years	5,032,259	407,613	4,624,646
50-64 years	1,979,457	320,672	1,658,785
65-74 years	919,531	245,515	674,016
75 years +	895,366	314,273	581,093
Pregnant women	121,362	NA	NA
HCW (active)	239,740	NA	NA
Total 1-64 years	8,810,808	835,406	7,965,050

*: HCW are also included in healthy adults and in persons with co-morbidities as no data were available to extract them.

4.2 INFLUENZA SEASONS

The timing, duration and characterization of the 9 Belgian activity seasons are provided in Table 7. It should be noted that the seasons are defined based on outpatient ILI cases, thus not necessarily reflecting the occurrence of severe (admitted) cases. Of the 9 influenza seasons over 2000-2009, none presented a high intensity but matching was good in 6/9 seasons.

Table 7: Influenza activity seasons in Belgium, 2000-09

Seasons	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09
Influenza activity (weeks)	45-14	49-17	2-17	43-6	48-14	3-18	52-13	48-17	47-18
Duration (weeks)	21	20	15	15	18	15	13	21	23
Intensity	low	medium	medium	medium	medium	low	medium	low	medium
Matching	good	good	good	poor	good	poor	good	relative	good

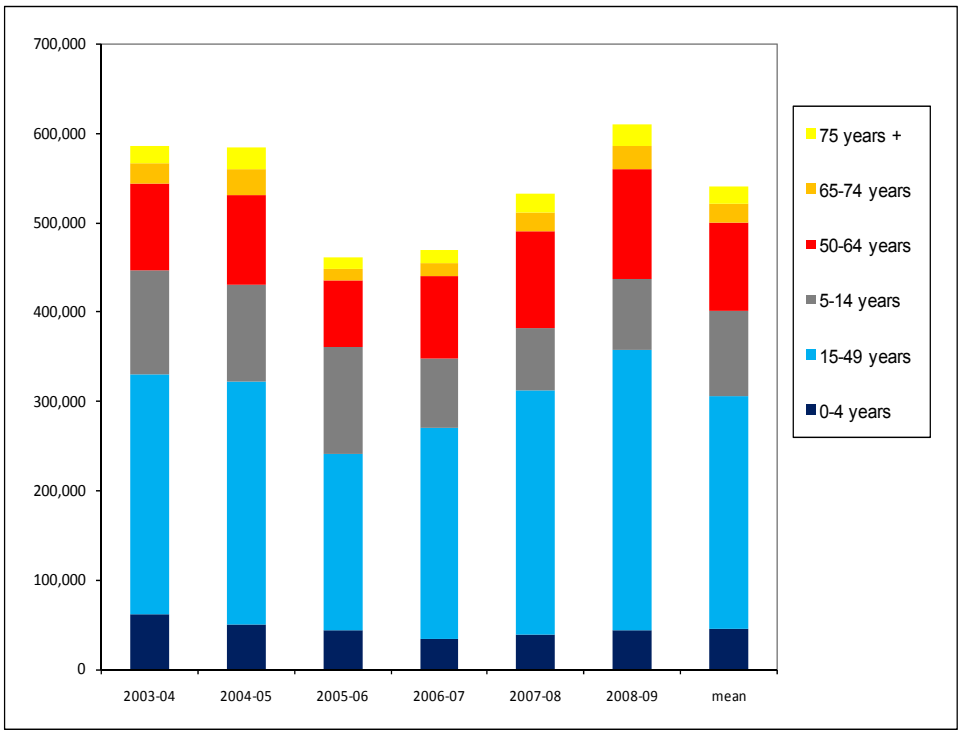
4.3 INFLUENZA BURDEN BY INFLUENZA SEASON

4.3.1 Outpatient cases of ILI and confirmed influenza

Number and description of ILI and laboratory confirmed ILI cases (further named "influenza cases") reported by the sentinel GPs over the 6 influenza seasons (i.e. week 40 to week 20) are described in details in Appendix 2 and summarized below.

The estimates of ILI and influenza cases consulting at GP offices in Belgium, by age group, are described in Figure 1 and Figure 2 respectively, and ILI seasonal variations are shown in Figure 3 and Figure 5.

Figure 1: Estimated ILI cases by age group and influenza season, 2003-04 to 2008-09 and season mean



The mean number by season amounts to an annual average of 540,890 ILI and 285,951 influenza cases. Influenza cases represent in average 53% of ILI cases, with the lowest proportion in the elderly aged 75+ (41%) and the highest in the school aged children (64% in the 5-14 years). Incidences of ILI and influenza (Table 8) are also systematically highest in children and lowest in the elderly. Overall, the number of ILI cases in the children 0-14 years of age, adult 15-64 years and the elderly ≥65 years represented 26%, 67% and 7% of all ILI cases, respectively. Similar age patterns are seen for influenza cases, though a difference is observed in children <5 years: the mean incidence rate in the <5 years is lower than in older children due to a lower proportion of influenza positive ILI in this group (48% in average). This is probably explained by the high rate of respiratory syncitial virus (RSV) causing ILI in young children.

Figure 2: Estimated influenza cases by age group and influenza season, 2003-04 to 2008-09 and season mean

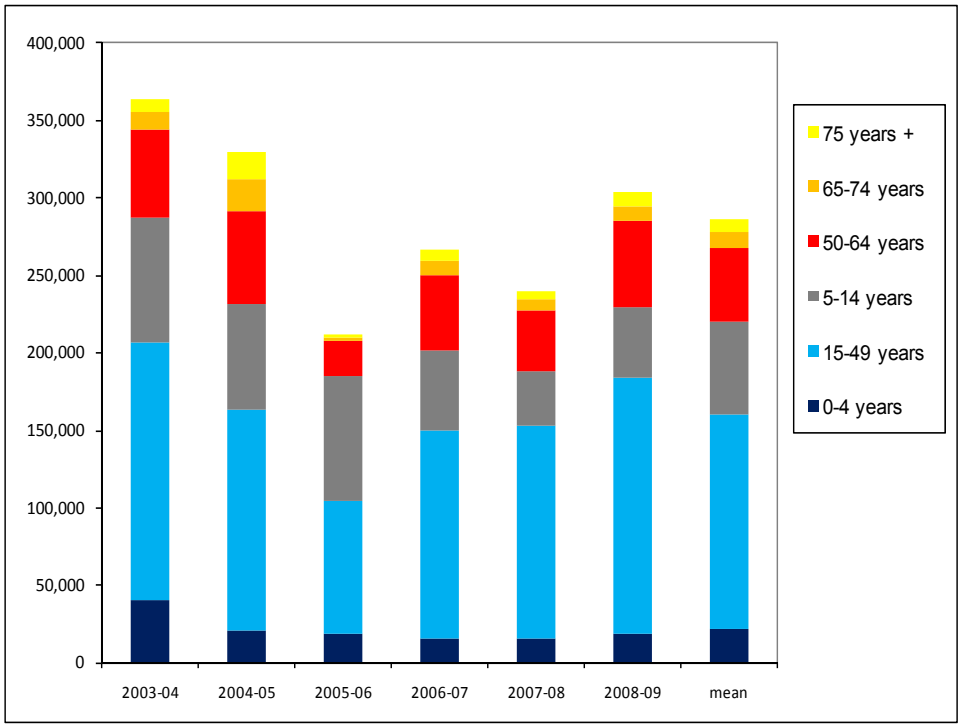


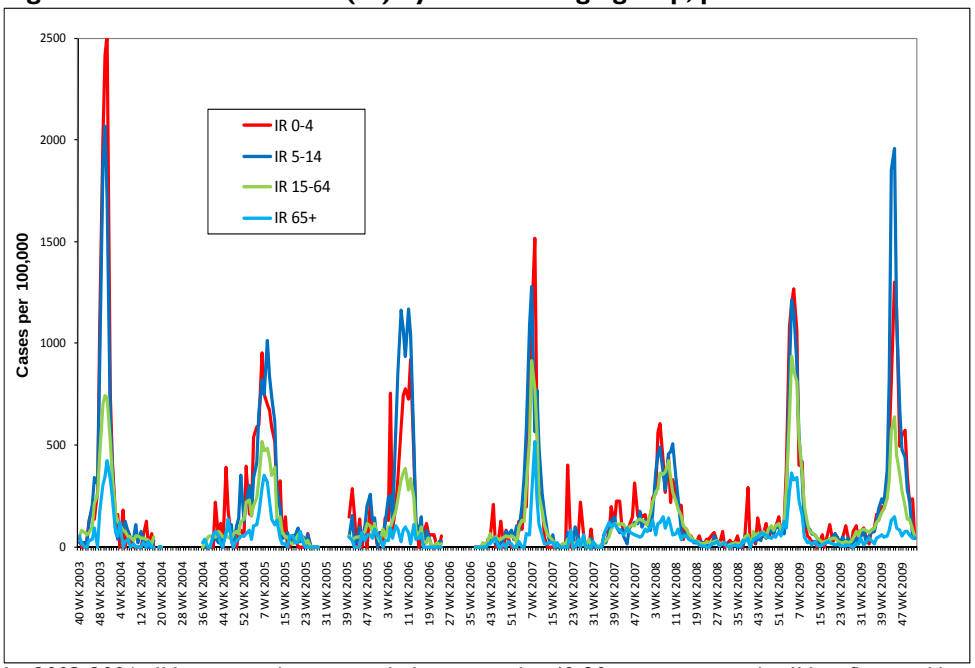
Table 8: Estimated incidence rate (per 1,000) of ILI and influenza cases over influenza seasons, mean of 2003-04 to 2008-09 seasons

Age group	ILI	Influenza
0-4 years	78.0	37.4
5-14 years	78.4	49.8
15-49 years	51.9	27.6
50-64 years	52.4	24.7
65-74 years	22.3	10.9
75 years +	22.6	9.4
Total	51.5	27.2

ILI: Influenza-like illness.

Figure 3 also shows that age-specific incidences varied across the seasons, according to the circulating virus characteristics. For instance, the highest influenza rate was observed in the <5 years in 2003-04 (71.2 per 1000), when the new A Fujian variant was predominating, and represented the double of the incidence observed in the other seasons in this group (30.8 per 1000).

Figure 3: ILI incidence rate (IR) by week and age group, period 2003-09



In 2003-2006, ILI were only reported during weeks 40-20 approximatively. ILI: influenza like illness.

A wide literature review did not show evidence of significantly higher or lower baseline ILI and influenza rate in the three specific groups (persons with co-morbidity, pregnant women and HCWs). There were however 2 exceptions:

- In the pregnant women with co-morbidity, the rate of physician visits for acute respiratory infections were 20% more frequent in their 3rd trimester than in the year before pregnancy (relative risk [RR]: 1.2; 95% CI 1.1-1.4).[51] However, acute respiratory infections are not an outcome of this study, and pregnancy in itself is already increasing the rate of consultations – and certainly if they also have co-morbidities.
- In Belgian GPs, an overall higher level of immunity against circulating influenza viruses (based on serological levels) has been observed in the unvaccinated group during 2 seasons (80% and 42% in 2002 and 2003, respectively).[52, 53] However, the situation of GPs cannot be extrapolated to all HCW.[54] Likewise, a multivariate analysis of a German cohort of HCWs showed that these were not at higher risk of serologically-confirmed ILI than the non-HCWs (RR=1.09; p=0.70). HCWs were less susceptible to the previous and current influenza viruses than non-HCWs. Interestingly, household contact with children was the main significant risk factor for influenza confirmed cases in two studies.[53, 55]

We did not find prospective studies comparing the incidence of ILI or laboratory confirmed influenza in persons with co-morbidities to those in persons without co-morbidities, except in children with asthma. Most studies that were found showed an increased risk of developing clinical complications post-influenza in this group, but this is reflected in the section "Hospitalizations".[56, 57] In the General Practice Research Database (UK), a population based study showed a slightly higher prevalence of chronic diseases in patients with a diagnose of ILI than in controls. The risk was particularly increased for subjects with respiratory conditions. But no incidence assessment was provided for these groups.[57]

Because the literature did not show a consistent relative excess in ILI and influenza rates in these groups, we based estimates in these specific groups on the ILI and influenza incidence rates in the same age group (Table 9). For the outcomes in HCW, we applied all season incidence rates (in the 15-64 years of age, as no data are available on the 20-64 years) to the 2008 denominator. As the proportion of persons with co-morbidities by age is only available for 2008 (HIS 2008), we assumed that this proportion was similar over the last 6 seasons (2003-04 to 2008-09) and computed the numbers accordingly.

Table 9: Estimated numbers of ILI and influenza in HCW, pregnant women and persons with co-morbidities (mean of 2003-04 to 2008-09 seasons)

Group	ILI	Influenza
HCW (15-64 years)	12,467	6,425
Pregnant (15-49 years)	6,106	3,243
Co-morbidities <65 years:	46,382	24,099
0-4 years	3,456	1,659
5-14 years	5,716	3,632
15-49 years	21,067	11,204
50-64 years	16,143	7,604

ILI: Influenza like illness.

4.3.2 Admissions for influenza and pneumonia

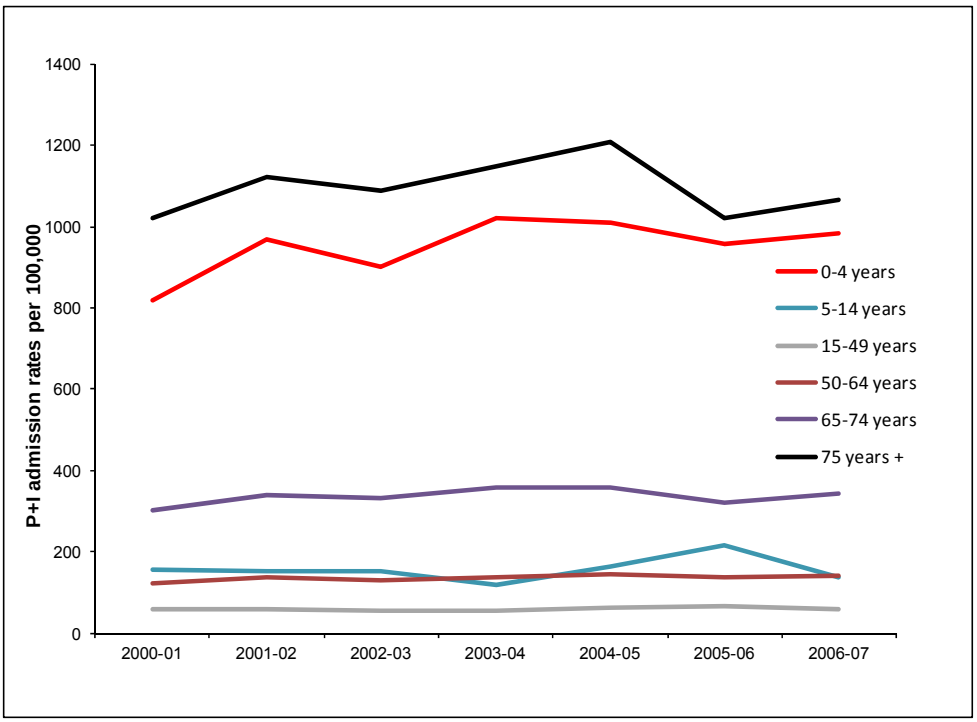
4.3.2.1 Admissions by age group

The number of influenza and pneumonia admissions in influenza seasons, main diagnosis, by age group, is presented in Table 10, and admission rates for P+I are presented in Figure 4. Influenza as main diagnosis represents 57% of all admissions with a code influenza, and pneumonia as main diagnosis represents 53% of all pneumonia admissions. This proportion tends to decrease with age, likely due to a higher rate of complications in older ages - that may appear as main diagnosis.

Table 10: Number of MCD admissions for influenza and pneumonia (main diagnosis) by age group and influenza season, 2000-07

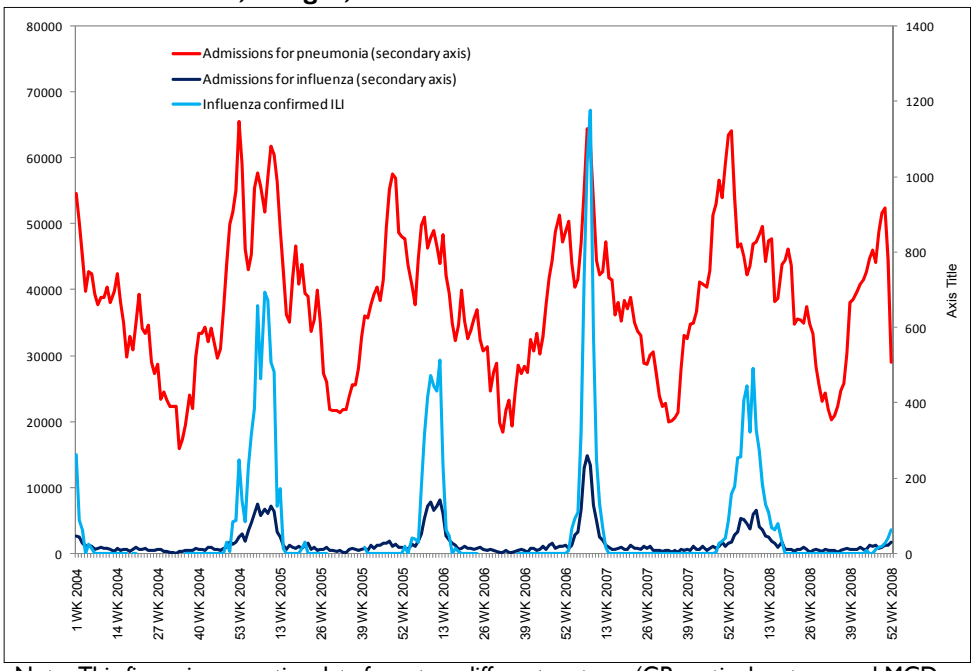
Epidemic season	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Mean
Influenza admissions (main)								
0-4 years	180	735	270	595	514	505	685	498
5-14 years	227	360	299	189	291	426	262	293
15-49 years	317	475	333	378	375	362	392	376
50-64 years	56	149	70	104	107	78	106	96
65-74 years	44	104	48	102	92	50	72	73
75 years +	71	229	91	195	204	83	160	148
Total	895	2,052	1,111	1,563	1,583	1,504	1,677	1,484
Pneumonia admissions (main)								
0-4 years	4,551	4,846	4,907	5,248	5,265	5,017	5,069	4,986
5-14 years	1,680	1,526	1,601	1,295	1,728	2,204	1,412	1,635
15-49 years	2,565	2,558	2,538	2,440	2,825	3,029	2,532	2,641
50-64 years	2,045	2,250	2,240	2,387	2,573	2,542	2,589	2,375
65-74 years	2,894	3,178	3,168	3,382	3,373	3,034	3,142	3,167
75 years +	7,540	8,383	8,481	9,029	9,731	8,566	9,121	8,693
Total	21,275	22,741	22,935	23,781	25,495	24,392	23,865	23,498

Figure 4: Admission rates for influenza and pneumonia (main diagnosis) by age group and influenza season, 2000-07



Overall, the number of influenza admissions per season is low (range 895-2,052 by influenza season) but varies widely across seasons. The season with the maximum number of cases also varies with age – reflecting the age specific pathogenicity of influenza strains. Again, the highest admission rates are consistently reported in children less than 5 years, followed by the 5-14 years and the elderly above 75 years of age. In the period 2004-08 (in which the week of admission could be computed), the weekly distribution of influenza admissions is closely correlated to the distribution of influenza outpatient cases (Figure 5) and confirms the high variability of influenza across seasons.

Figure 5: Weekly number of admissions for influenza and pneumonia, GP visits for influenza, all ages, 2003-08



Note: This figure is presenting data from two different systems (GP sentinel systems and MCD hospital admissions).

The number of pneumonia admissions is much higher (exceeding 20,000/season) as all microbiological aetiologies are included – resulting in a low specificity for influenza. Numbers of admissions show mild variations across seasons. Trends over time do not indicate any impact of the conjugate pneumococcal vaccination, but this vaccine was only included in January 2007 in the infant vaccination schedule. Pneumonia admission rates are highest in the two extremes of life, with a mean around 10/1000 in the ≥75 years and the <5 years, followed by the 65-74 years. The pneumonia admissions also show a marked seasonal pattern whose peak lasts largely longer than the influenza season (Figure 5). Indeed, 62% of annual pneumonia admissions occurred during the influenza season compared to 85% of annual influenza admissions, as pneumonia are caused by many other pathogens. MCD data provide little information on causing pathogens because 65% of pneumonia admissions are coded as bronchopneumonia or pneumonia with organism unspecified.

4.3.2.2 Admission by co-morbidity status

More than half of P+I admissions are reported in persons with co-morbidities. This proportion represents only 20% for influenza but 55% for pneumonia admissions, and increases with age (Table 11 and Figure 6). In the elderly (65+), a majority of admissions for pneumonia and influenza (60-85%) are among patients with co-morbidities, while the proportion of all persons ≥75 years having reported at least one co-morbidity was 35% in 2008 (HIS 2008).

Table 11: Number of influenza and pneumonia admissions by co-morbidity status and age group, by influenza season (mean 2000-01 to 2006-07)

	Influenza			Pneumonia		
	Comorbidities[1]		% co-morbidity in admissions	Comorbidities[1]		% co-morbidity in admissions
	Yes	No		Yes	No	
0-4 years	22	475	4%	318	4668	6%
5-14 years	20	274	7%	186	1450	11%
15-49 years	53	323	14%	884	1757	33%
50-64 years	53	52	50%	1,604	771	68%
65-74 years	44	30	60%	2,578	589	81%
75+	107	41	72%	7,403	1,290	85%
Total	298	1195	20%	12,973	10,525	55%

1: Co-morbidities as defined in the recommendations for influenza vaccination in Belgium: all patients with a underlying chronic disease, even stabilized, involving lungs, heart, kidney, liver or metabolic and immune disorders, defined in ICD codes.

The admission rates in patient with and without co-morbidity are shown over 3 influenza seasons (2004-05 to 2006-07) because only recent denominator data are available for this group. Admissions rates and the relative risk (RR) of admission in persons with co-morbidity compared to those without co-morbidity is presented in Table 12. In average, persons with co-morbidity have a 8-fold higher risk of admission for P+I, and the RR increases with age.

The few published studies including the same co-morbidities and outcomes generally found lower RRs in adults. Irwin estimated a RR for influenza admissions in all co-morbidities of all ages at 5.5 compared to 1.6 for influenza admission in MCD data, but few patients were >65 years of age.[56] Nichol showed an adjusted OR for influenza and pneumonia admissions in the elderly (>65 years) at 3.3 (95% CI 2.8-3.9) for "high risk" co-morbidities (heart or lung disease) and 1.6 (95% CI 1.2-2.0) for "intermediate risk" co-morbidities (diabetes, renal disease etc.).[58] One reason of the higher RR in our study may be an underestimation of the Belgian denominator for persons with co-morbidities (and thus over-estimation of incidence).

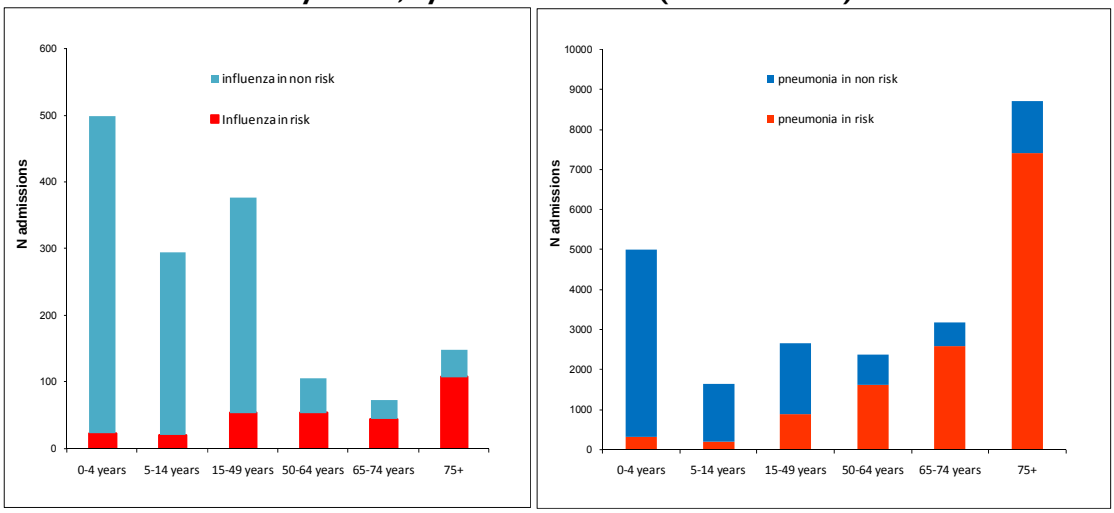
However, since outcomes, population, influenza seasons and vaccine uptake in the literature differed from our study, we decided to use the MCD data for parameters on admissions in persons with co-morbidities.

Table 12: Admission rates (per 100,000) for influenza and pneumonia in persons with and without co-morbidity by large age group, mean of 3 influenza seasons (2004-05 to 2006-07)

	Influenza		Pneumonia		P+I		
	Co-morbidity		Co-morbidity		Co-morbidity		RR (95% CI)
	No	Yes	No	Yes	No	Yes	
0-14 years	50.4	40.4	377.0	482.8	427.4	523.2	1.2 (1.17-1.28)
15-49 years	7.0	13.2	41.0	223.4	48.0	236.6	4.9 (4.7-5.1)
50-64 years	3.2	17.6	50.9	572.3	54.1	589.9	10.9 (10.5-11.3)
65+	5.0	28.6	140.1	1,913.0	145.0	1,941.6	13.4 (13.1-13.7)
Total	14.0	22.6	117.9	998.8	131.9	1,021.5	7.7 (7.7-7.8)

P+I: Pneumonia and influenza. RR: Relative risk. Only admission rates for these 3 seasons are reported here because we have no estimation on the number of persons with co-morbidity before this period.

Figure 6: Number of influenza and pneumonia admissions by age group and co-morbidity status, by influenza season (mean 2000-07)



4.3.2.3 *Admissions in pregnant women and their infants*

The MCD dataset received does not allow the identification of pregnancy status. The literature review showed an excess in respiratory admissions during pregnancy, but evidence was unclear and sometimes conflictual. Overall, a significantly higher risk of admissions related to seasonal influenza was found in healthy women in the second half of pregnancy, and earlier among women with co-morbidities, but the same trend was observed for admissions outside influenza periods.[21, 51, 59, 60] However, most studies compared the risk of influenza admissions in pregnant women to the risk in non pregnant (e.g. same women, previous year), while pregnancy in itself already increases the overall rate of admission. Other studies compared the risk of admissions in influenza seasons compared to non-influenza seasons. In a US cohort study, Black et al found a very low rate of P+I admissions in pregnant women, even lower than the Belgian admission rate in the 15-49 years (18.2 vs. 31/100,000 in Belgium).[61] A recent review concluded that there is no evidence for significantly higher risk of admissions due to seasonal influenza for the healthy woman in early pregnancy; the admission rate in these women appears not significantly different from that of other healthy young adults.[21]

However, a substantial excess of admissions was described in the H1N1 2009 pandemic influenza and this strain is expected to circulate the next influenza seasons. No Belgian data are available, but data from the CDC surveillance showed an excess of admission rates in pregnant women with confirmed or probable H1N1 influenza, compared to the general population (RR=4.3, 95% CI 2.3-7.8).[62] However, US data may not be completely applicable to the Belgian context; for instance, obesity was an important risk factor and has a different prevalence in Belgium compared to the US.

The number of admissions in infants <6 months (potentially protected by mother vaccination) was not available for this study – and imprecise data on infants <1 years did not allow for possible extrapolation. We could thus not address the indirect protection from vaccinated mothers to their infant.

As estimates in pregnant women are not available for Belgium, we opted for 2 parameters (Table 13):

1. High case: similar admissions rate as during the 2009 H1N1 pandemic in the US;
2. Low case: same admission rate as in the 15-49 years.

Table 13: Estimated numbers of influenza and pneumonia admissions in pregnant women by season, two scenarios

	Study	Criteria	Rate for Belgium	Estimated nbr admissions by season
Low case	Belgian MCD data by age group	Based on admission rates for 15-49 yrs	60.3/100,000	73
High case	Jamieson 2009 on H1N1 and Belgian MCD data[62]	Belgian P+I admission rates 15-49 yrs and RR=4.3 for influenza admissions vs. rates in general population	85.2/100,000	103

4.3.2.4 Admissions in HCWs

No study reported on the relative risk of admissions for influenza and pneumonia in HCWs. However, HCWs are not at higher risk of serologically-confirmed ILI than non-HCWs and seem even better protected against influenza.[52, 55, 63] We thus assumed that HCWs have the same rate of P+I admissions as the general population of the same age (Table 14). We applied incidence rates to the 2008 denominator.

Table 14: Estimated number of influenza and pneumonia admissions in HCWs by influenza season

Total number HCW	Rate in Belgium	Estimated nr admissions P+I	Comments
239.740	80.4	193	Based on rate in 15-64 years

P + I: Pneumonia and influenza. HCW: Health care worker.

4.3.3 Deaths from influenza and pneumonia

4.3.3.1 Deaths by age group

Total numbers of deaths from influenza and pneumonia in influenza seasons, by age group (Table 15), are calculated by applying the proportions of MCD annual deaths (week 40 to week 39) that occurred during influenza seasons (week 40 to week 20) to the annual data from death certificates. The proportions of annual deaths that occurred during influenza seasons were in average 87% for influenza and 66% for pneumonia deaths, and were relatively homogenous across seasons and age group.

Table 15: Number of influenza and pneumonia deaths by age and influenza season

	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Mean
Influenza deaths (main)								
0-4 years	0	0	0	0	0	0	0	0
5-14 years	0	0	0	0	0	0	0	0
15-49 years	2	2	2	1	2	0	1	1
50-64 years	1	4	0	1	3	0	1	1
65-74 years	0	24	11	10	6	2	9	9
75 years +	51	141	34	125	151	34	106	92
Total	54	171	47	136	162	36	117	103
Pneumonia deaths (main)								
0-4 years	1	2	2	1	2	2	2	2
5-14 years	0	0	2	1	2	0	0	1
15-49 years	31	32	34	22	29	34	32	30
50-64 years	81	97	107	86	113	93	83	94
65-74 years	264	266	282	264	291	235	195	257
75 years +	2,180	2,267	2,385	2,418	2,576	2,361	2,051	2,319
Total	2,557	2,663	2,812	2,792	3,013	2,725	2,363	2,704

The majority of these influenza and pneumonia deaths are found in the elderly (97% and 95%, respectively, in the ≥ 65 years). Influenza deaths only represent 4% of all P+I deaths. Mean death rates by age show very high rates in the elderly, as expected, particularly in those ≥ 75 years (Table 16). Rates largely vary by season for influenza, but are relatively stable across seasons for pneumonia (Appendix 2: results on Influenza disease burden, Table 50). Published studies have shown that institutionalized elderly have higher risk of death from influenza and pneumonia, but we could not stratify data by residence status. However, we assessed the impact of this limitation in the sensitivity analysis.

Table 16: Death rates (per 100,000) for influenza and pneumonia, by age, in an influenza season (mean seasons 2000-01 to 2006-07)

Age group	Influenza	Pneumonia	P+I
0-4 years	0.0	0.3	0.3
5-14 years	0.0	0.1	0.1
15-49 years	0.0	0.6	0.6
50-64 years	0.1	5.2	5.3
65-74 years	0.9	26.7	27.6
75 years +	11.4	287.5	298.9
Total	1.0	26.0	27.0

P + I: Pneumonia and influenza.

4.3.3.2 Deaths by co-morbidity status

The numbers of deaths estimated by co-morbidity status and age group, occurring during an influenza season, is described in Table 17. Co-morbid patients accounted for 86% of influenza deaths and 86% of pneumonia deaths. For pneumonia, this proportion tended to increase with older age.

Table 17: Estimated deaths from influenza and pneumonia by co-morbidity status and age, in an influenza season (mean 2000-01 to 2006-07)

	Influenza			Pneumonia		
	Comorbidities[1]		% co-morbidity in admissions	Comorbidities[1]		% co-morbidity in admissions
	Yes	No		Yes	No	
0-4 years	0	0	NA	1	1	53%
5-14 years	0	0	NA	0	0	32%
15-49 years	1	0	100%	21	10	69%
50-64 years	1	0	100%	74	20	79%
65-74 years	7	2	80%	219	38	85%
75+	78	13	86%	2005	315	86%
Total	88	15	86%	2320	384	86%

1: Co-morbidities as defined in the recommendations for influenza vaccination in Belgium: all patients with a underlying chronic disease, even stabilized, involving lungs, heart, kidney, liver or metabolic and immune disorders. Defined in ICD codes in Appendix 1.

Death rates in persons with and without co-morbidity are presented in Table 18, together with the relative risk (RR) of death in persons with co-morbidities compared to those without co-morbidities, over three epidemic seasons (2004-05 to 2006-07). The RR were the highest in children <15 years but only 2 deaths were recorded in this age group in average, and the 95% CI is thus large. All RR were very high and highly statistically significant (except in the 5-14 years in which the RR could not be computed as there were no death in children with co-morbidity).

Table 18: Death rates (per 100,000) for influenza and pneumonia by co-morbidity status and age, in an influenza season (mean 2004-05 to 2006-07)

	Influenza		Pneumonia		P+I		
	Comorbidity		Comorbidity		Comorbidity		RR P+I (95% CI)
	Yes	No	Yes	No	Yes	No	
0-4 years	0.0	0.0	3.3	0.1	3.3	0.1	43.6 (12.1-157.1)
5-14 years	0.0	0.0	0.0	0.1	0.0	0.1	NA
15-49 years	0.2	0.0	5.4	0.2	5.7	0.2	26.9 (20.2-35.8)
50-64 years	0.4	0.0	26.2	1.2	26.6	1.2	22.7 (18.6-27.8)
65-74 years	2.1	0.0	80.2	4.9	82.4	4.9	16.8 (14.4-19.5)
75 years +	33.5	0.0	714.9	46.6	748.4	46.6	16.1 (15.2-17.0)
Total	7.7	0.0	173.9	3.5	181.6	3.5	51.2 (49.4-53.2)

P + I: Pneumonia and influenza. RR: Relative risk.

These RR were compared to those found in published studies using comparable outcomes (deaths from influenza and pneumonia, ICD code), see Table 53 in Appendix. All published studies showed lower associations between co-morbidity status and risk of deaths from pneumonia or/and influenza (range relative risk [RR] or odd ratio [OR] 2.2 – 15.6) than in our Belgian analysis. However, these studies are older, those using the same outcome only involved patients with diabetes (with a relatively low risk of

complications), and none of these studies involved persons with "any co-morbidity". For this reason, it was decided to consider two scenarios for the parameters:

1. One high/best case based on Belgian data;
2. One low/worst case based on risk in diabetes, applying RR/OR from published studies to admission rates in healthy adults, by age group (Table 19).

Table 19: Estimated number of deaths from influenza and pneumonia in persons with co-morbidities 1-64 years of age, by influenza season

Scenario	Criteria used	Estimated nb deaths / season	Comments
Low case: Based on studies on diabetes	RR=4.0 in 25-64 years Rate 0.39/100,000	18	RR applied to MCD rates in healthy, by age group
High case: Belgian data (mean)	MCD crude data in Belgium	99 mean (range 83-115)	MCD data

RR: Relative risk. MCD: Minimal Clinical Dataset.

4.3.3.3 Deaths during pregnancy

Based on an extensive literature review, we found that no robust data showed an excess of mortality associated with seasonal influenza during pregnancy. However, mortality excess was shown with the H1N1 2009 pandemic influenza, and this strain is circulating in the following influenza season. The most recent CDC study reported 30 deaths on 692 reported pregnant women (4.3%) with mortality outcome known.[64] However, 39% of these deaths were among obese women. We thus also opted for 2 scenarios (Table 20):

1. High case: same death rate as during the 2009 H1N1 pandemic. As Belgian data are not available, we used US data on the proportion of pregnant with influenza H1N1 who died. This is likely to represent a more severe situation than what occurred in Belgium, due a higher prevalence of obese pregnant women in the US compared to Belgium;
2. Low case: same death rate as in the 15-49 years.

Table 20: Estimated number of influenza and pneumonia deaths (mean) in pregnant women and HCW by influenza season

Group	Population (2008)	Death rate by 100,000	Estimated nbr deaths / season	Comments
Pregnant low case	121,500	P+I: 0.6	0.8	Based on rate 15-49 years
Pregnant high case	121,500	4.3% deaths in all influenza cases	144	Applying case fatality ratio from H1N1 in US pregnant women to influenza rates in BE
HCW	239,740	P+I: 1.8	4.4	Based on rate in 15-64 years

P + I: Pneumonia and influenza.

4.3.3.4 Deaths in HCW

As the literature review did not show an increased risk of dying from respiratory diseases among HCWs, we applied the mortality rate in the 15-64 years to the number of HCWs in 2008. The estimated number of deaths from influenza and pneumonia is provided in Table 20.

4.4 INFLUENZA BURDEN DURING VIRAL ACTIVITY SEASONS

The number of outcomes that occurred during the more specific seasons of viral activity (i.e. limited to the period when the influenza virus is circulating) is described in Table 21. The proportion of outcomes occurred during influenza seasons (week 40 to week 20) that also occurred during activity seasons represent for all ages 87%, 95%, 84% and 94% of ILI, influenza outpatient cases, influenza admissions and deaths from influenza, respectively. As expected, the majority of influenza outpatient cases and influenza deaths occurred during this period. Surprisingly, 16% of influenza admissions occurred outside the activity season: as illustrated in Figure 7 many influenza admissions (red line) occurred outside the influenza activity period (black line). This could be due to late complications of influenza infections, to sporadic and imported cases, or to wrong coding of influenza, but we could not investigate this issue. As expected, smaller proportions of pneumonia admissions and pneumonia deaths were found in this period (62% and 64%, respectively), as these are more frequently caused by other pathogens. These proportions did not vary substantially across age groups and seasons (see further details in Appendix 2).

Table 21: Number of outcomes that occurred during activity seasons, by age group (mean of seasons)

	Outpatient		Admissions		Deaths	
	ILI	Influenza	influenza	pneumonia	influenza	pneumonia
0-4 years	39,949	20,794	438	2,955	0	1
5-14 years	86,767	57,780	255	1,041	0	1
15-49 years	224,832	131,039	295	1,610	1	20
50-64 years	86,230	45,770	76	1,438	1	58
65-74 years	17,102	9,183	58	1,955	9	161
75 years +	15,746	7,820	126	5,557	84	1,489
Total	470,626	272,385	1,248	14,556	96	1,729

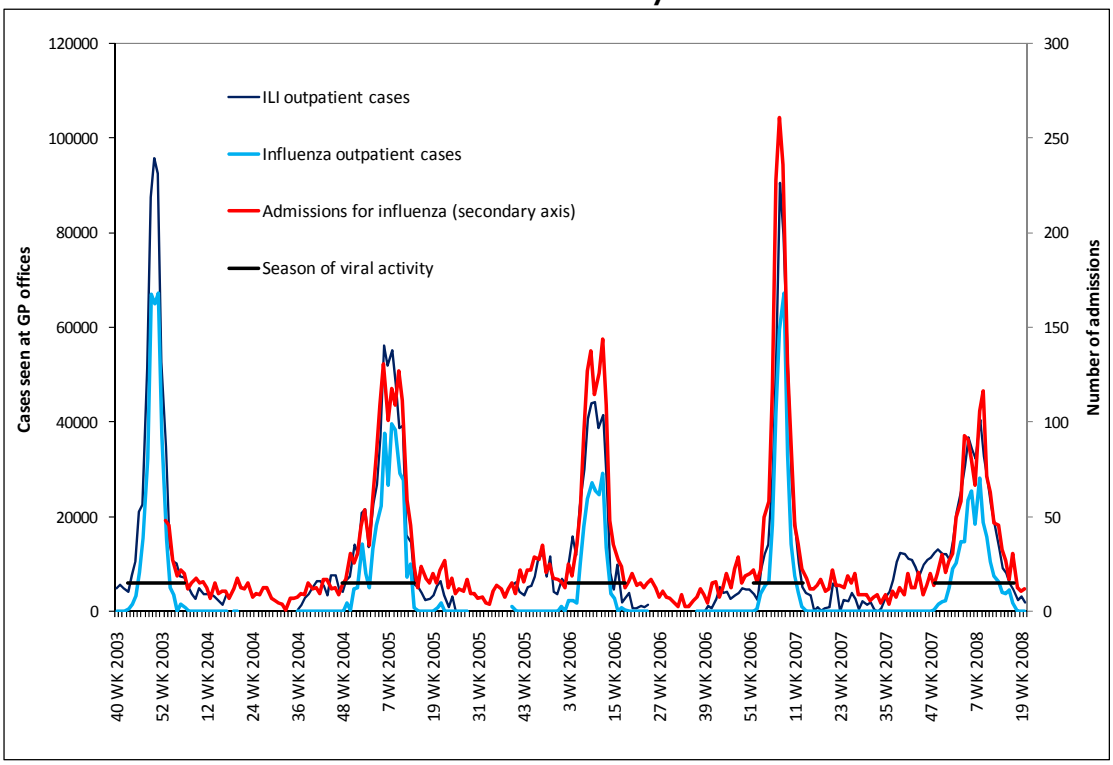
ILI: Influenza like illness.

Table 22: Number of outcomes that occurred during the activity seasons in specific groups (mean of seasons)

	ILI outpatient	Influenza outpatient	Admissions P+I	Deaths P+I
HCW	10,779	6,191	120	2.8
Pregnant women	5,279	3,075	46 (low case) 70 (high case)	0.5
Co-morbidities <65 years	40,423	23,076	1,883	62.7

ILI: Influenza like illness. P+ I: Pneumonia and influenza. HCW: Health care worker.

Figure 7: Weekly number of outpatient cases of ILI and influenza, admissions for influenza and duration of viral activity season



4.5 INFLUENZA VACCINE EFFECTIVENESS (IVE)

Further details are provided in Appendix 4 and 5.

Several Cochrane systematic reviews have been published on influenza vaccine efficacy (IVE) in different groups, covering healthy adults,[13] the elderly,[12] persons with chronic lung disease,[9-11, 65] and health care workers working with the elderly.[14]

However, these reviews have many limitations for the determination of IVE parameters for this model: they included many primary studies involving other vaccines than the classical TIV currently used in Belgium (e.g. live aerosol or adjuvanted vaccines),[13] other outcomes,[12, 13] or not adjusting for important confounders;[12, 13] they missed a number of eligible studies in their search;[66-70] they included mostly old studies, dating from periods with higher intensity and tended thus to overestimate IVE;[12, 13] some reviews pooled IVE from adjuvanted vaccines with TIV, some meta-analyses pooled different outcomes and populations;[12] and a last update drastically changed the conclusions though the 2 new studies did not change substantially the main effect measures.[13, 71]

For these reasons, the results of the Cochrane meta-analyses are not used to inform our parameter estimates. Primary studies included in Cochrane reviews and fitting with selection criteria (see Methodology) were retrieved, and additional literature searches were conducted to identify primary studies involving efficacy and effectiveness data collected from 2000 onwards in these groups.

4.5.1 IVE parameters in healthy adults (15-64 years)

IVE parameters are summarized in Table 23 and Table 24, and further described in the next sections.

Table 23: IVE parameters for influenza in healthy adults (95% CI)

		Intensity		
		Medium and high	**Low**	**Total**
Match	**Good**	62% (47-72%) Best case	45% (18-63%)	56% (43-65%)
	Relative	70% (55-80%)	NA	Not calculated
	Poor	NA	Not defined (NS)	Not calculated
	Total (pooled)	65% (55-73%)	39% (15-56%)	NA
	Best case			62% (47-72%)
	Worst case			Not defined (NS)

NS: Non statistically significant.

Table 24: IVE parameters for admissions and deaths from pneumonia and influenza in healthy adults

Outcome	Age group	IVE estimate	95% CI
Admissions	15-64 years	12.4%	1.6-22.0%
Deaths	15-64 years	Best case: 12.4%	1.6-22.0%
	15-64 years	Worst case: 0%	NA

4.5.1.1 ILI and influenza laboratory confirmed ILI

Data on VE for (not laboratory confirmed) ILI were heterogeneous, likely depending on the epidemiology of concomitant aetiologies of ILI, and were mostly not statistically significant - or statistics were not clear.[72-74] In addition, the studies involving also laboratory confirmed ILI had a much lower proportion of positive than seen in Belgian ILI data (13% vs. 57% in Belgium[72] and 6% vs. 44% in Belgium for similar seasons)[73]. This may be due to the differences in case definitions and swabbing criteria; the Belgian case definition is more specific as it includes sudden onset and fever as clinical criteria, as opposed to more sensitive definitions form these studies. As ILI are thus not comparable between Belgian data and published IVE for ILI, we decided to include in the model only IVE for influenza.

Six eligible RCTs measured IVE for influenza in healthy adults.[66-68, 72-74] The range of IVE estimates was wide (16-75%). We categorized results by study seasons (matching and intensity),[e] but we pooled high and medium intensity seasons because IVE were very similar (62-75% and overlapping 95% CI), and the distinction between high and medium season was not very specific. After categorization, no heterogeneity in IVE was detected, and a minimum of 1800 subjects was included in each category. As expected, pooled IVE estimates by type of season (Table 25) show higher values in good matching seasons (56%) compared to poor matching seasons (22%, non significant) and higher values in high/medium intensity seasons (65%) compared to low intensity (39%). Table 23 shows the IVE estimates by season category, used as parameters. These estimates fit relatively well with the IVE estimated by recent adjusted case-control studies, although these involved all adults (with and without co-morbidities), see appendix 4.[75-80]

For the best case scenario, we selected the IVE estimated in a season with good matching and high intensity (62%); as the IVE in seasons of poor matching and low intensity was non significant, we did not estimate the number of influenza cases prevented in the worst case scenario.

[e] Characteristics of season were described in studies, based on population surveillance (not on placebo group), or retrieved from national surveillance data.

Table 25: Pooled IVE estimates for influenza by season characteristic

Season characteristics	N subjects	Pooled IVE (95% CI)
High/medium intensity, any matching[66, 67, 72]	9,518	65% (55-73%)
Low intensity, any matching[68, 73, 74]	14,893	39% (15-56%)
Good match, any intensity[68, 72, 74]	16,342	56% (43-65%)
Poor match, any intensity[73]	6,203	22% (-40 to 57%), NS
High/medium season and good match[72]	7,652	62% (47-72%)
High/medium season and relative match[66, 67]	1,866	70% (55-80%)
Low season and good match[68, 74]	8,690	45% (18-63%)
Low season and poor match[73]	6,203	22% (-40 to 57%), NS

NS: Non significant. IVE: Influenza vaccine effectiveness/efficacy.

4.5.1.2 Admissions for influenza and pneumonia

Very few studies have evaluated IVE for this outcome because it is rarely observed in healthy adults. Only one eligible observational study (a US adjusted cohort) involved admissions for influenza and pneumonia, using the same ICD codes, and estimated it at 12.4% in healthy adults aged 50-64 years over 10 influenza seasons (1997-2007), Table 26.[81] This study used an additional method for adjusting for unknown confounders ("difference of difference") and only covered adults ≥50 years of age. Though differences in health care settings may bias measures of IVE, this IVE estimate is consistent with those from other studies that involved related outcomes or were older (15% for community acquired pneumonia admissions and 11% for respiratory admissions by pooling of 4 older studies),[13, 69] but they were not significant, likely due to the very low number of admissions in healthy adults.

4.5.1.3 Deaths from influenza and pneumonia

No eligible study involved mortality outcomes in this group, which is likely due to the very low mortality from P+I in healthy adults (28 deaths by epidemic season in Belgium). Two scenarios were thus considered: one best case, with the same IVE than measured against P+I admissions (12.4%), assuming that the ratio death/admission is similar among admissions prevented or not; and one worst case with IVE considered to be 0%.

4.5.2 IVE parameters in elderly (65 years and above)

Altogether, one RCT, 5 adjusted cohort studies and a pooled analysis of 5 recent case-control studies were eligible.[81-87] Results are summarized in Table 26 and described below by outcome.

Table 26: IVE parameters in the elderly, by age, co-morbidity status and outcome

Outcome	Age group	All	No co-morbidity	Co-morbidity
Influenza[87]	All 65+	59.1% (15-80%)	59.1% (15-80%)	59.1% (15-80%)
Influenza[87]	65-74	65.4% (16-86%)	65.4% (16-86%)	65.4% (16-86%)
Influenza[87]	75+	59.6% (-73-91%)		
Admissions for P+I[88]	All 65+	27% (23-32%)	27% (23-32%)	27% (23-32%)
Admissions for P+I[88]	65-74	27% (23-32%)	27% (23-32%)	27% (23-32%)
Admissions for P+I[88]	75+	27% (23-32%)		
Deaths from P+I[85]	All 65+	12% (8-16%)		
Deaths from P+I[85]	65-74	NA	21%* (11-29%)	29%* (22-34%)
Deaths from P+I[85]	75+	Not significant Best case: 12% (8-16%) Worst case: 0%		

* Based on 65-84 years by lack of other data. P+I: pneumonia and influenza. NA: Non available.

4.5.2.1 ILI and influenza laboratory confirmed ILI

Two studies were eligible, one pooled analysis of 5 recent case-control studies from 5 EU countries, and a case control study in Romania.[87, 89] As cases of the Romanian study were included in the pooled analysis, only the later was retrieved.[87] Other studies including 2000-08 did not provide stratified estimates for the elderly or involved other outcomes.[69, 75-79] No studies stratified for the presence of co-morbidities and most studies estimating IVE against influenza showed a low confounding effect of co-morbidities.[77, 78, 87] We assumed the same IVE parameters for influenza in patients with and without co-morbidity (Table 26). Persons aged 75 years and above are considered altogether, with or without co-morbidities, in our model. No data by season are available. This selected IVE estimate is from an influenza season with good match and medium-high intensity (depending on the study countries), which is the most frequently seen in recent Belgian seasons (5/9 seasons had a good match and a medium intensity, and IVE were similar across high and medium intensity seasons).

4.5.2.2 Admissions for influenza and pneumonia (P+I)

Many studies mostly use broader admission outcomes, such as all-cause admissions, winter admissions or admissions for any respiratory causes. Four adjusted cohort studies were eligible, involving US cohorts in the period 1996-2007.[81, 83, 84, 86] The 3 first studies (the same US cohort over time) found IVE for P+I admissions ranging 20-32% across seasons, which were consistent with the older adjusted cohorts.[12, 85] The more recent cohort study estimated IVE against admissions for P+I in all elderly over 10 influenza seasons at 8.5% (95% CI 3-14%), which is much lower than all other studies, but it did not adjust for all known confounders (e.g. co-morbidities and health care use). It used a different method to adjust for unknown confounders, and differed in population and diagnosis.

Eligible and older studies showed that IVE for admissions for P+I did not differ in elderly with or without co-morbidities,[72-74] and in good match and poor match seasons.[84, 86] IVE tended to be lower during milder intensity seasons in a UK cohort, but no pooled estimate was provided.[85] No quantitative estimates by age group were provided, but cohort studies showed (in graphs) that the IVE were generally consistent among the age groups, even in the ≥85 years of age, where IVE was significant in all valid studies, except for the 90 years and above with high risk. The same parameter is thus applied to all age groups.

We thus selected the pooled IVE from the US cohort (27%; 95% CI 23-32%), for healthy elderly and those with co-morbidities, and in poor and good matching seasons (Table 26). As the adjustment used by Baxter for unknown confounders could not be validated, and considering that other included studies achieved a good adjustment for unknown confounders (i.e. IVE outside influenza season was close to 0), we did not consider Baxter results for parameter determination.[81]

4.5.2.3 Deaths from influenza and pneumonia

The effectiveness of TIV vaccination to prevent deaths in the elderly is a subject of debate. Many observational studies have showed an impressive effect of TIV vaccination, and recent meta-analyses of such studies concluded that TIV vaccination prevented around 50% of all-cause winter mortality in the elderly.[12, 90] However, other researchers showed that these results were flawed by important selection biases and confounding factors; after adjustment, no significant effect was observed - or sometimes a detrimental effect.[18, 91, 92] An obstacle to further research in this field is that RCTs in the elderly are no longer conducted for ethical concerns.

No IVE studies against P+I deaths, adjusting for confounders and involving TIV, covered periods after 2000. The most recent study meeting the other criteria was selected, a well adjusted cohort from UK, though it involved deaths from pneumonia, influenza and chronic bronchitis over the 10 seasons 1989-1999.[85] IVE for deaths P+I was measured overall, by risk and by age group; vaccination was only effective in individuals ≤85 years of age, as IVE was negative or non-significant at 0% in the 85 years and above (Table 26).

4.5.3 IVE parameters in 1-64 years with co-morbidities

IVE parameters in elderly ≥65 years of age with co-morbidities are described above. IVE results for adults 1-64 years of age with co-morbidities are summarized in Table 27 and Table 28, and described below by outcome.

Four Cochrane systematic reviews and 3 small primary RCTs were found, but did not involved the selected outcomes, settings or periods.[9-11, 65, 93, 94] Most observational studies were not eligible.[95-98]

Table 27: IVE parameters for influenza in adults 1-64 years with co-morbidities

		Intensity		
		Medium and high	**Low**	**Total (pooled)**
Match	**Good**	62%	42%	51%
	Relative	75%	-	75%
	Poor	-	Not defined (NS)	Not defined
	Total (pooled)	64%	40%	-

Table 28: IVE parameters in adults 1-64 years with co-morbidities, by outcome

Outcome	IVE estimate	95% CI
Admissions for P+I	63%	16-80%*
Deaths from P+I, best case	63%	16-80%*
Deaths from P+I, worst case	29%	20-38%

* Not published but personal communication from the author. P+I: Pneumonia and influenza; IVE: Influenza vaccine effectiveness/efficacy.

4.5.3.1 Influenza

No IVE study estimating IVE against GP attended influenza in persons with co-morbidities were found. In most studies adjusting for major confounding factors, co-morbidities had a low confounding effect.[77, 87] We assume that the IVE against influenza is similar in patients with and without risk factors, and parameters from healthy adults are thus selected (Table 27).

4.5.3.2 Admissions for influenza and pneumonia

Only a Dutch, well adjusted cohort study in adults 18-64 years of age with any co-morbidities, was eligible, Table 28.[50] It showed a IVE for hospitalisation due to influenza and/or pneumonia at 63% in 1999-2000 (CI provided by the author at 16-80%), in a season with high intensity and good match. As the evidence for this high IVE is limited to a single study, we reviewed other RCTs and adjusted studies involving other hospitalization outcomes.[95, 97, 98] Most results were consistent with the high estimate measured by Hak: in the same cohort, influenza vaccination was associated with a 87% (95% CI 39-97%) reduction in acute respiratory disease and cardio-vascular hospitalizations, and a 72% reduction in all hospitalisations in adults (18-64 years) with diabetes;[97, 99] two RCTs found elevated IVE in patients with COPD (67% for all hospitalizations and 59% for admitted influenza-related exacerbations), but these were non significant, likely due to small size.[65] Only Gilbertson found lower IVE (12% and 16%) for P+I admissions in a retrospective cohort but it involved patients with end stage renal disease and most were >65 years of age.[96] We thus felt confident in this IVE parameter.

4.5.3.3 Deaths from influenza and pneumonia

No eligible study included deaths from influenza and pneumonia as outcome. Most studies only assessed IVE on winter all-cause mortality, which is prone to bias.

We thus selected two scenario for IVE parameters:

1. Best case, same IVE as for admissions for P+I in the same group (63%);
2. Worst case: same IVE as for deaths P+I in elderly 65-74 years of age with co-morbidities (29%).

4.5.4 IVE parameters in HCWs

For direct effect, the same parameters as those in healthy adults (15-64 years) are used (see 3.1). The inconclusive evidence on indirect effect from published studies may be due to the inability of TIV to prevent virus replication.

4.5.5 IVE parameters in pregnant women

For the prevention of outcome in pregnant women, the same parameters as those in healthy adults (15-64 years) are used, and are concordant with results from immunogenicity studies.[100, 101] In infants, we found IVE parameters from several studies against ILI and admissions for influenza but we could not compute the impact on infants by lack of data on infant influenza burden.

5 IMPACT CALCULATIONS

5.1 VACCINE NEEDS BY SCENARIO

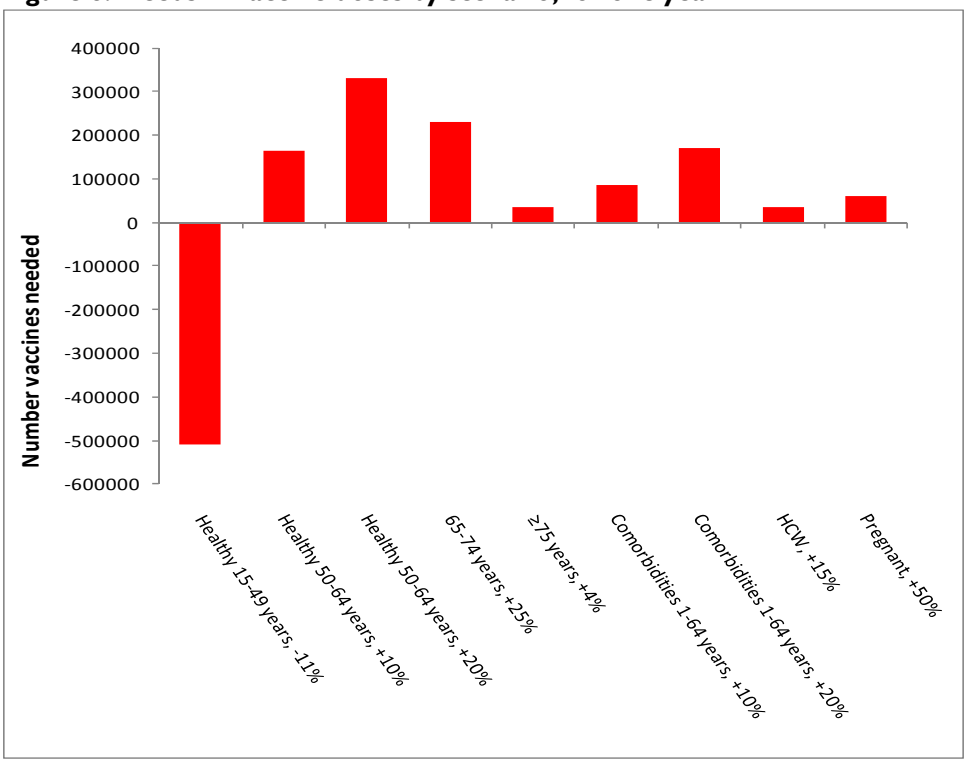
The number of TIV vaccines required to implement each scenario (defined as a change in uptake) is presented in Table 29 and Figure 8. It is based on the additional number of persons to immunize in each scenario compared to the 2008 situation, assuming one dose by person, (i.e. no waste of doses has been accounted for).

Table 29: Number of influenza vaccine doses required to implement each vaccination scenario

Scenarios	N doses*
1-64 years with co-morbidities: +10%	83,576
1-64 years with co-morbidities: +20%	169,152
65-74 years: +25%	229,883
≥75 years: +4%	35,815
Healthy 50-64 years: +10%	165,878
Healthy 50-64 years: +20%	331,757
Health care workers: +15%	35,961
Pregnant women: +50%	60,681
Healthy 15-49 years: -11%	-508,711

*: These amounts do not take duplications between groups into account: HCW may also be included in healthy adults and in persons with co-morbidities, but no data were available to extract them.

Figure 8: Needs in vaccine doses by scenario, for one year



The scenario in healthy adults of 15-49 years of age represents the gain in vaccine doses that would be achieved if the 11% currently vaccinated persons of this group would not be vaccinated. Though this scenario would be difficult – if not impossible – to implement, it indicates that the gain in vaccine doses (around 500,000) would be sufficient to ensure a large additional uptake of the priority groups: 446,915 vaccine doses would be needed to reach 75% uptake in the elderly, increase by 10% uptake in persons with co-morbidities, vaccinate 50% of pregnant women and increase the HCW uptake by +15%.

5.2 IMPACT OF EACH VACCINATION SCENARIO IN AN INFLUENZA SEASON

For each vaccination scenario, results are presented as a mean, best case and worst case. In addition, results for a distribution of recent influenza seasons is shown when relevant. Results show high variations across seasons for outpatient influenza cases, due to high variability of incidence and vaccine effectiveness values across seasons. However, low differences are observed for other outcomes due to a relative stability of burden and IVE parameters across seasons.

We could not compute the total number of ILI that could be prevented by these vaccination scenarios for two reasons: most IVE estimates for ILI were not significant, due to the difficulty of achieving sufficient power for this (less specific) outcome; and the retrieved studies included very different outcomes than those reported in Belgium: case definition differed and were mostly less specific, as reflected by the very low proportion of ILI that are influenza laboratory confirmed in adults compared to the Belgian situation (6-13% in studies vs. 44-57% in Belgium for similar seasons and age group).[72,73,97] We could thus estimate the impact of influenza vaccination on ILI influenza-confirmed cases but not on non-confirmed ILI cases.

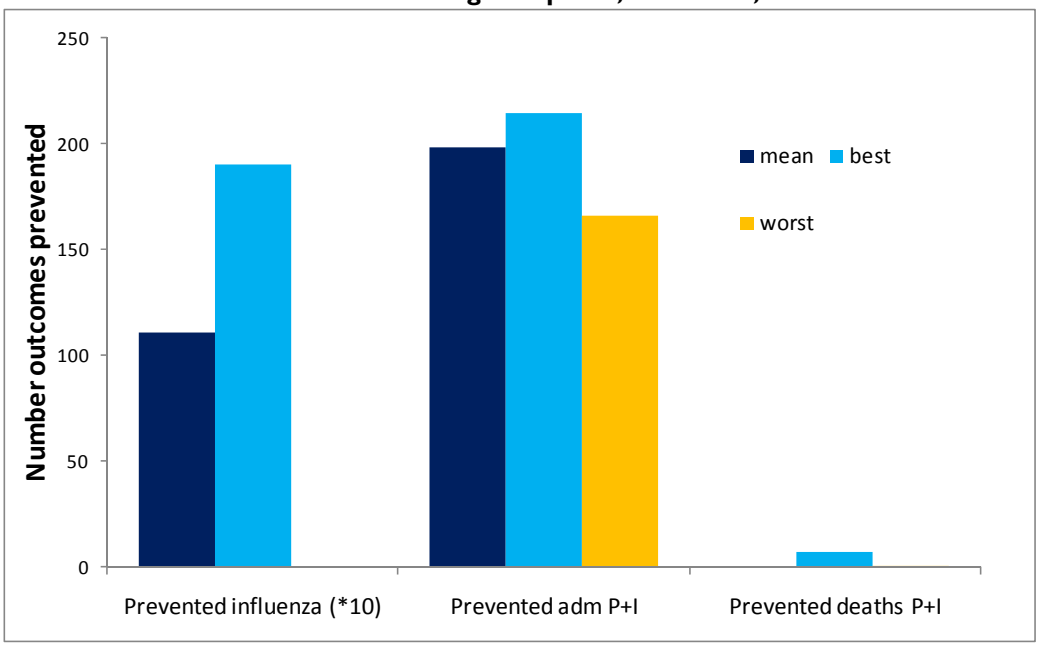
A summary of numbers of prevented outcomes by scenario is presented in Table 30, and results are presented graphically below, under each scenario.

5.2.1 Vaccination of persons 1-64 years old with co-morbidities

In the persons 0-64 years of age with co-morbidities, the current overall uptake is currently low at 20%, with variations across ages (from 8-9% in the 15-34 years to 39% in the 55-64 years). We calculated that an estimated mean of around 1100 influenza cases, 200 admissions and a few number of deaths could be prevented by rising the uptake by 10% in this group (Figure 9). A rise of 20% would double these estimated prevented outcomes.

In both best and worst case scenarios, the benefits in terms of deaths are extremely low (7 and 0.5 deaths respectively for an uptake of +10%), although the best case assumes an IVE as high as 63% for P+I mortality. This is due to a relative low number of deaths from P+I in this group (around 100/season).

Figure 9: Number of prevented outcomes in persons 1-64 years of age with co-morbidities with a 10% higher uptake, in a mean, best and worst case

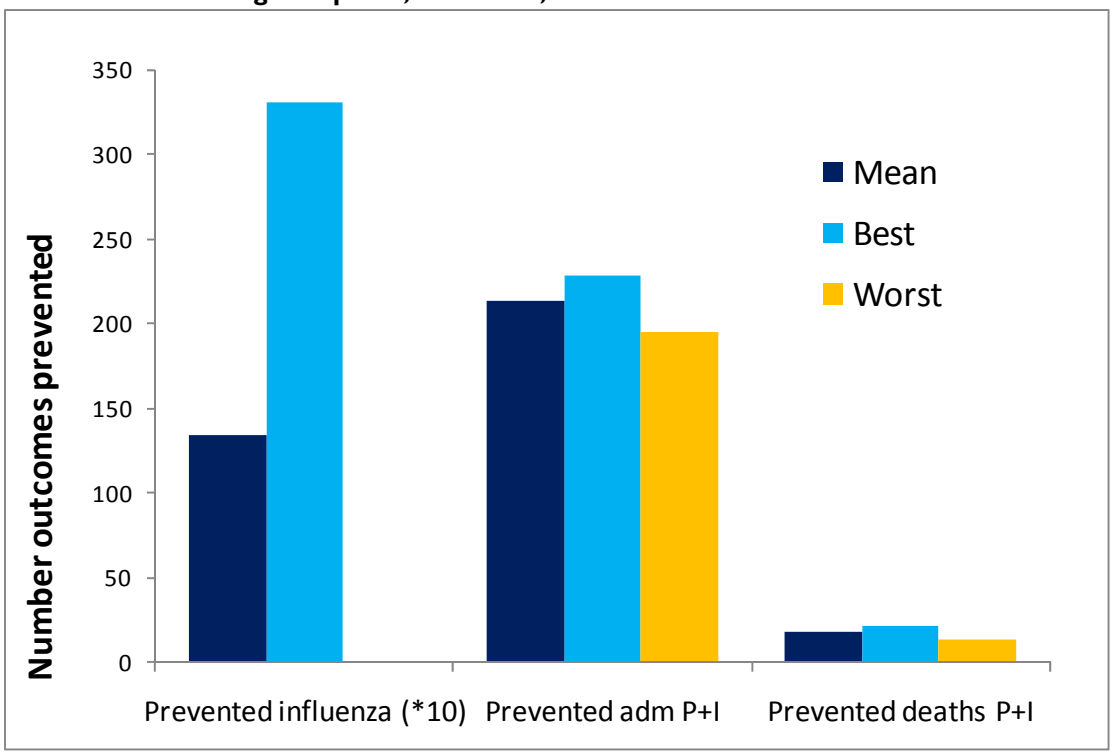


Influenza: number of cases divided by a factor 10, for scale visibility. Prevented deaths: no mean case could be calculated by lack of IVE parameter. P+I: Pneumonia and influenza.

5.2.2 Vaccination of the elderly 65-74 years of age

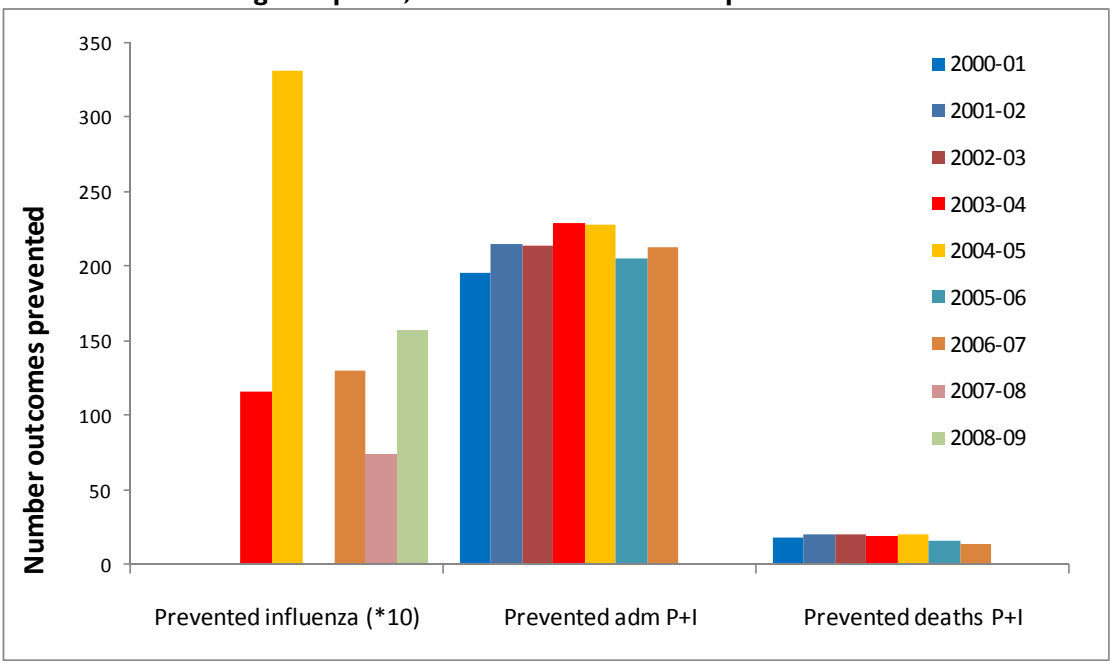
In the elderly 65-74 years of age, a mean of 1346 outpatient influenza cases, 214 admissions and 18 deaths (21 and 14 for best and worst case, respectively) can be prevented by rising the current uptake by 25% to reach the 75% WHO target coverage (Figure 10). Though the number of prevented deaths is very low, the vaccination of the 65-74 years with co-morbidities (representing around 26.7% in this age group) would prevent 89% of the prevented deaths (16/18 mean prevented deaths). Figure 11 illustrates the high variability of vaccination benefits across seasons for outpatient cases. For the season 2005-06 (worst case), characterized by a predominance of influenza B, a low intensity in the elderly, the lowest proportion of influenza confirmed, and a poor match with the vaccine strain, no number of prevented outpatient cases could be predicted. If we would use the IVE point estimate of 22% for poor match and low intensity season (non significant), we would estimate that only 158 influenza cases could be prevented.

Figure 10: Number of prevented outcomes in elderly 65-74 years of age with a 25% higher uptake, in a mean, best and worst case.



Influenza: number of cases divided by a factor 10, for scale visibility. P+I: Pneumonia and influenza.

Figure 11: Number of prevented outcomes in elderly 65-74 years of age with a 25% higher uptake, based on the last season parameters*



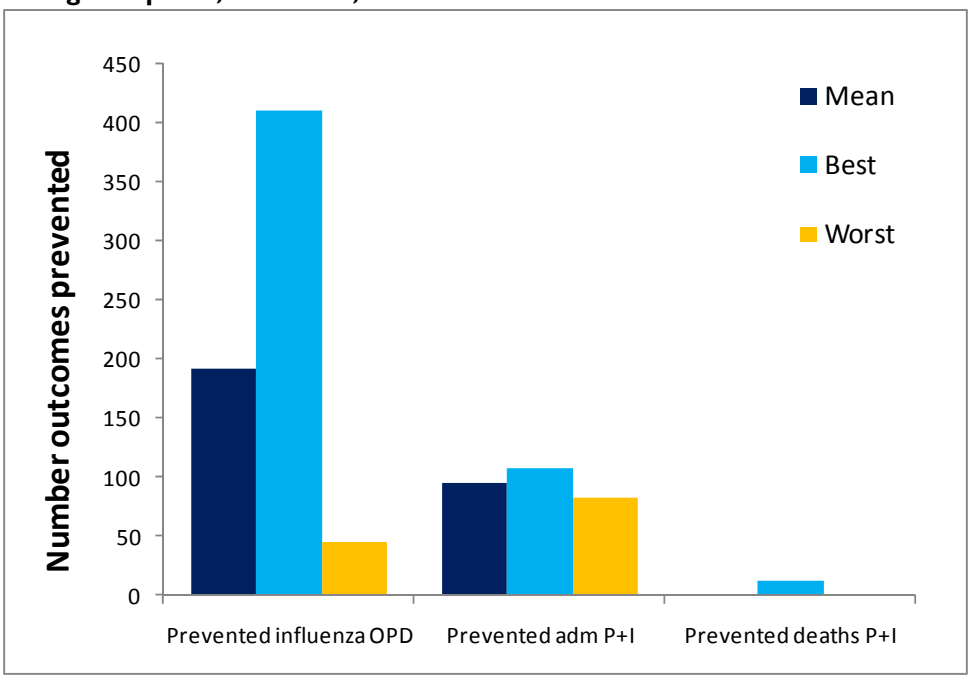
Influenza: number of cases divided by a factor 10, for scale visibility. P+I: Pneumonia and influenza.
*: Based on available data (2003-04 to 2008-09 for influenza; 2000-01 to 2006-07 for admissions and deaths).

5.2.3 Vaccination of the elderly ≥75 years of age

The vaccination in the elderly ≥75 years of age considers only a 4% rise in uptake, as the current uptake (71% in 2008) is close to the WHO target (75%). Benefits in terms of prevented outcomes are thus low for this vaccination scenario (191 influenza outpatient, 95 admissions P+I and 0-13 deaths), even though most admissions and deaths occur in this group. However, the ratio of severe outcome by vaccine dose is high in this group (see Table 30).

As only one IVE value for influenza outpatient cases was available from one study, we considered a "mean" case, and did not compute results by season. For prevented deaths, we only computed one best and one worst case as IVE estimates are still unclear.

Figure 12: Number of prevented outcomes in elderly aged ≥75 years with a 4% higher uptake, in a mean, best and worst case

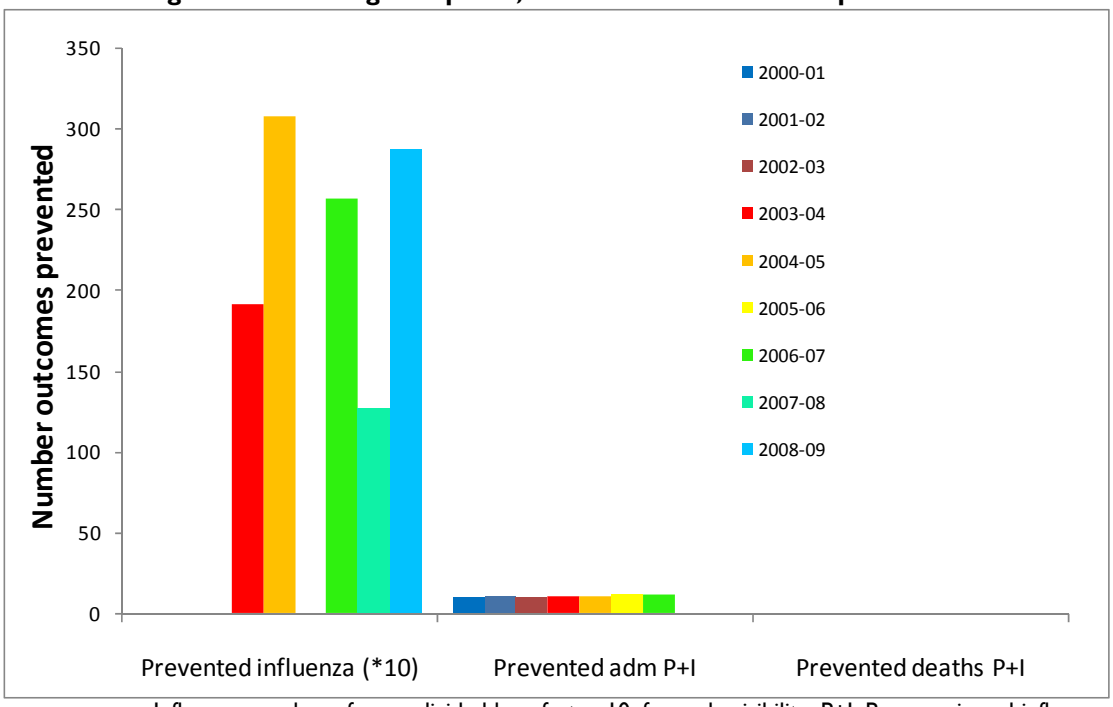


Only a mean case could be calculated by lack of IVE parameters by season type. Prevented deaths: no mean case could be calculated by lack of IVE parameter. P+I: pneumonia and influenza.

5.2.4 Vaccination of healthy adults 50-64 years

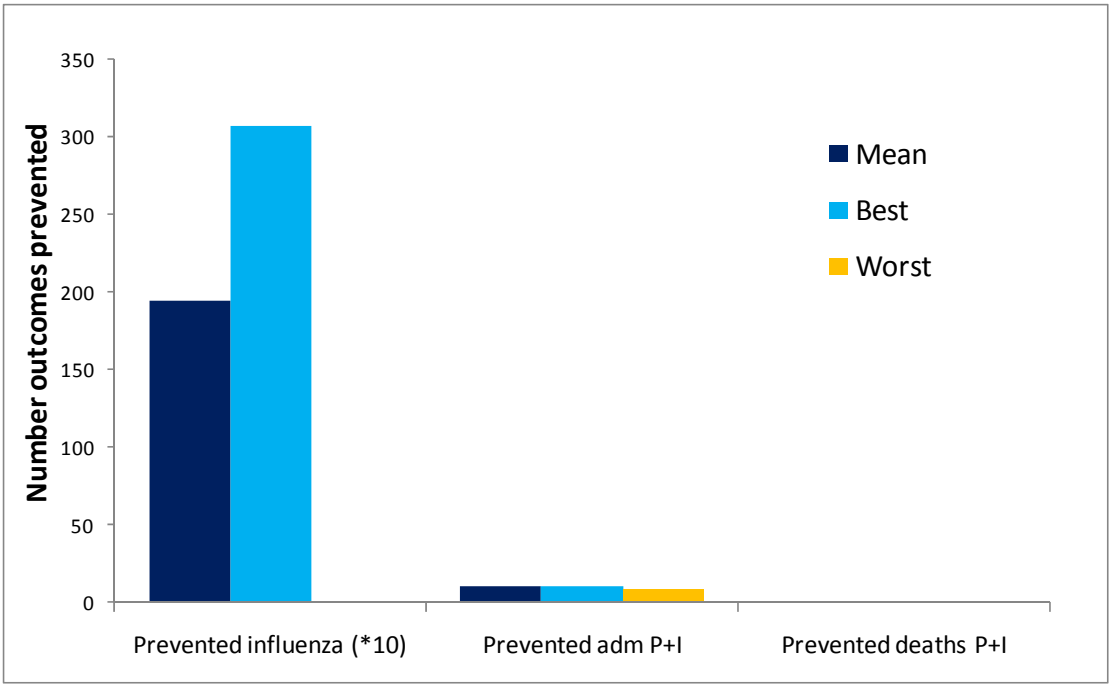
Influenza vaccines are today recommended in this group, but current uptake is still low (25%). The results of a vaccination scenario adding a 10% uptake are shown in Figure 13 and Figure 14. As admissions and deaths are not frequent in healthy adults, the benefit of this strategy is mostly in terms of reducing outpatient cases: an estimated mean of 2,000 outpatient influenza cases can be prevented by rising the uptake by 10% in this group, but only 10 P+I admissions and between 0 (worst) and 0.3 (best case) P+I deaths. Rising the uptake by 20% is only doubling this benefit. The potential indirect effect of vaccinating this wide group is not within the scope of this study, but will be assessed in Phase II of this study.

Figure 13: Number of prevented outcomes in healthy adults 50-64 years of age with a 10% higher uptake, based on the last season parameters



Influenza: number of cases divided by a factor 10, for scale visibility. P+I: Pneumonia and influenza. *: based on available data (2003-04 to 2008-09 for influenza; 2000-01 to 2006-07 for admissions and deaths.

Figure 14: Number of prevented outcomes in healthy adults 50-64 years of age with a 10% higher uptake, in a mean, best and worst case

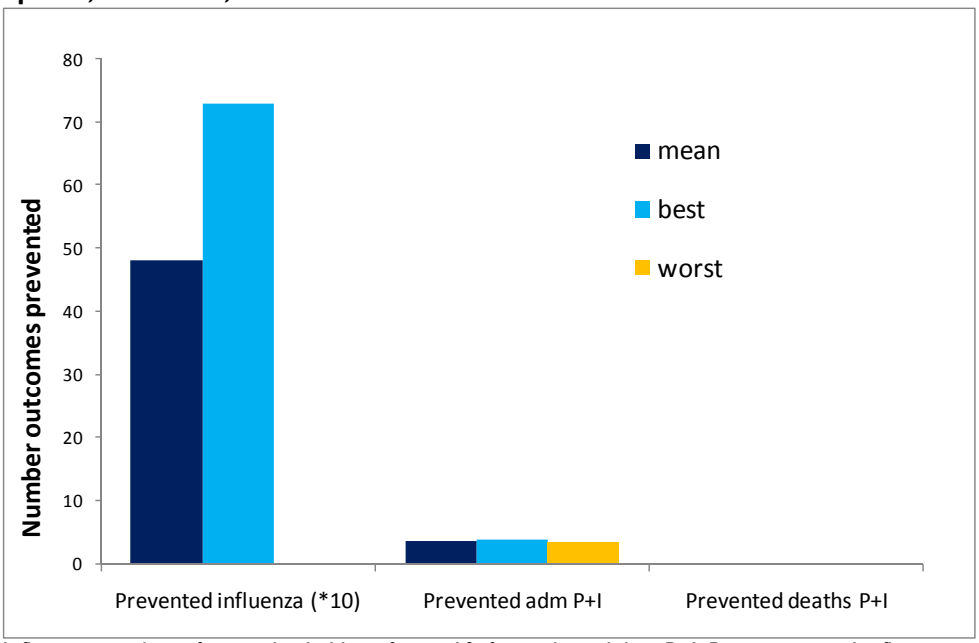


Influenza: number of cases divided by a factor 10, for scale visibility. P+I: Pneumonia and influenza.

5.2.5 Vaccination of HCW

In the HCW, 461 influenza cases, 4 admissions and no death can be directly prevented by rising the uptake by 15% - to reach an uptake of 50% in this group (Figure 15). Burden data on HCWs and number of HCWs are not specific enough to compute prevented outcomes by season; therefore, only estimates for a mean case (or best/worst when appropriate) are presented. The indirect effect achieved by implementing this strategy is however not measured by this model, and will be covered in the Part II of this study.

Figure 15: Number of prevented outcomes in HCW with a 15% higher uptake, in a mean, best and worst case



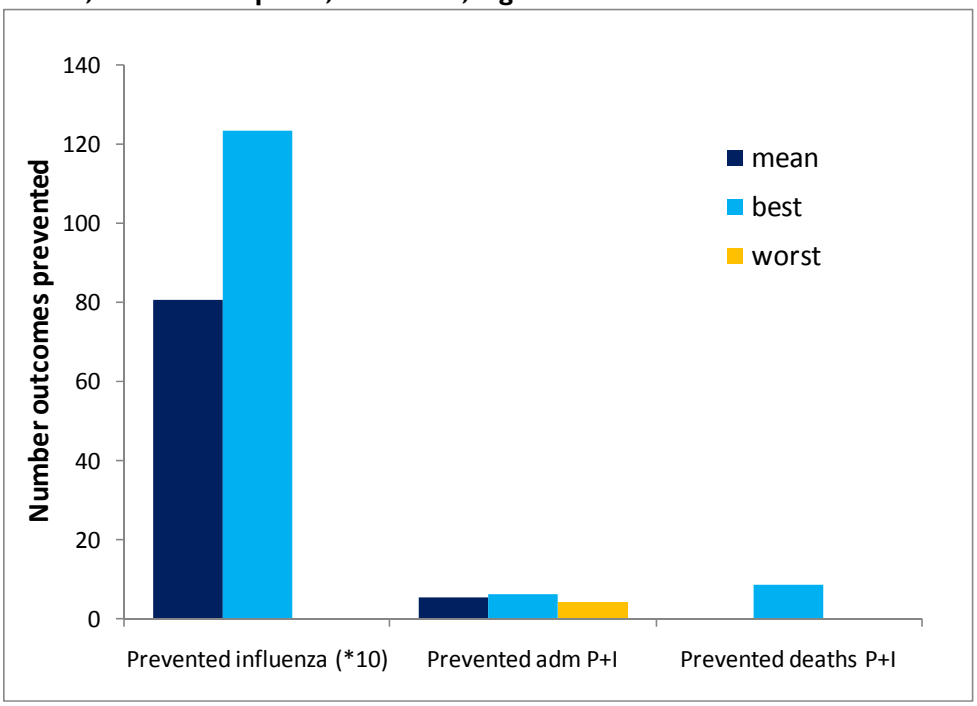
Influenza: number of cases divided by a factor 10, for scale visibility. P+I: Pneumonia and influenza.

5.2.6 Vaccination of pregnant women

In pregnant women, an estimated mean of 770 influenza cases could be prevented by rising the uptake by 50% (Figure 16). Regarding admissions and deaths, we explored two extreme scenarios: under the most conservative scenario (low case i.e. same parameters as for non-pregnant), 5 admissions and no deaths would be prevented; under a H1N1–like scenario (high case), 6 admissions and 9 deaths would be prevented.

As no data on influenza burden in infants 0-6 months was available in Belgium, the vaccination benefit on this group could not be calculated.

Figure 16: Number of prevented outcomes in pregnant women by influenza season, with a 50% uptake, in a mean, high and low case

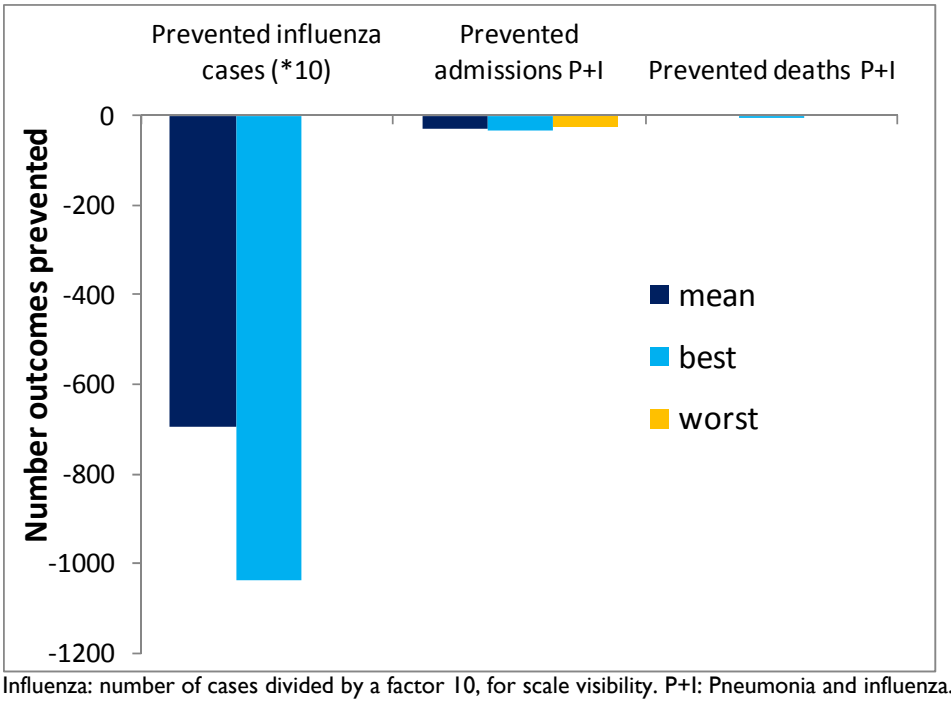


Influenza: number of cases divided by a factor 10, for scale visibility. P+I: Pneumonia and influenza.

5.2.7 Not vaccinating healthy adults 15-49 years

This vaccination scenario shows the additional outcomes that would occur if the 11% currently vaccinated persons of this group would not be vaccinated. Figure 17 shows that an additional 6,600 influenza outpatient cases (mean) would occur, but only 28 admissions and an estimated 0.2 deaths under the best assumptions (Figure 17).

Figure 17: Number of additional outcomes that are predicted to occur if healthy adults 15-49 years of age are no longer vaccinated in a mean, best and worst case



Influenza: number of cases divided by a factor 10, for scale visibility. P+I: Pneumonia and influenza.

5.3 IMPACT OF EACH VACCINATION SCENARIO IN AN ACTIVITY SEASON

The impact of each scenario in an activity season is obviously lower than in an influenza season, as it systematically involves a smaller number of weeks. The number of influenza outpatient cases prevented is only slightly lower than in the analysis by influenza season, as very few influenza cases (around 5%) occurred outside the period of viral activity. But the impact on admissions and deaths by activity season represents a range of 60-64% and 63-79% respectively, of the one estimated in an influenza season, and this proportion varies with the target groups (100% in the best case for pregnant because the same US parameter is used).

The impact of all scenarios is summarized in Figure 19 and Table 30, and details by target group are provided below.

5.3.1 Vaccination of persons 1-64 years with co-morbidities

In the persons 0-64 years of age with co-morbidities, we estimated that a mean of 1,080 outpatient influenza cases, 121 admissions and 0.5 to 5 deaths can be prevented by rising the uptake by 10%. A rise of 20% would double these estimated prevented outcomes.

5.3.2 Vaccination of the elderly 65-74 years of age

In the elderly 65-74 years of age, a mean of 1,200 outpatient influenza cases, 136 admissions and 7-15 deaths can be prevented by rising the current uptake by 25%.

5.3.3 Vaccination of the elderly ≥75 years of age

Benefits in terms of prevented outcomes for a 4% rise in uptake would even be lower, at 186 influenza outpatient cases, 61 admissions and 0-9 deaths.

5.3.4 Vaccination of healthy adults 50-64 years

The impact of increasing by 10% the uptake in this group would amount to a mean of 1903 outpatient influenza cases, 10 admissions and between 0 (worst) and 0.2 (best case) deaths. Rising the uptake by 20% is doubling this benefit.

5.3.5 Vaccination in HCW

In the HCWs, a mean of 445 outpatient influenza cases, 2.2 admissions and no death would be prevented by rising the uptake by 15%.

5.3.6 Vaccination of pregnant women

In pregnant women, a mean of 733 outpatient influenza cases and 3.6 admissions could be prevented by rising the uptake by 50%. Under the worst case scenario, 3 admissions and no death would be prevented; under the best case scenario, 4 admissions and 9 deaths would be prevented.

5.3.7 Not vaccinating healthy adults 15-49 years

Under this vaccination scenario, a mean of 6,276 additional influenza outpatient cases would occur, together with 18 admissions and an estimated 0.4 deaths under the best case scenario.

5.4 SUMMARY OF IMPACT BY VACCINATION SCENARIO

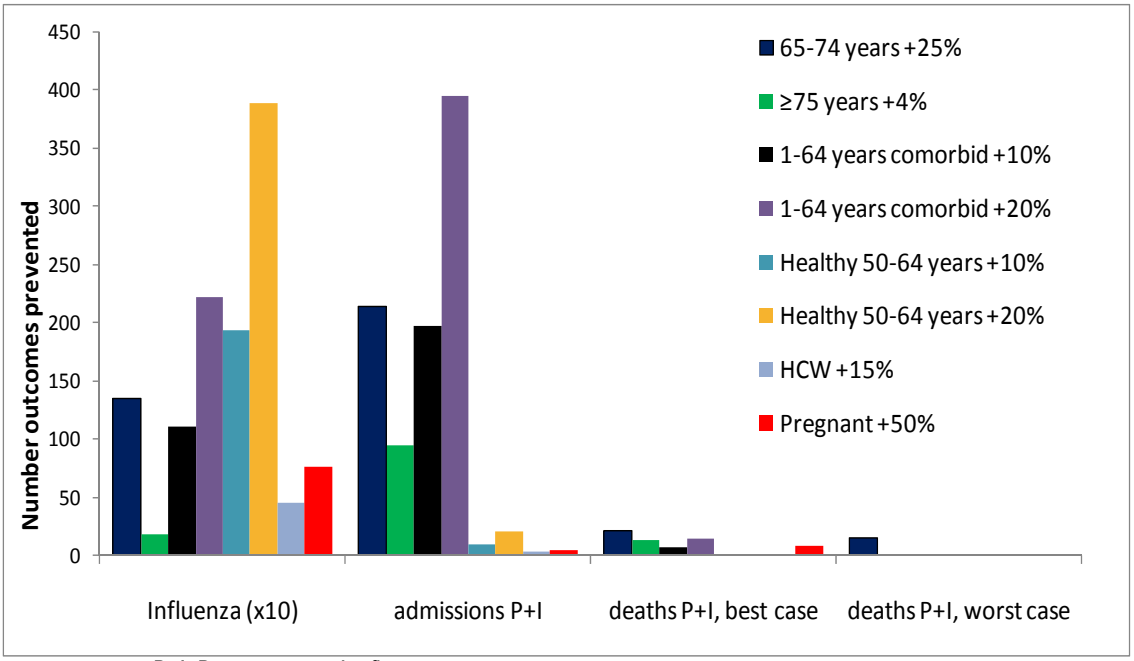
Table 30 summarizes the benefit predicted in each vaccination scenario in both types of season and by outcome, as well as the outcome prevented by 10,000 vaccine doses and the number that should be vaccinated to prevent one outcome. Table 31 presents the same findings for 5 defined strategies, which involve a combination of vaccination scenarios.

Table 30: Prevented outcomes for each vaccination scenario in both types of season (total number and by 10,000 vaccine doses), mean case, best and worst case for deaths

Target group	65-74 years	≥75 years	1-64 yrs with co-morbidities		Healthy 50-64 yrs		HCW	Preg-nant	Healthy 15-49 yrs
Change in uptake	+25%	+4%	+10%	+20%	+10%	+20%	+15%	+50%	-11%
N vaccines needed	229,883	35,815	85,576	169,152	165,878	331,757	35,961	60,681	-508,711
By influenza season									
N outcomes prevented by influenza season									
Influenza (mean)	1346	191	1110	2219	1947	3894	461	770	-6624
Admissions P+I (mean)	214	95	198	396	10.2	20	3.6	5.5	-28
Deaths P+I, best case	21	13	7	15	0.3	0.6	0.1	9	-0.2
Deaths P+I, worst case	14	0	0.5	1	0	0	0	0	0
N outcomes prevented by 10,000 vaccine doses, by influenza season									
Influenza (mean)	59	53	130	130	117	117	128	127	-130
Admissions P+I (mean)	9.3	26.7	23.4	23.4	0.6	0.6	1.0	0.9	-0.6
Deaths P+I, best case	0.9	3.7	0.9	0.9	0.0	0.0	0.0	1.5	0.0
Deaths P+I, worst case	0.6	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0
Number needed to vaccinate to prevent one outcome, by influenza season									
Influenza (mean)	171	187	76	76	85	85	78	79	77
Admissions P+I (mean)	1,075	375	428	428	16,254	16,254	10,018	11,084	17,926
Deaths P+I, best case	10,708	2,737	11,660	11,660	530,340	530,340	430,093	6,797	2,524,811
Deaths P+I, worst case	16,083	NA	162,023	162,023	NA	NA	NA	NA	NA
By activity season									
N outcomes prevented by activity season									
Influenza (mean)	1194	186	1080	2161	1903	3806	445	733	-6276
Admissions P+I (mean)	136	61	121	243	10.2	20	2.2	3.6	-18
Deaths P+I, best case	15	9	5	10	0.2	0.4	0.1	9	-0.4
Deaths P+I, worst case	7	0	0.5	1	0	0	0	0	0.0
N outcomes prevented by 10,000 vaccine doses, by activity season									
Influenza (mean)	52	52	128	128	115	115	124	121	-123
Admissions P+I (mean)	5.9	17.1	14.4	14.4	0.6	0.6	0.6	0.6	-0.4
Deaths P+I, best case	0.7	2.6	0.6	0.6	0.0	0	0	1.5	0
Deaths P+I, worst case	0.3	0	0.1	0.1	0	0	0	0	0

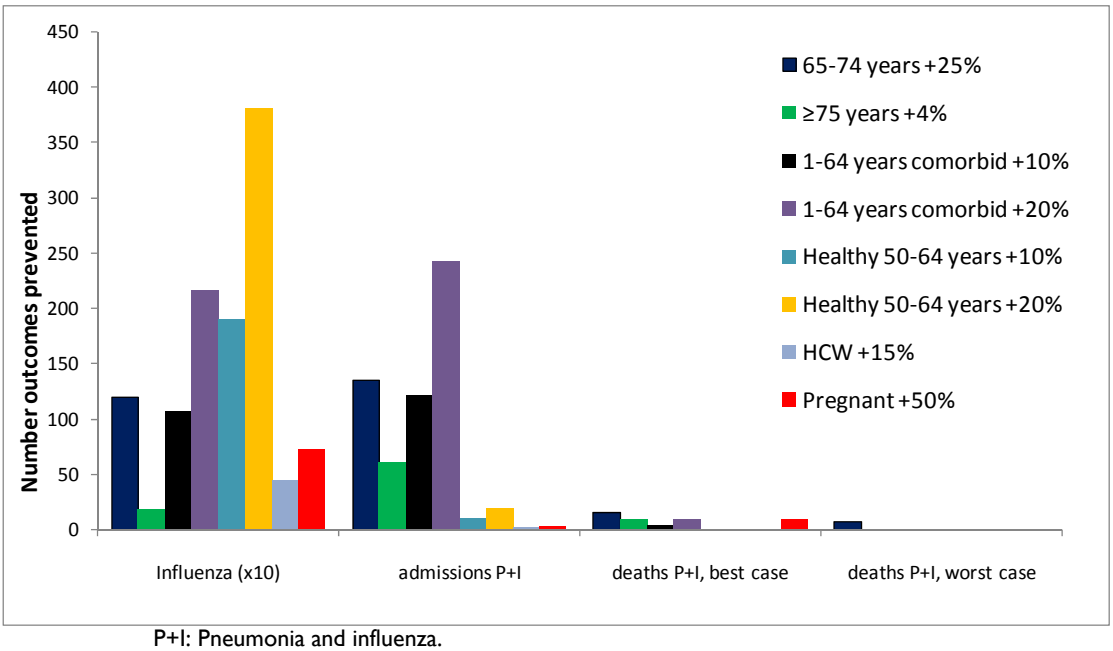
P+I: Pneumonia and influenza. HCW: Health care worker. Influenza refers to GP attended influenza cases.

Figure 18: Mean prevented outcomes by vaccination scenario and by influenza season



P+I: Pneumonia and influenza.

Figure 19: Mean prevented outcomes by vaccination scenario and by activity season



P+I: Pneumonia and influenza.

In the analyses for both types of season, the strategies targeting adults <65 years of age, with or without co-morbidities, would prevent the most outpatient cases by vaccine dose (Table 30). For instance, increasing by 20% the uptake of the healthy 50-64 years and those aged 1-64 years with co-morbidities (strategy 5, Table 31) would prevent 6,113 and 5,967 influenza cases (2.2% of all influenza cases), together with 416 and 263 admissions P+I (1.8% and 1.1% of all) in the analysis by influenza season and activity season, respectively, at a cost of 500,000 doses. However, this would only prevent between 1-15 deaths by influenza season.

The strategies that would prevent the most admissions by vaccine dose are those vaccinating the persons with co-morbidities and the elderly ≥75 years of age. Persons with co-morbidities currently have a low uptake (around 20%), and increasing it by an additional 20% would prevent 396 admissions in an influenza season and 243 in an activity season, and a range of 1-15 deaths. However, targeting the elderly ≥75 years would not bring a high absolute benefit (95 and 61 admissions) as this group has already an uptake of 71%, and the WHO target (75%) may be difficult to exceed.

As the "young" elderly (65-74 years) have only a 50% uptake, a significant rise (25%) is required to reach the 75% WHO target. However this scenario would require around 230,000 doses to achieve a relatively moderate decrease in outpatient cases (1,346 and 1,194), admissions (214 and 136) and deaths (21 and 15 under the best case) in an influenza and activity season, respectively. This can be explained by a lower impact by vaccine dose on outpatient cases than when vaccinating adults <65 years, as well as a lower impact on admissions than the vaccination of persons with co-morbidities and the elderly >75 years.

The optimal strategy to prevent deaths is difficult to establish: the most efficient strategy – presenting the best ratio death P+I prevented/vaccine dose - is achieved by targeting the elderly ≥75 years in the best case (3.7 and 2.6 deaths/10,000 doses), but the proposed scenario (+4%) would only prevent 13 and 9 deaths by influenza and activity season, respectively. The same goes with vaccinating pregnant women, even under a high/best case scenario (mortality similar to one found with the H1N1 pandemic strain). Even the maximum strategy (Strategy 3: all target groups, high uptake) would only prevent 59 and 44 deaths under the best case, for influenza and activity season respectively, at a cost of 863,000 vaccine doses (51% of reimbursed vaccines in 2008).

Table 31: Prevented outcomes for a combination of vaccination scenarios (total number and by 10,000 vaccine doses), mean case, best and worst case for deaths

Target groups	Strategies				
	Strategy 1	**Strategy 2**	**Strategy 3**	**Strategy 4**	**Strategy 5**
	All elderly 75% + co-morbidities 20%	Healthy 50-64 yrs 20% + HCW & pregnant	All groups, higher uptake*	All groups, lower uptake**	Healthy 50-64 yrs 20% + co-morbidities 20%
N vaccines needed	434,849	428,399	863,248	612,794	500,909
N outcomes prevented by influenza season					
Influenza	3,757	5,125	8,882	5,825	6,113
Admissions P+I	705	29	734	526	416
Deaths P+I, best case	49	10	59	51	15
Deaths P+I, worst case	15	0	15	15	1
N outcomes prevented by 10,000 vaccine doses, by influenza season					
Influenza	86	120	103	95	122
Admissions P+I	16.2	0.7	8.5	8.6	8.3
Deaths P+I, best case	1.1	0.2	0.7	0.8	0.3
Deaths P+I, worst case	0.4	0.0	0.2	0.2	0.0
N outcomes prevented by activity season					
Influenza	3,541	4,984	8,525	5,542	5,967
Admissions P+I	440	26	466	335	263
Deaths P+I, best case	34	9	44	39	10
Deaths P+I, worst case	8	-	8	8	1[2]
N outcomes prevented by 10,000 vaccine doses by activity season					
Influenza	81	116	99	90	119
Admissions P+I	10.1	0.6	5.4	5.5	5.3
Deaths P+I, best case	0.8	0.2	0.5	0.6	0.2
Deaths P+I, worst case	0.2	0.0	0.1	0.1	0.0

P+I: Pneumonia and influenza. HCW: Health care worker.
*: 10% uptake for elderly 65-74 years of age and persons with co-morbidities
**: 20% uptake for elderly 65-74 years of age and persons with co-morbidities

The healthy adults aged 15-49 years are not currently targeted by the recommendations but 11% of them are vaccinated. If this group would not be vaccinated, a mean of 6,624 and 6,276 additional influenza outpatient cases would be expected to occur, but only 28 and 18 additional admissions and no death, by influenza and activity season respectively. Though this scenario is not realistic (vaccines can be bought in retail pharmacies), it would make 500,000 doses available to increase the uptake of key target groups. For instance, these doses would allow to implement strategy 1 or strategy 5 (Table 31), preventing in an influenza season 705 and 416 admissions, and 49 and 15 deaths under the best case, respectively.

The increased vaccination of HCWs and pregnant women shows a very limited impact in terms of prevented outcomes (<1000 outpatient influenza and <6 admissions for each), even when applying parameters related to the H1N1 pandemic strain (best case for pregnant). This is partly due to the low number of persons involved, but also to the inability of our model to account for any indirect effect (protecting patients of HCW and infants of mother vaccinated while pregnant), due to the lack of data.

The strategy aiming at high uptake in all target groups (Strategy 3) would obviously prevent the maximum number of outpatient influenza cases (around 9,000), admissions (734) and deaths (15-59), but at a cost of 863,000 doses.

An efficient alternative is to increase uptake in the highest risk groups only (as in Strategy 1: reach 75% in all elderly and +20% in persons with co-morbidities): it would prevent in a mean influenza season less outpatient cases (3,757) but a similar number of admissions (705) and deaths (15-49) compared to Strategy 3, for only half the number of vaccine doses (435,000 vs. 863,000).

All strategies involving persons with co-morbidities present the advantage of having a high impact on admissions, due to the high admission burden and high vaccine effectiveness in this group, while also having a high effect on outpatient cases and some effect on deaths (Strategy 1, 3, 4 and 5).

All results also show a high variability of vaccination benefit on outpatient cases, due to the variability of influenza season intensity and matching with vaccine strains. The benefits on admissions are more stable from season to season, as these outcomes did not show wide variations – even those only coded as influenza.

5.5 UNCERTAINTY AND SENSITIVITY ANALYSES

To assess the level of uncertainty around our impact estimates, we looked at probability distributions for the impact in influenza seasons in terms of outcomes presenting higher uncertainty (influenza outpatient and death), by running 1000 Monte-Carlo simulations. For the impact on influenza outpatient cases, the analysis is performed only for the best case, as the non significant IVE in a worst case season did not allow to compute it; additionally, this impact is by definition surrounded by a very high level of uncertainty. The best and worst case were computed for deaths. The distribution of each outcome (mean and 95% confidence interval) is presented below. Note that the mean presented here is a mean of the 1000 simulations for a best or a worst case, and is not a mean of the predicted impact in recent influenza seasons, as presented before.

Table 32: Results from the uncertainty analysis around impact estimates

Target group	Mean	95% confidence interval	
		lower level	upper level
Healthy 50-64 years, +10% uptake			
impact influenza best	3013	2181	3777
impact deaths best	0	0	1
impact deaths worst	0	0	0
Healthy 15-49 years, -11% uptake			
impact influenza best	-10187	-12265	-7762
impact deaths best	0	0	0
impact deaths worst	0	0	0
1-64 years comorbid, +10% uptake			
impact influenza best	1878	1449	2213
impact deaths best	7	1	9
impact deaths worst	0	0	1
65-74 years, +25% uptake			
impact influenza best	3253	2343	4082
impact deaths best	21	16	25
impact deaths worst	10	6	14
75+ years, +4% uptake			
impact influenza best	324	-568	674
impact deaths best	13	8	18
impact deaths worst	0	0	0
Health care worker, +15% uptake			
impact influenza best	721	555	861
impact deaths best	0	0	0
impact deaths worst	0	0	0
Pregnant women, +50% uptake			
impact influenza best	1217	955	1436
impact deaths best	9	1	16
impact deaths worst	0	0	0

Results highlight the high level of uncertainty around estimates of influenza cases in the elderly ≥75 years of age (with unknown benefit), due to a low number of ILI cases that are swabbed by the sentinel system. On the contrary, estimates of prevented deaths in the elderly show relatively low levels of uncertainty. Estimates of prevented deaths in the non elderly, show high levels of uncertainty, even in a best case scenario, due to low numbers.

In the sensitivity analysis, we first adjusted the influenza burden in the elderly to their vaccine uptake, by adding the outcomes prevented by this vaccination. We used the same model, and calculated the underestimation of impact that we made by using the current burden. If we took into account the existing 50% vaccine uptake in the 65-74 years of age, the vaccination scenario in this group (25% additional uptake) would prevent an additional 382 outpatient influenza cases, 29 P+I hospitalizations and 3 P+I deaths in an average season, that would be added to the 1,346 outpatient influenza cases, 214 P+I hospitalizations and 18 deaths estimated in the baseline case. If we take into account the 71% vaccine uptake in the elderly ≥75 years of age, we find that an additional 81 outpatient influenza cases and 18 P+I admissions would be prevented in an average season by a 4% higher uptake, compared to our baseline case. We could not calculate the additional deaths prevented due to too many uncertainties around the vaccine protection against deaths in this group. This analysis suggests that we underestimated the vaccination impact on outpatient influenza in the elderly (463 additional cases in an average season), but that the underestimation in terms of overall numbers of admissions and deaths was probably marginal.

We also adjusted the influenza burden of the elderly to reflect the lower burden of the community-dwelling elderly, based on parameters from the literature and partial Belgian data. As outpatient influenza cases are not reported to be more frequent in elderly in institutions, we did not adjust for this outcome. On the contrary, several studies highlighted the higher frequency of admissions and deaths in institutionalised elderly compared to community-dwelling elderly.[102,103] As we did not find age-specific parameters in these studies and age is certainly a major confounder, we extracted the number of P+I admissions and deaths among patients coded as coming from an institution from MCD data. In the 65-74 years, institutionalized patients represented 5% of all P+I hospitalizations and 9% of all P+I deaths. In the 75 years of age, these accounted for 19% of all P+I hospitalizations and 27% of all P+I deaths. If we exclude the outcomes that can be attributed to institutionalized elderly, the vaccination scenario in the elderly[f] would prevent 28 fewer P+I hospitalizations (11 in 65-74 years and 17 in the ≥75 years) in an average season, compared to the baseline case (309 admissions). We cannot compute the number of P+I deaths prevented because we have no data on the number of admissions and deaths among in non-institutionalized patients with and without co-morbidities. This analysis suggests that the overestimation made in terms of admissions is minimal (9% for this group).

[f] 25% and 4% additional uptake in the 65-74 years and the ≥75 years, respectively

6 DISCUSSION

This study aims at predicting the impact of several influenza vaccination scenarios on influenza-related visits to GP, admissions for influenza and pneumonia and deaths due to influenza and pneumonia in Belgium. These vaccination scenarios involve an increase in uptake in the main target groups for vaccination: the elderly, persons with co-morbidities, adults aged 50-64 years, health care workers and pregnant women. This study, using a simple static model, used Belgian data on influenza disease burden to the widest extent possible. However, these results underestimate the predicted impact of influenza vaccination because we could not include ILI cases seen at emergency rooms and by paediatricians, and because it is known that influenza and pneumonia coded outcomes, such as admissions and deaths, underestimate the number of true influenza-related outcomes. We limited the admission and death underestimation by selecting vaccine effectiveness parameters on exactly the same outcome (admissions discharge data, ICD9 coded influenza and/or pneumonia). Furthermore, this underestimation is not precluding the comparison of the different vaccination scenario and strategies, as the level of underestimation should not differ across groups (with the exception of children).

Each scenario shows different impact on each outcome, and the priority setting in targeting groups would depend on the programme objective:

1. Vaccinating the persons with co-morbidities is the most efficient option to prevent admissions, with the highest number of admissions avoided per vaccine dose (23/10,000). The uptake in this group is currently low (20% in those <65 years in 2008) and increasing it by an additional 20% would prevent 396 admissions in an influenza season, at a cost of 167,000 vaccines. Targeting the elderly ≥75 years would prevent a similar number of admissions per dose, but would not bring a high absolute benefit (95 prevented admissions only) as 71% of this group is already vaccinated, while we aim at reaching the WHO target of 75%. Exceeding this high target may be difficult to implement.
2. The strategies that prevent the most outpatient cases are those targeting the <65 years of age, with or without co-morbidities, as these groups present the best ratio prevented case per vaccine dose. However, increasing influenza uptake in adults 50-64 years without co-morbidities by 20% would only prevent 20 admissions because admissions are very uncommon in this group. Conversely, increasing uptake in persons with co-morbidities would prevent a substantial number of outpatient cases as well as admissions.
3. A vaccination programme that would aim at reducing influenza-related mortality should focus on the elderly, in as most deaths are among these ages. However, the "maximum" strategy (high uptake in all groups), would only prevent 59 deaths in the best case, at a cost of 850,000 vaccines.
4. The best strategy to decrease the epidemic curve by reducing influenza transmission could not be assessed in this static model. Several studies have predicted a large impact of vaccinating school age children in reducing influenza transmission and protecting the most vulnerable groups – who are not always effectively protected by vaccination.[104] For this reason, a second part of this study will address this issue and use dynamic transmission modelling to predict the impact of such strategies.

A surprising finding of our study is that none of the proposed strategies is really effective in preventing deaths coded as influenza and pneumonia. A main reason is that 75% of these deaths are reported in elderly ≥75 years, a group in which the efficacy of influenza vaccination in preventing deaths is unclear and debated. Indeed, targeting the elderly ≥75 years prevents the highest number of prevented deaths per vaccine dose in a best case (4/10,000), but the proposed scenario would only prevent a limited number of deaths per influenza season. We also showed that 88% of elderly who died during

hospitalization also suffered from co-morbidities, and it is not clear whether influenza vaccination would really prevent (or delay) influenza-related death in these persons.

Another reason is that IVE estimates for deaths were lacking, and we had to select a best and a worst case to estimate vaccination impacts on this outcome. Other scenarios would prevent a lower number of deaths per dose (<1/10,000), except in pregnant women in a best case.

We can thus conclude that, based on current knowledge, influenza vaccination is not very effective in reducing deaths – at least based on deaths coded as pneumonia and influenza. This conclusion could be revised if future analyses (e.g. using regression models) would better estimate the number of deaths that are attributable to influenza.

Benefits in terms of prevented deaths obviously have different implications if they concern young persons, pregnant women or elderly ≥75 years of age. This aspect is not taken into account in this analysis as all deaths were given the same weight, but will be analyzed thoroughly in the cost-effectiveness analysis that will be included in the Part II of this study.

Vaccinating persons <65 years with co-morbidities presents the advantage of preventing a sizeable number of both outpatient and hospitalization cases. There is however a risk of overestimating the impact on admissions as we use a high IVE parameter (63%) estimated in a season with good match and high intensity. If we compute the impact by lowering this IVE parameter to 50%, this strategy is still very efficient in terms of outpatient and admissions, and can reach a high impact (314 admissions instead of 396 with 20% additional uptake).

The 65-74-years old, who have a 50% uptake (to be compared to the WHO target of 75%) and are not yet affected by immune senescence, were considered as a potentially important target group by stakeholders. However, our study showed that around 230,000 vaccines would be required to achieve a moderate impact in this group (1346 outpatient cases, 214 admissions and 21 deaths under the best case), though we underestimated the impact on outpatient cases by not taking uptake into account in the baseline burden. This relatively low impact is explained by the lower vaccination impact on outpatient cases compared to vaccinating younger subjects, as well as the lower impact on admissions than the vaccination of the elderly ≥75 years or the adults with co-morbidities.

The increased vaccination of HCWs and pregnant women shows a limited impact in terms of prevented outcomes (<1000 influenza cases and 4-6 admissions). This is partly due to the low number of persons involved, but also because our model does not account for any indirect effect (protecting patients of HCW and infants of mother vaccinated while pregnant).

Our results show a high variability of vaccination benefit on outpatient cases across seasons, due to the variability of influenza season intensity and matching with vaccine strains. This is also confirmed by the uncertainty analysis. Future influenza seasons are unpredictable, and we showed that vaccinating during a season with low intensity and poor match will provide an uncertain benefit on outpatient cases. Our analysis also suggest that admissions for influenza and pneumonia are less influenced by these variations: indeed, the number of admissions was relatively stable, even during the 2005-06 season that showed the lowest intensity; and IVE in the elderly did not differ between seasons with poor or good match in US cohorts studies over 10 seasons.[84, 86] We also did not take into account that the 2009 H1N1 strain would circulate in the next influenza seasons (as this was unknown when this study was initiated), and our predictions may not fully apply to this strain – that show lower attack rates in the elderly.

If the healthy adults aged 15-49 years (who are not currently targeted by the recommendations) would not be vaccinated, 500,000 additional doses could be available to increase the uptake of key target groups. With this strategy, an additional 6600 influenza outpatient cases, 28 additional admissions and no death would be expected to occur in these adults by influenza season, but these doses would allow to prevent 416-705 admissions if they would be used to increase uptake in persons with co-morbidities

and either the 50-64 years or the elderly, respectively, and a small number of deaths. This scenario is however maybe not realistic, and the possible herd immunity effect of vaccinating this large group has not been estimated in this study.

We did not find similar studies in other EU countries. The other studies that addressed the broad question of prioritizing target groups dealt mainly with pandemic influenza;[105, 106] the few studies that also addressed seasonal influenza were mainly looking at the indirect effect of vaccinating specific groups.[104, 107-109]

This study has a number of other limitations. We had to make a number of assumptions and extrapolations for missing parameters; we however tried to assess each assumption (as shown in Table 5) and mitigated their effect, for instance by complementing with data from the literature, and using a best and worst case scenario for uncertain estimates. We used hospital discharge data to estimate the number of admissions related to influenza, but these are linked to hospital financing and ICD coding is not standardized in Belgium. We can thus not be certain that MCD coding was always correct. However we used the same outcome for parameters on IVE for admissions and it has been suggested that influenza and pneumonia coding are rarely influenced by financing. This is probably not true for co-morbidities, which allow for a higher reimbursement of admissions, and this may have lead to overestimate their burden. An important limitation is that we used non-specific outcomes such as pneumonia admissions and deaths to estimate the impact of influenza vaccination, and we saw that these outcomes were not closely correlated to the intensity of influenza seasons. However, this is also reflected in the IVE parameters, which used the same outcomes and did not show significant variations across seasons with good and poor matching. In the Part II of this study, we will estimate the number of influenza-attributable P+I admissions and deaths through regression analysis, and will be able to assess the impact of this potential bias.

Another approximation was to categorize season matching based on similarities between circulating and vaccine strains; this classification is not precise, as vaccine effectiveness is not always correlated to this degree of similarities. Recent studies suggested that the antigenic distance, i.e. sequence difference between the vaccine and circulating strains, is strongly correlated with vaccine effectiveness.[2] However, this information was not available to us.

Another methodological issue was that the swabbing of ILI patients was "ad hoc" and not systematic, and some experts suggested that experienced sentinel GPs are more likely to swab patients that are influenza positive (due to clinical ability to detect them) – which would overestimate the influenza outpatient burden. Indeed, the proportion of ILI that were influenza positive is very high in Belgium (~50%). However, unpublished French studies also found that the sentinel GP are also more likely to swab vaccinated patients – which would tend to underestimate the influenza burden. The IPH virologist of this network showed however that the case definition of reported and swabbed ILI is the same and did not consider that GPs have this selection bias. Furthermore, this bias – if present – is likely to be stable over time.

Our main weakness was the lack of good IVE estimates for mortality in the elderly. After initial claims for a substantial benefit of influenza vaccination on all-cause deaths in the elderly, this has been refuted by many studies.[18, 110] Well conducted studies assessing these parameters have not yet published results, but are highly needed.

We also lacked Belgian data on influenza burden in pregnant women. We mitigated this obstacle by selecting a high/best case based on pandemic H1N1 US parameters. However, the predicted impact was not as high as expected: under the best case (similar to US H1N1 pandemic severity), a 50% uptake would prevent 6 admissions and 9 deaths, but this is even unlikely to apply to Belgium considering the very higher prevalence of obesity (now a known risk factor) in US affected pregnant women in these studies. But this strategy would also prevent a number of hospitalizations in infants born from these women, and we could not compute this indirect benefit. The same also goes for the benefit of vaccinating HCWs, as we did not find parameters to take into account the indirect effect on patients, except in nursing homes – that were not included in this study.

7 CONCLUSIONS ON PRIORITY SETTING

The priority setting in targeting groups for influenza vaccination would depend on the programme objective:

- If the programme objective is to **prevent outpatient cases**, children and adults <65 years of age, with or without co-morbidities, should be targeted. However, increasing influenza uptake in healthy adults would only prevent a few admissions in a best case scenario. The prediction of prevented outpatient cases also involves the highest level of uncertainty and variability, mostly due to unpredictable seasons and changing influenza strains.
- If the vaccination programme aims at **reducing severe disease, such as admissions**, the most effective strategy would target the persons 1-64 years old with co-morbidities. Current uptake in this group is only 20%, and a 20% increase in uptake would prevent on average around 400 admissions and 1-15 deaths. Another possible strategy is to increase the uptake in elderly ≥75 years, but this has a low feasibility and, hence, a low potential impact as the current uptake in this group is already high.
- None of the strategies would be able to substantially **decrease deaths from influenza and pneumonia**. Most of these deaths are found in the elderly ≥75 years, and it is not clear whether increasing influenza vaccination in this group could really prevent (or delay) additional influenza-related deaths. Based on current knowledge, influenza vaccination is not very effective in reducing deaths – at least deaths coded as caused by pneumonia and influenza. This conclusion could be revised if we would be able to better estimate the number of deaths that are attributable to influenza.

We did not assess strategies to decrease the epidemic curve by reducing influenza transmission. Several studies have predicted a large impact of vaccinating school age children in reducing influenza transmission, and therefore reducing the exposure of most vulnerable groups. This aspect will be addressed in the Part II of this study.

If the young healthy adults would not be vaccinated, the 500,000 vaccines currently used to cover them could target groups at high risk.

All strategies involving persons with co-morbidities present the advantage of having a high impact on admissions, due to the high admission burden and high vaccine effectiveness in this group, while also having a high effect on outpatient cases and some effect on deaths. This advantage persists even when we decrease the IVE – that might be overestimated - to less favourable values.

Targeting the HCWs and pregnant women does not yield an important benefit in terms of prevented outcomes, but this result may be due to the inability of our model to account for the indirect vaccination effect.

A surprising finding is that, whatever the scenario, the number of prevented outcomes is small compared to the total influenza burden: the maximum strategy would only prevent 3% of all outpatient cases, 3% of P+I admissions and 1.4% of all P+I deaths (best case). Though we probably underestimated the real benefit of influenza vaccination because our study is restricted to pre-specified outcomes, the use of more effective influenza vaccines (e.g. using live attenuated viruses or adjuvants) is likely to represent a more effective strategy. These vaccines are expected to be available in Belgium in a near future.

8 APPENDIX 1: DATA SOURCES AND METHODS TO ESTIMATE MEDICAL BURDEN AND UPTAKE

As a major factor influencing medical burden is the nature of the circulating viruses and their variability in terms of incidence, severity, and affected target groups we used data from 6-7 influenza Belgian seasons for each outcome, broken down by week or month of onset, to take seasonal variability into account.

8.1 CURRENT VACCINE UPTAKE

Influenza vaccine uptake data, estimated by the HIS 2008, were received from the IPH on the following study groups: each age group and patients with co-morbidity. In addition, IMA and INAMI/RIZIV estimate every year the uptake by age group based on reimbursed doses (for elderly mainly).

No data are available on the uptake in pregnant women, which is assumed to be negligible. Uptake in HCWs was found in several reports and publications:

- Surveys in GPs
- Surveys in hospital health care workers
- Surveys in health care workers in nursing homes
- HIS survey 2008

8.2 INFLUENZA SEASONS

As we use non-specific outcomes, it is important to calculate the burden of disease on the periods of influenza virus circulation only. Outside these seasons, influenza viruses are not circulating, and non-specific outcomes such as ILI and pneumonia are thus mostly caused by other pathogens (that may also vary in frequency). Disease burden occurring outside the influenza season is thus not likely to be prevented by influenza vaccination, either because it is not due to influenza, or because vaccinees may no longer be protected by the yearly vaccine due to drifts in circulating influenza strains.

The *influenza season* classically corresponds to the period during which the influenza virus may circulate, and is defined in Belgium as the period between week 40 to week 20 of the next year. However, the period during which the influenza virus is circulating each year, or *viral activity season*, varies by year and by country, and its duration is systematically narrower (10-20 weeks). The criteria to determine this period also varies across countries and studies, but is usually based on the incidence of ILI and/or the number of positive ILI samples (Table 33).

Table 33: Criteria defining influenza activity period

Study	Criteria ILI rate	Criteria lab
Beran[a] [72, 73]		Begin: 1st week with 2 positive cases End: last week with last positive
Michiels (case control in BE)[52]		Begin: >1 positive in 2 weeks
Nichol and Nordin (US HMO cohort)[a] [83, 84, 86]		Begin: 1st isolate sent to CDC End: last isolate sent to CDC
Mangtani (UK cohort)[a] [85]	Begin: ILI>=50/100,000 End: ILI<50/100,000	
Baxter (US cohort), season[a] [81]		Begin: 1st of 2 weeks w/ 2 isolates End: last of 2 weeks w/ 2 isolates
Jackson (US case control)[69]		Begin: 1st week w/ >=50 isolates End: last week w/ >= 50 isolates
Hak (Dutch cohort)[99]	Begin: ILI exceeding baseline	

[a]: Studies used to derive vaccine effectiveness estimates. ILI: Influenza like illness.

The determination of activity seasons in Belgium was based on the following criteria as used in most vaccine effectiveness studies that served to derive estimates for our model:

- Beginning of the influenza activity season: the first week of the 2 weeks in which the first 2 laboratory confirmed ILI cases are reported.
- End of the influenza activity season: the last week of the last 2 weeks in which the last 2 laboratory confirmed ILI cases of the season are reported.

These criteria were applied to data on laboratory confirmed ILI cases reported by the Sentinel Network of GPs (see below). We used the dataset on the 2003-04 to 2008-09 seasons; for 2002-03, we used historical data provided by the IPH (figure 4); and for the 2000-01 and 2001-02 seasons, we used Belgian data provided in the European Influenza Surveillance Scheme (EISS) annual reports. We thus determined the beginning and end of each season in the 2000-2009 period. We also calculated the proportion of annual cases occurring during this period for each outcome (ILI, admissions and deaths) that occurred.

We characterized the past 8 Belgian seasons in terms of influenza viral intensity on one hand, and matching between the vaccine and circulating strains on the other hand:

- **Influenza intensity**: high, medium and low, as defined in the IPH or EISS reports.
- **Matching** between the vaccine and circulating strains: good, relative and poor.

Characterization in terms of level of influenza intensity and matching was provided in the IPH annual reports on influenza for the 6 seasons from 2003-04 to 2008-09, and in EISS reports for the missing years, and/or by the experts from the National Influenza Centre.

8.3 POPULATION FIGURES

Population figures by age group were obtained from the FPS Economy - Directorate-general Statistics and Economic Information through the SPMA website (http://www.wiv-isp.be/epidemio/spma/). Figures on pregnant women are not available as such, but the number of live births (or first birth cohort) from SPMA was used.[111]

The HIS 2008 provided the proportion of specific co-morbidities (self reported), corresponding to the conditions for which the influenza vaccine is recommended, by age group, in the representative population sample studied.

We collected figures on the numbers of HCWs from INAMI/RIZIV databases (Cellule Data management INAMI), by category, updated in February 2009. As not all HCWs registered in the INAMI databases are involved in health care services, we also looked for the proportion of HCWs that were "active" in health care services in INAMI annual reports.

Population figures by age group were based on the SPMA data, by year and age group.[111] We took as mid-season population the midyear population, which is defined as:

(pop year1 + pop year2)/2

To estimate the number of patients with co-morbidities, we applied the proportion of co-morbidities by age group, as provided by the HIS 2008, to the corresponding general population figures by age group of the last 3 seasons.

We selected all HCWs categories and computed them in five larger groups. To estimate the number of HCWs that are involved in the daily work of health care services, we took the proportion of GPs that were active in 2008 (82.4%) and applied them to the other categories, assuming that this proportion is similar for non-GP HCWs (INAMI 2008).

8.4 OUTPATIENT CASES OF INFLUENZA-LIKE ILLNESS AND INFLUENZA

8.4.1 ILI cases reported to the IPH Sentinel Network of GPs

Data on ILI and influenza cases over the last 6 pre-pandemic influenza seasons (2003-04 to 2008-09) were collected from sentinel networks of GPs coordinated by the IPH. Each week, the GPs reported the total number of total consultations and ILI consultations by four age groups, using a standardized registration form; case definition and age groups are described in Table 34. Hospitalisation and vaccine status are also recorded but were not used for this analysis due to incomplete records.

A first sentinel network, specifically dedicated to influenza surveillance, was constituted of 40-60 GPs located across Belgium and recorded cases during the influenza season only (weeks 20 to 40). [40] This network, initiated in 1985 under the EISS coordination, reported an average of 2500 ILI cases by season. Since autumn 2007, this network is integrated into the network of the Sentinel General Practitioners (SGPs), totalling around 200 GPs.[44] These GPs recorded cases during the whole year (weeks 40 to 39), reporting in average 10,000 ILI cases by season. This second nationwide network represents approximately 1.8% of all Belgian GP and is representative of the Belgian population. It has been conducting a voluntary surveillance of various health problems since 1985 and has proved to be a reliable surveillance system for a wide variety of health-related epidemiological data e.g. on diabetes, stroke, cancer, accidents.[42, 43] The same methodology has been used over the study period in the two networks.

The population covered is not precisely known, but is estimated by a method advised by EISS: each GP is assumed to cover a population that is calculated by dividing the Belgian population by the number of active GPs in Belgium, by year and by region. The IPH database on ILI provides the estimated denominator for each week, according to GP participation.

Several methodological issues need to be considered when using these sentinel ILI data to estimate incidence to the population:

- The objective of this GP registration is not to calculate incidence rates but to detect the beginning of the influenza virus circulation, and to monitor influenza activity and circulating strains.
- This system does not cover cases seen by paediatricians and in emergency rooms. Incidence rates calculated by this network are thus an under-estimation of the true incidence.

Data on these missing cases cannot be extrapolated from other countries as wide variations are seen across countries, strongly dependant on health seeking behaviour and other factors. This study is therefore limited to ILI cases seen at GP offices. The lack of data from paediatricians should have a limited impact as the only children involved in the vaccination scenarios are the children with co-morbidities, which are a limited group.

ILI in specific groups other than the given age groups (i.e. co-morbidities, pregnant women and HCWs) are not available from this GP database. No other Belgian data have been found, and we performed a literature search to assess whether ILI incidence in these groups differs from the general population, and if so, which values can be used.

8.4.2 ILI laboratory results from the IPH National Influenza Centre

In addition, a sample of ILI patients from all ages are swabbed by the GPs during the influenza activity period and tested for influenza. All samples are sent to the National Influenza Centre (NIC) and tested by nested RT PCR for influenza A/B; positive A influenza are further tested for H3/H1. In addition, a subset of samples is cultured and the isolates are sent to the London WHO reference Centre.

Every year, around 1000 cases are swabbed, but this sampling of ILI cases is “ad hoc” and thus not systematic. The network is organized on a way that the ILI cases reported and those swabbed are not systematically the same persons.

Table 34: Characteristics of the ILI databases from the IPH GP network

Characteristic	ILI cases reported	ILI cases swabbed
Selection criteria	Acute respiratory infection with influenza syndrome, defined as sudden onset, fever and myalgia.	ILI case, no criteria (ad hoc sampling)
Period with data	6 seasons, 2003-09	6 seasons, 2003-09
N participating GPs	40-50 in 03-07, 160-200 after 2007	40-60 in 03-06, 90-100 after 2006
Data available	Aggregated: N cases/ week / age group	Individual: case with DoB, week onset, result PCR
Age available	Age groups: 0-4, 4-14, 15-64, 65+	All ages (DoB is available)
Number of annual cases included	1800-3000 in 2003-07 (avg 2493) 8800-10,000 from 2007 (avg 9606)	770-1150 (avg 1009)
Seasons involved	weeks 40-20 in 03-07, 40-39 later	weeks 40-39 but few cases in weeks 20-39
Denominator	Calculated by week, according to the N reporting GP by week	Not calculated (sample from ILI reported)

DoB: date of birth. ILI: influenza like illness. Avg: average.

8.4.3 Estimation of total ILI and influenza cases

Data on ILI were extrapolated to the entire population. ILI data were available for the week 40 2003 to week 52 2009. Based on data on ILI and denominators provided in the sentinel GP database, we have calculated:

- Incidence rate of ILI by week and age group
- Total number of ILI by week and age group, by applying the age-specific incidence rates to each age-specific population figures.
- Total number of ILI cases by season (by epidemic season and activity period), by summing the weekly ILI cases

Based on the database on laboratory influenza results, we have calculated:

- The proportion of ILI that are positive for influenza by week and age group. However, the number of children and elderly cases that are swabbed every week were too low to yield a proportion of positive swabs for every week. We thus calculated the average proportion of positive cases over each influenza season.

By applying this proportion to the relevant number of ILI cases by week and age group, we have calculated:

- Total number of influenza cases by week and season (epidemic season and activity period) and by age group
- Incidence rate of influenza by season and age group

As the sentinel GP database is stratified in wider age groups (4 age groups) than those selected for this study (6 age groups), we extrapolated the incidence of larger age groups to smaller age groups to estimate the total number of ILI in the 6 age groups (e.g. ILI incidence in 15-65 years was used for incidence in the 15-49 and the 50-65 years). We assumed that ILI incidence was homogenous across these large age groups; An European study showed that the ILI excess rates over 5-13 seasons in 3 EU countries were grossly homogenous across the 15-24, 25-44 and 45-64 years, and very similar in the 65-74 and ≥75 years.[47, 48]

A wide literature search assessed evidence of higher or lower baseline influenza rate in the three specific groups (co-morbidity, pregnant women and HCWs), in order to adjust overall rates of the relevant age group, if needed.

8.5 HOSPITAL ADMISSIONS FOR INFLUENZA AND PNEUMONIA

As hospital admissions for influenza may often be attributed to a complication (mainly pneumonia) and thus coded as such, we searched for admissions due to influenza and those to pneumonia. Though influenza may also lead to other complications, only these two outcomes – for which vaccine efficacy has been estimated – are considered in the research question of this study.

8.5.1 Source of data

Minimal Clinical Data (MCD) on hospitalizations due to influenza disease and pneumonia over 2000-2007 were received from the Technical Cell (Federal Public Service for Public Health and RIZIV/INAMI). The registration of MCD is mandatory for Belgian hospitals, and a specific set of data need to be recorded for each hospitalized patient. In addition, these data are linked to Hospital Billing Data (HBD), which allows to calculate the cost of hospitalisation per diagnosis. It is thus possible that the coding of diagnosis and co-morbidity is biased by financial implications. As the coding system and its validity in terms of diagnosis have not been assessed, care must be taken in the interpretation of MCD data.

All patients discharged in Belgian hospitals between 2000 and 2007 with a diagnosis of influenza or pneumonia, either as primary (main), secondary diagnoses/ complication, including one of the following codes, have been selected:

- 480 Viral pneumonia
- 481 Pneumococcal pneumonia
- 482 Other bacterial pneumonia
- 483 Pneumonia due to other specified organism
- 484 Pneumonia in infectious diseases classified elsewhere
- 485 Bronchopneumonia, organism unspecified
- 486 Pneumonia, organism unspecified
- 487 Influenza

Only the month of admission and the year of birth are available in the MCD database. However, in the HBD the exact dates are available, since 2004. Groups of co-morbidities were identified based on the presence of ICD-9 CM codes of the medical conditions for which influenza vaccine is recommended in Belgium. Patients with at least one co-morbidity are identified, according to the codes described in

Table 35: ICD codes corresponding to the GSS/HGR recommendations for influenza vaccination

CSS/HGR recommendations for underlying diseases (2009-10)	ICD9 codes
Chronic pulmonary disease	491-496, 500-508
Chronic heart disease	393-398, 402-404, 410-414, 415-417, 425-429
Chronic liver disease	571-573
Chronic renal disease	581-588
Chronic metabolic diseases	250-258
Chronic neuro-muscular disease	320-326, 330-337, 340, 710
Immune deficiencies (primary and secondary)	279, 200-208

No Belgian data are available on influenza admissions in pregnant women; the literature has been searched to estimate the excess risk in pregnant women compared to adult women. For health care workers (HCW), the same estimates for admissions have been assumed than for the general adult population.

8.5.2 Estimation of admission parameters

The numbers of admissions for influenza and pneumonia are based on the "main" (or principal) MCD diagnosis, because we aim to estimate the number of admissions that could be prevented if the patient did not suffer from influenza. We could not perform a revision of all admission dossiers to assess the reliability of influenza main diagnosis coding, given the huge number of admissions.

Based on the principal secondary diagnoses/complications, the following categories have been defined in exploratory analyses. In final analyses, only data on principal diagnosis have been retained.

1. **Influenza** as primary diagnosis
2. **Pneumonia** as primary diagnosis, with **influenza** as comorbidity / complication
3. Other primary diagnosis, with **influenza** as comorbidity / complication
4. Subtotal all **Influenza** (groups categories 1, 2, 3)
5. **Pneumonia** as primary diagnosis, without influenza as comorbidity / complication
6. Other primary diagnosis, with **pneumonia** as comorbidity / complication
7. Subtotal all **Pneumonia** (groups categories 2, 3, 4)
8. Total (all hospitalization)

MCD data have been aggregated by season (Influenza season: all admissions from October to April included) month, age group (0-4, 5-14, 15-49, 50-64, 65-74, +75), and all analysis are stratified for the presence/absence of co-morbidities. Only the year of birth is available in the MCD. Age is thus defined as if all patients would be born on the first January of their year of birth.

The season is based on the date of admission of the patient. Admission week is not available in the MCD dataset, only the month. The theoretical influenza season (week 40 to week 20) has been approximated by the period from October to April (included) as periods both closely correspond. For the influenza activity season, which is more precise and vary each year, starting at any week of the months, we linked the HBD dates of patients to derive a proxy of the admission week. However, this was only available for the 2004-08 years. After comparing the number of admissions during all activity seasons based on the week of admission (exact definition) and those based on the month of admission, we found that the calculation by month would only add overall 2% and 7% of admissions for influenza and pneumonia respectively (all ages and all seasons). We thus opted for the definition by month as this can be applied to the entire study period.

Patients with co-morbidity are patients admitted for at least one co-morbidity. For these patients, we considered using all diagnoses (main and secondary diagnoses) because we assumed that the main diagnosis is more frequently related to the co-morbidity than to influenza or pneumonia. We calculated the numbers of admissions in co-morbid patients by age group and season. As there are no Belgian studies on the quality of the coding of co-morbidity for patients admitted for influenza, we compared estimates derived from the MCD data to those published from other countries for validation purpose. We calculated a ratio of "admission rate in co-morbid / admission rate in non co-morbid patients" (relative risk or RR), using as denominator for co-morbid patients the age-specific proportion of these diseases estimated by the HIS 2008, applied to the age-specific population figures.

Experts reported that many children presenting with fever may be admitted for a 24 hour observation period and might have been coded as influenza, thus inflating the number of influenza admissions, though they represent a much smaller burden on health care services. We thus analyzed the frequency of admissions with a length of stay of 1 day to assess this possible bias.

The number of admissions for influenza and pneumonia among pregnant women could not be computed from the current MCD dataset, as this variable was not available. We reviewed the literature to assess any excess in admissions. We also compared the risk of MCD admissions in women of children bearing age (in influenza season) with the one in males from the same age group (comparing sex ratio across age cohorts).

8.6 DEATHS FROM INFLUENZA AND PNEUMONIA

As deaths from influenza may often be attributed to a complication (mainly pneumonia), the deaths due to influenza and pneumonia were selected as outcome.

Fort each death in Belgium, a death certificate is filled in by a physician, and the cause(s) of death are recorded. This certificate is collected and further filled in by the communes and sent to the relevant Community, where the diagnosis is transformed into codes and data are compiled. Since 1998, more details on the causes of death may be recorded, following the international rules of the WHO and the ICD-10 codes ("International Classification of Diseases (10th revision).[g] After validation and analysis at community level, the data on causes of death are centralized at national level.

8.6.1 Cause-specific deaths from Flanders, Wallonia and Brussels

As national compilation of causes of death is severely delayed, data on influenza-specific and pneumonia-specific deaths (ICD-10 J10-18) have been requested from each Community, by age, influenza season of onset (as calendar years may have 0 or 2 influenza seasons), classification of cause of death (immediate, underlying and associated) for each diagnosis. At the time of request, the time limitation of estimates to the influenza seasons had not been considered, and data by week were not requested.

Data from the French Community only covered the season 2004-05.

Data provided by the Community registers do not contain information on specific groups (pregnant women, persons with co-morbidities and HCWs). A literature search has been performed to assess excess mortality estimates in these groups and possibly apply them to the Belgian context. As literature estimates on excess deaths were not consistent and not complete on persons with co-morbidities, we also assessed the hospital deaths from MCD data.

8.6.2 In hospital deaths from MCD database

The number of patients hospitalized for influenza of for pneumonia and deceased during their hospitalisation was computed based on MCD data, by age, month, reason of admission and presence of co-morbidity. Death during hospitalization does not imply that the reason of hospitalization was the cause of death. However, there was a high level of overlapping between the numbers of deaths from the Communities and from MCD data in all age groups <65 years.

As more details were available on MCD deaths (presence of co-morbidity, month of onset), we used MCD data to calculate the time distribution of influenza and pneumonia deaths in the influenza seasons. We also calculated the relative risk (RR) of dying from influenza and pneumonia in patients with co-morbidities, and confronted it to other studies.

g http://www.zorg-en-gezondheid.be/Cijfers/Cijfers-over-sterfte/#waar

8.6.3 Estimation of mortality parameters

The numbers of deaths for influenza and pneumonia are also based on the "main" diagnosis, because we aim to estimate the number of deaths that could be prevented if the patient did not suffer from influenza or pneumonia. The main (or initial) cause of death is defined in accordance with the encoding rules of the WHO, as the diseases or injuries which are at the base of a reaction chain of morbidities that finally lead to death.[111] We could not perform a revision of death certificates to assess the reliability of diagnosis coding, but we address this issue in the sensitivity analysis.

As data from the French Community only covered the season 2004-05, we imputed data for the other seasons, by applying the proportion of deaths from the French community on all national deaths in 2004-05, by age group.

MCD deaths have been aggregated by season and month, age group, and all analysis are stratified for the presence/absence of co-morbidities. We used MCD deaths to complete parameters that could not be derived from community data, to calculate the following:

The proportion of annual deaths (from influenza and pneumonia) that occur during the seasons (influenza season and activity season). Indeed, community deaths were only received by year; this assumes that this proportion is similar for cases that did not die in hospitals.

The number of deaths that occurs in patients with co-morbidity, based on the proportion of MCD deaths occurring in co-morbid patients, assuming that patients who died at home from influenza and pneumonia presented the same prevalence of co-morbidities than those dying in hospitals.

8.7 TARGET GROUP FOR SEASONAL INFLUENZA VACCINATION IN BELGIUM

In Belgium, seasonal influenza vaccination is currently recommended for the following groups, by order of priority (2007-2008 season:[22]

Group 1: persons at high risk of complications:

- all persons aged 65 years and above
- persons living in institutions
- all patient above 6 months of age with a chronic disease involving lung, heart, kidney, liver or from metabolic and immunological origin
- children from 6 to 18 months under long term therapy with aspirin

Group 2: all staff working in the health sector that could be in direct contact with the persons from group 1.

Group 3: Pregnant women that would be in the second or third trimester at the time of vaccination

Group 4: Persons aged 50 to 64 years, even those not identified as being at risk and particularly those smoking, having a drinking problem, and obese persons

Regarding the universal vaccination of young healthy children, the Health Council considered that available evidence is currently not sufficient to propose this strategy.[112]

9 APPENDIX 2: RESULTS ON INFLUENZA DISEASE BURDEN

9.1 INFLUENZA ACTIVITY SEASONS

The timing, duration and characterization of the 9 Belgian activity seasons are provided in Table 36. The season definition and duration differ from those defined in the IPH annual reports for 2 reasons: there were no strict criteria in IPH reports for defining activity seasons before 2007-08; and the IPH concept of activity season is meant to identify the influenza seasonal outbreak, while we aim to capture all events which could potentially be prevented by influenza vaccination.

Table 36: Description of influenza activity seasons in Belgium, 2000-2009

Seasons	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09
Influenza activity (weeks)	45-14	49-17	2-17	43-6	48-14	3-18	52-13	48-17	47-18
Duration (weeks)	21	20	15	15	18	15	13	21	23
Level activity	low	medium	medium	medium	medium	low	medium	low	medium
Matching	good	good	good	poor	relative	relative	good	good	good

It should be noted that the seasons are defined based on ambulant ILI cases, thus not necessarily reflecting the occurrence of cases of severe (admitted) cases. On these 9 influenza seasons, none presented a high level of activity.

9.2 POPULATION FIGURES

The number of persons with and without co-morbidities by age group and other target groups in 2008 is provided in Table 37.

Table 37: Population estimates for the different target groups, 2008

Age / target group	Total	With co-morbidity	Healthy
0-4 years	595,442	45,254	550,188
5-14 years	1,203,650	72,219	1,131,431
15-49 years	5,032,259	407,613	4,624,646
50-64 years	1,979,457	320,672	1,658,785
65-74 years	919,531	245,515	674,016
75 years +	895,366	314,273	581,093
Pregnant women	121,362	NA	NA
HCW (active)	239,740	NA	NA
Total 1-64 years	8,810,808	835,406	7,965,050

ILI: Influenza like illness. HCW: Health care worker. NA: Not applicable.

9.3 ILI AND INFLUENZA CASES BY INFLUENZA SEASON

9.3.1 Cases reported and swabbed by the network

A total of 29,182 ILI cases have been reported by the sentinel GPs over the 6 influenza seasons (Table 38). During 2003-07, reporting was limited to a first network and involved 49 GPs in average, reporting an average of 2328 cases (range 1793-3040), during the influenza season (weeks 40 to 20). In 2007-09, the two merged networks involved 198 GPs and reported an average of 8597 ILI cases. The mean number of cases reported by GPs did not vary over the two periods (47.8 and 43.4 respectively).[h]

The number of ILI that were swabbed was relatively stable (mean 989), as the target sample was limited at around 1000 samples. A lower number was sampled (N=779) in 2005-06, a season with low intensity. The proportion of ILI that was swabbed decreased after 2007 due to an increase in reported ILI caused by a larger number of reporting GP. The age distribution of swabbed ILI was relatively stable over the period but the proportion of swabs among adult cases (15-65 years) tended to increase over time. There was a tendency to sample more adult cases than children and elderly, as an average of 11%, 17%, 18% and 12% all ILI were swabbed over the 6 seasons in the age groups 0-4, 5-14, 15-64, and ≥65 years respectively. As ILI is also less frequent among elderly, few elderly ILI cases were swabbed per season (range 14-29 swabs in the ≥75 years, Table 38).

The proportion of positive swabs varied by influenza season (mean 54%, range 47-62%) and likely reflected circulating virus characteristics. For instance, the highest positivity rate (62%) was observed during the 2003-04 season, which was dominated by the new drift variant A/Fujian/411/2002 strain which was not matched with the influenza vaccine of that year (Paget 2005). The positivity rate also varied by age, with the highest proportion of positive swabs consistently found in the 5-14 years (mean 64%) and the lowest in the elderly of 75 years of age and above (mean 43% but range 15-70%).

Table 38: ILI cases reported and swabbed by GP, by influenza season (weeks 40- 20), 2003-2009

	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09
Total ILI cases reported	3040	2524	1793	1955	8385	8808
N GPs reporting	56	57	41	41	196	200
Avg N ILI reported/GP	54.3	44.3	43.7	47.7	42.8	44.0
Total samples / swabs	1062	987	779	1165	948	993
Total positive swabs	658	551	367	668	448	501
% ILI swabbed (total)	35%	39%	43%	60%	11%	11%
% positive samples	62%	56%	47%	57%	47%	50%
N GPs swabbing	66	50	42	101	89	NA
N swabs in 0-4 years	70	49	72	53	35	28
N swabs in 5-14 years	205	189	205	186	129	122
N swabs in 15-49 years	599	542	380	686	608	601
N swabs in 50-64 years	106	122	78	150	128	163
N swabs in 65-74 years	34	45	19	36	20	35
N swabs in ≥75 years	27	23	13	29	14	21

ILI: Influenza like illness. Avg: average. GP: General practitioner

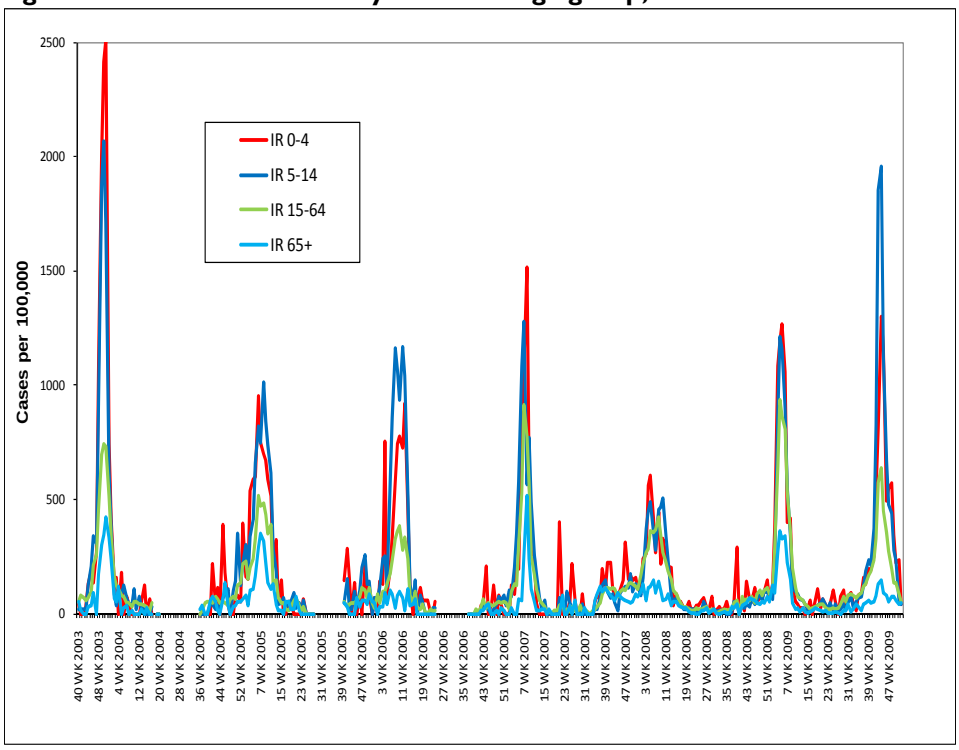
[h] Statistic tests could not be computed by lack of data on the activity of each GP

9.3.2 ILI in the Belgian population

Figure 20 shows the weekly incidence rate of ILI by age group. Incidence is systematically highest in children and lowest in the elderly, but they vary in intensity by season and age patterns, according to the circulating virus characteristics. For instance, the Fujian strain in 2003-04 showed the highest intensity and affected predominantly the children, as described in other EU countries.[113] The 2005-06 season had a mild intensity due to a predominant B strain, with a much lower incidence in the elderly (14 per 1000 in the season).

A Belgian study based on computerized GP network (Intego in Flanders) showed almost identical ILI curves over 4 seasons (1999-2003), with rises in frequency and timing corresponding to those from the IPH network. However, a high rate of ILI was observed in the Intego network.[41]

Figure 20: ILI incidence rate by week and age group, 2003-09



The estimated total number of ILI cases by influenza season is provided in Figure 1: . We assumed that ILI incidence was similar in the 15-49 and in the 50-64 years, as well as in the 65-74 years and the 75 years and above, as shown in other EU studies.[47, 48]

Overall, ILI attack rates during the influenza period were highest in children 0-14 years (average 78/1000 similar in both <5 and 5-14 years) which represented 26% of all ILI cases, Figure 22. This was followed by the adults 15-64 years (52/1000) representing 67% of all cases. And finally the elderly ≥ 65 years had an attack rate of 22/1000 and represented only 7% of all cases (3.9% and 3.6% for the 65-74 and the ≥ 65 years respectively).

Table 39: Estimated number of ILI cases by age group and influenza season (weeks 40 to 20)

	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09
0-4 years	61,997	49,913	44,220	34,190	38,526	43,984
5-14 years	116,229	107,771	119,088	78,171	69,823	80,514
15-49 years	268,091	272,377	197,111	235,880	273,814	313,250
50-64 years	97,416	101,729	75,298	92,541	107,706	123,218
65-74 years	23,167	28,205	13,437	14,402	21,774	25,329
75 years +	19,395	24,707	12,246	13,955	21,202	24,663
Total	586,294	584,702	461,399	469,139	532,846	610,958

A wide literature review did not show evidence of significantly higher or lower baseline ILI rate in the three specific groups (co-morbidity, pregnant women and HCWs), with 2 exceptions:

- The proportion of pregnant women that experienced ILI resulting in health care utilization (inpatient and outpatient) was 8.3% in a large US study, but there was no comparison with non-pregnant women.[59] In Belgium, we found a proportion of 4-6% of the age group 15-49 years consulted a GP for ILI, varying across seasons. In the pregnant women with co-morbidities, the rate of physician visits for acute respiratory infections (which is not an outcome of this study) were 20% more frequent in their 3rd trimester than in the year before pregnancy (RR 1.2 95% CI 1.1-1.4).[51] However, pregnancy in itself is already increasing the rate of consultations.
- Among Belgian GPs, moderate evidence suggest an overall higher level of immunity (based on serological levels) with significant lower rates of upper respiratory infections compared to patients (OR 0.27, 95% CI 0.14–0.51).[63] However, the situation of GPs cannot be extrapolated to all HCW.[54]

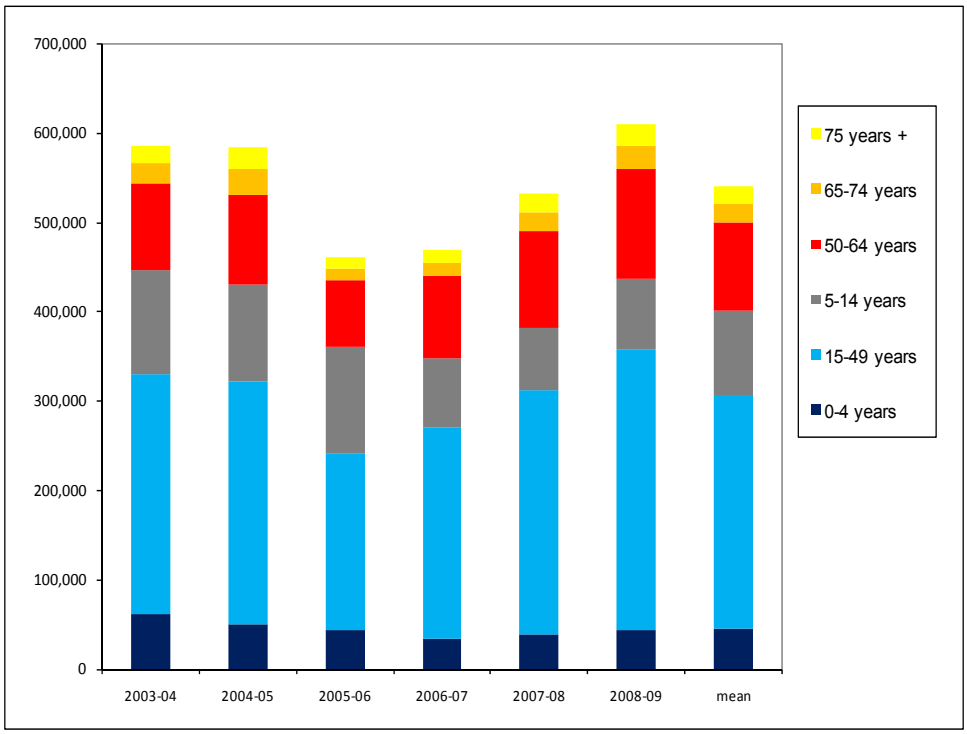
In persons with co-morbidities, no prospective study involving ILI and compared to persons without co-morbidities were found, except in children. Most studies showed an increased risk of developing clinical complications post-influenza in persons with co-morbidities, which is reflected in the section "Hospitalizations".[56, 57]

As the data did not show a consistent relative excess in ILI rate in these groups, it was therefore decided to base the ILI estimates in these groups on the ILI rate in the same age group. We thus applied the incidence rate of ILI of the respective age groups to the denominators for each group.

9.3.3 Influenza in the Belgian population

Estimates of influenza cases, by age, are provided in Figure 21 using the average positivity over each influenza season by age group. Estimates using the weekly proportion of positive cases were in average 95% lower than those based on the yearly average, with the lowest proportion in the elderly (74%). This is because samples are missing during several weeks in the older age groups, and this would thus underestimate numbers of influenza cases during those weeks.

Figure 21: Estimated influenza cases by age group and influenza season, 2003-04 to 2008-09 and season mean



The mean number by season amounts to an annual average of 540,890 ILI and 285,951 influenza cases. Influenza cases represent in average 53% of ILI cases, with the lowest proportion in the elderly aged 75+ (41%) and the highest in the school aged children (64% in the 5-14 years). Incidences of ILI and influenza (Table 8) are also systematically highest in children and lowest in the elderly. Overall, the number of ILI cases in the children 0-14 years of age, adult 15-64 years and the elderly ≥65 years represented 26%, 67% and 7% of all ILI cases, respectively. Similar age patterns are seen for influenza cases, though a difference is observed in children <5 years: the mean incidence rate in the <5 years is lower than in older children due to a lower proportion of influenza positive ILI in this group (48% in average). This is probably explained by the high rate of respiratory syncitial virus (RSV) causing ILI in young children.

The total number of influenza cases per season amount to 285,951 in average (range 212,195-363,880), representing 50% of estimated ILI. This proportion slightly differs from the proportion of swabbed cases (54%) because extrapolation to the population stratified by age has adjusted this proportion for age distribution.

Overall, influenza attack rates during the epidemic period were highest in children, with an average of 50/1000 and 37/1000 in the 5-14 years and the <5 years respectively, which represented 29% of all influenza cases, Figure 22. The lower attack rates in the <5 years compared to older children is explained by a lower proportion of positive ILI, likely explained by the high rate of RSV causing ILI in this age group. This was followed by the adults (28 and 25/1000 in the 15-49 and 50-64 years respectively) representing 65% of all cases.

And followed by the elderly with an attack rate of 11 and 9/1000 in the 65-74 and 75 years and above respectively, representing 6% of all cases (3.6% and 2.8% for the 65-74 and the ≥ 65 years respectively).

The age specific attack rates also varied across the seasons. The highest rate was observed in the <5 years in 2003-04 (71/1000), under the new Fujian variant predominance, representing the double of the attack rates in other seasons (26-37/1000). In 2005-06, attack rate was very high in the 5-14 years (66/1000) while it was low in the adults (12-17/1000) and very low in the elderly (<3/1000).

This is explained by the predominance of influenza B (64% of strains), which is known to cause highest rates in school children.[38]

Table 40: Estimated number of influenza cases by age group and influenza season (weeks 40 to 20)

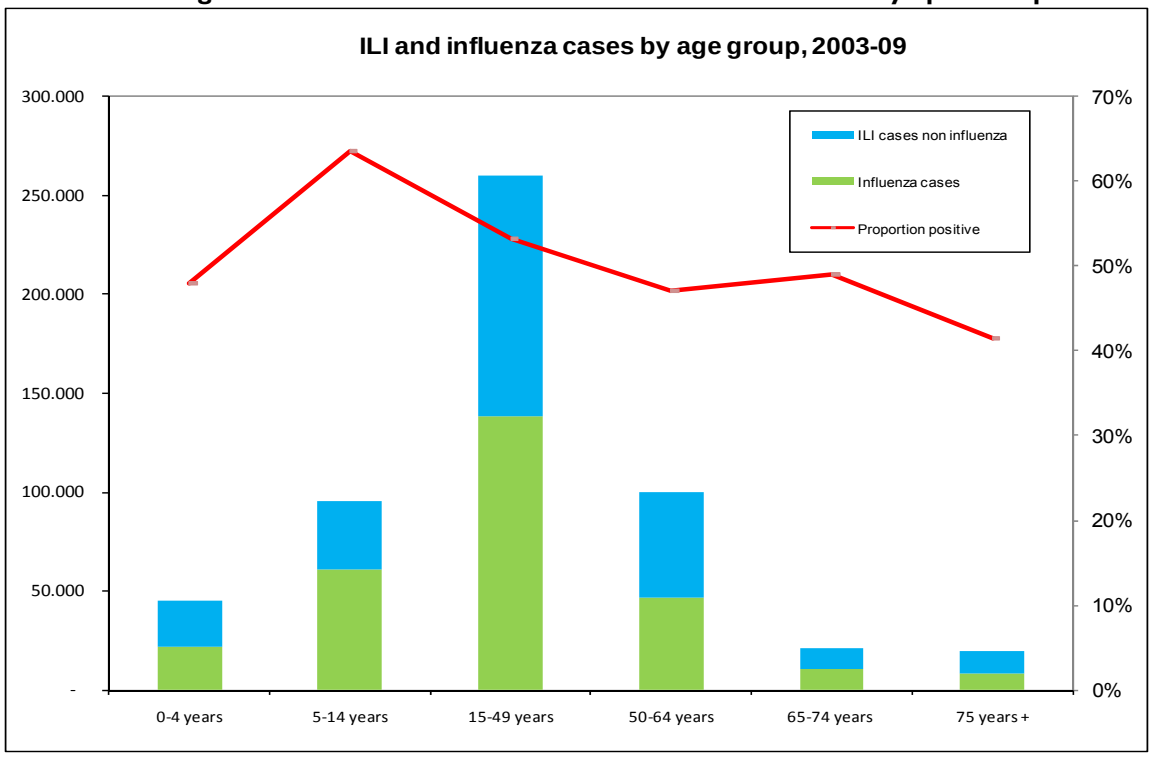
	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09	Mean
0-4 years	40,741	21,391	18,425	16,127	15,411	18,850	21,824
5-14 years	81,077	68,426	80,747	51,694	35,724	45,537	60,534
15-49 years	165,599	142,219	86,106	133,413	137,357	165,225	138,320
50-64 years	56,979	59,203	22,203	49,355	38,707	55,184	46,938
65-74 years	11,583	21,311	2,829	8,401	7,621	10,132	10,313
75 years +	7,902	17,188	1,884	7,218	4,543	9,396	8,022
Total	363,880	329,737	212,195	266,209	239,363	304,323	285,951

Table 41: Estimated numbers of ILI and influenza in HCW, pregnant women and persons with co-morbidities (mean over 2003-09)

Group	ILI	Influenza
HCW (15-64 years)	12,467	6,425
Pregnant (15-49 years)	6,106	3,243
Co-morbidities <65 years:	46,382	24,099
0-4 years	3,456	1,659
5-14 years	5,716	3,632
15-49 years	21,067	11,204
50-64 years	16,143	7,604

ILI: Influenza like illness. HCW: Health care worker.

Figure 22: Estimated numbers of ILI and influenza cases by epidemic period



The literature review did not show a consistent excess in the rate of confirmed influenza in specific groups (persons with co-morbidities, HCW and pregnant women) compared to non-risk groups:

- For HCW, a multivariate analysis of a German cohort showed that HCW were not at higher risk of serologically-confirmed ILI than non-HCW (relative risk =1.09, p=0.70). HCWs were less susceptible to the previous and current influenza viruses than non-HCW.[55] Likewise, a Belgian RCT showed high seroprotection rates against the circulating influenza virus in the unvaccinated group during 2 seasons (80% and 42% in 2002 and 2003, respectively).[52] However, Michiels specifies that the situation of GPs, who have yearly contact with influenza and who come in contact with high-risk persons, is not extrapolative to all HCW.[54] Interestingly, household contact with children was the main significant risk factor for confirmed ILI in two studies, with a strong dose-response relationship in one study.[52, 55]
- For pregnant women, no study documenting the rate of physician visit for confirmed influenza cases was found.
- In persons with co-morbidities, no prospective study involving laboratory confirmed influenza was found. Surveillance systems of laboratory confirmed influenza do usually not record co-morbidity status.

We thus decided to base the influenza estimates in these groups on the influenza and ILI rate in the same age group.[51, 55, 59, 63] We thus applied the incidence rate of the respective age groups to the denominators for each group, shown in Table 41.

9.4 ADMISSIONS FOR INFLUENZA AND PNEUMONIA BY INFLUENZA SEASON

9.4.1 Admissions by age group

The number of influenza and pneumonia admissions by age group and main diagnosis is presented in Table 42 for the influenza seasons (week 40 to 20), based on the MCD database. Influenza as main diagnosis represents 57% of all admissions with a code influenza, and pneumonia as main diagnosis 53% of all pneumonia admissions (Figure 23). For both diagnosis, this proportion varies with age, with a higher proportion of main diagnosis in children (range 69-88%) compared to the elderly (range 39-46%), which may be explained by a higher rate of complications that may appear as main diagnosis.

The number of influenza admissions is low (average 1484/season) but varies widely with the seasons (range 895-2052/season). The season with the maximum number of cases is not the same for all age groups – reflecting the age specific pathogenicity of influenza strains. 2000-01 was the lowest season for most age groups. The highest rate in the school aged children (5-14 years) was seen in 2005-06 together with lower rates in elderly (influenza B), Table 43. The highest rates are consistently reported in children under 5 years of age (average 86, range 31-128/100,000). In the above 5 years, admissions rates ranged 5-24/100,000 in average and were highest in the 5-14 years (range 15-35/100,000 by season) and the >75 years (range 10-30/100,000). Based on the years 2004-08 for which the week of admission could be computed, the weekly distribution of influenza admissions is closely correlated to the distribution of influenza cases at GP offices (Figure 24) and confirms the high variability of influenza across seasons. The distribution of influenza by week and by large age group is shown in Figure 25.

Table 42: Number of MCD admissions for influenza and pneumonia by age group and influenza season

Epidemic season	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Mean
Influenza admissions (main)								
0-4 years	180	735	270	595	514	505	685	498
5-14 years	227	360	299	189	291	426	262	293
15-49 years	317	475	333	378	375	362	392	376
50-64 years	56	149	70	104	107	78	106	96
65-74 years	44	104	48	102	92	50	72	73
75 years +	71	229	91	195	204	83	160	148
Total	895	2,052	1,111	1,563	1,583	1,504	1,677	1,484
Pneumonia admissions (main)								
0-4 years	4,551	4,846	4,907	5,248	5,265	5,017	5,069	4,986
5-14 years	1,680	1,526	1,601	1,295	1,728	2,204	1,412	1,635
15-49 years	2,565	2,558	2,538	2,440	2,825	3,029	2,532	2,641
50-64 years	2,045	2,250	2,240	2,387	2,573	2,542	2,589	2,375
65-74 years	2,894	3,178	3,168	3,382	3,373	3,034	3,142	3,167
75 years +	7,540	8,383	8,481	9,029	9,731	8,566	9,121	8,693
Total	21,275	22,741	22,935	23,781	25,495	24,392	23,865	23,498

Figure 23: Influenza and pneumonia admissions, main and secondary/associated diagnosis by age group, 2000-07

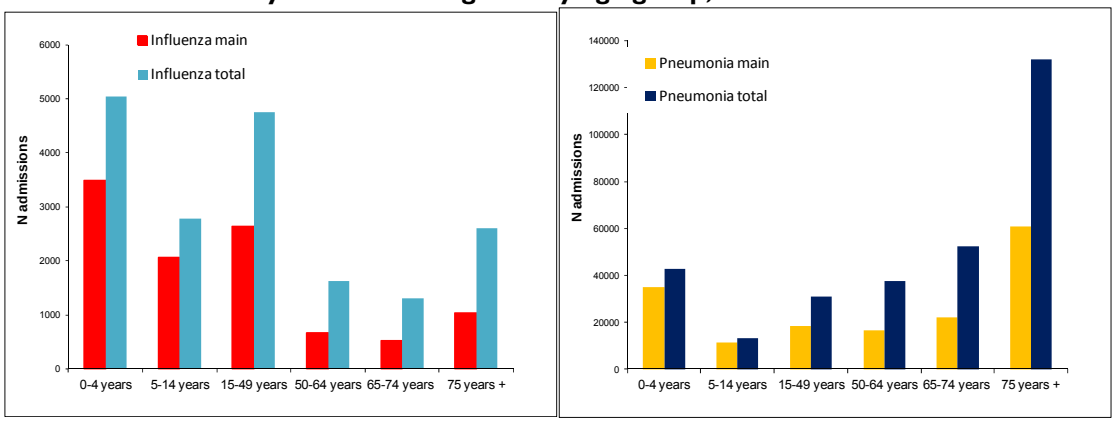


Figure 24: Weekly number of admissions and GP visits for influenza, all ages, 2003-08

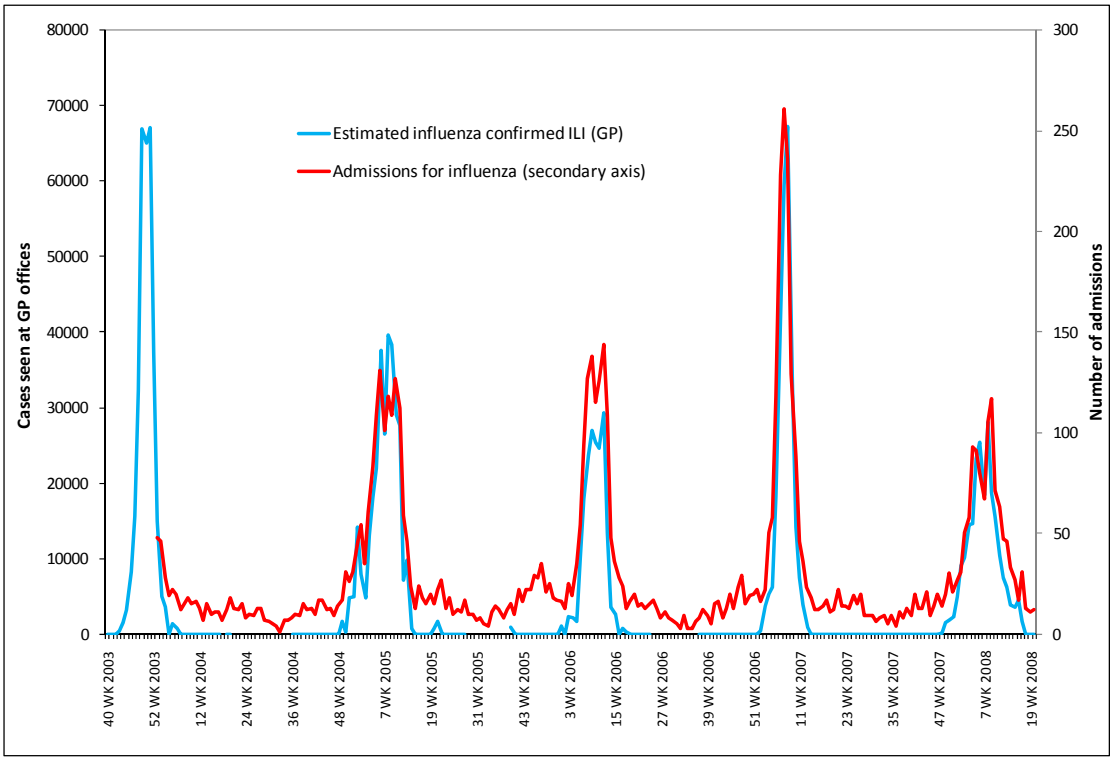


Figure 25: Weekly number of influenza admissions by age group, 2003-08

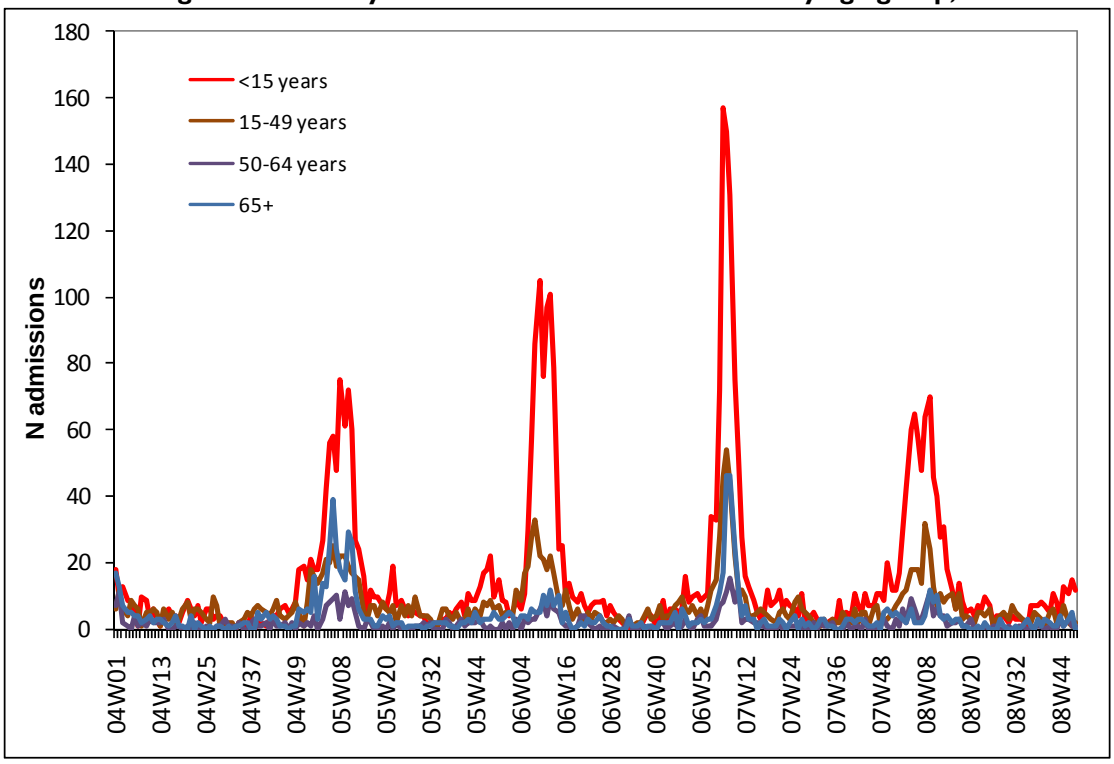


Table 43: Admission rates (per 100,000) for influenza, pneumonia and influenza + pneumonia (P+I) in epidemic seasons, by age group, 2000-07

	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Mean
Admission rate influenza								
0-4 years	31.2	127.5	47.0	104.0	89.7	87.4	117.0	86.3
5-14 years	18.5	29.3	24.3	15.4	23.8	35.0	21.6	24.0
15-49 years	6.3	9.5	6.7	7.6	7.5	7.2	7.8	7.5
50-64 years	3.2	8.5	3.9	5.8	5.8	4.2	5.5	5.3
65-74 years	4.5	10.7	5.0	10.6	9.5	5.2	7.7	7.6
75 years +	9.5	29.8	11.6	24.2	24.8	9.8	18.4	18.3
Total	8.7	19.9	10.8	15.1	15.2	14.4	15.9	14.3
Admission rate pneumonia								
0-4 years	788.4	840.6	854.5	917.5	918.7	868.6	866.1	864.8
5-14 years	136.8	124.2	130.2	105.5	141.3	181.0	116.5	133.6
15-49 years	51.3	51.3	50.8	48.8	56.5	60.5	50.5	52.8
50-64 years	118.4	128.4	125.8	132.0	140.0	135.5	134.5	130.8
65-74 years	296.6	327.6	327.6	349.8	349.0	316.7	334.7	328.8
75 years +	1009.9	1091.7	1077.3	1122.3	1181.8	1012.3	1047.4	1077.6
Total	207.5	221.1	222.0	229.2	244.6	232.8	226.3	226.3

The number of pneumonia admissions is much higher (average 23,498/season) as all microbiological aetiologies are included and does not vary much across seasons (range 22,741 to 25,495/season): all-age rates in the highest season exceeds the lowest season by 18% only. Admission rates are highest in the two extremes of life, accounting in average for 1077/100,000 in the ≥75 years and 865/100,000 in the <5 years, followed by the 65-74 years (329/100,000). The pneumonia admissions also show a marked seasonal pattern whose peak last largely longer than the influenza season shown by the GP visits for ILI (Figure 26). Indeed, 62% of annual pneumonia admissions occurred during the epidemic season compared to 85% of annual influenza admissions, as pneumonia are caused by many other pathogens and other agents.

Figure 27 illustrates the seasonal patterns of pneumonia in each age group and indicates the higher burden in the elderly ≥75 years of age. Interestingly, a first and high seasonal peak is observed in children <5 years every season (light blue), around weeks 49-51, and is concomitant to the RSV peak observed by the IPH sentinel laboratories.

Figure 26: Weekly number of pneumonia admissions and influenza GP visits, all ages, 2003-08

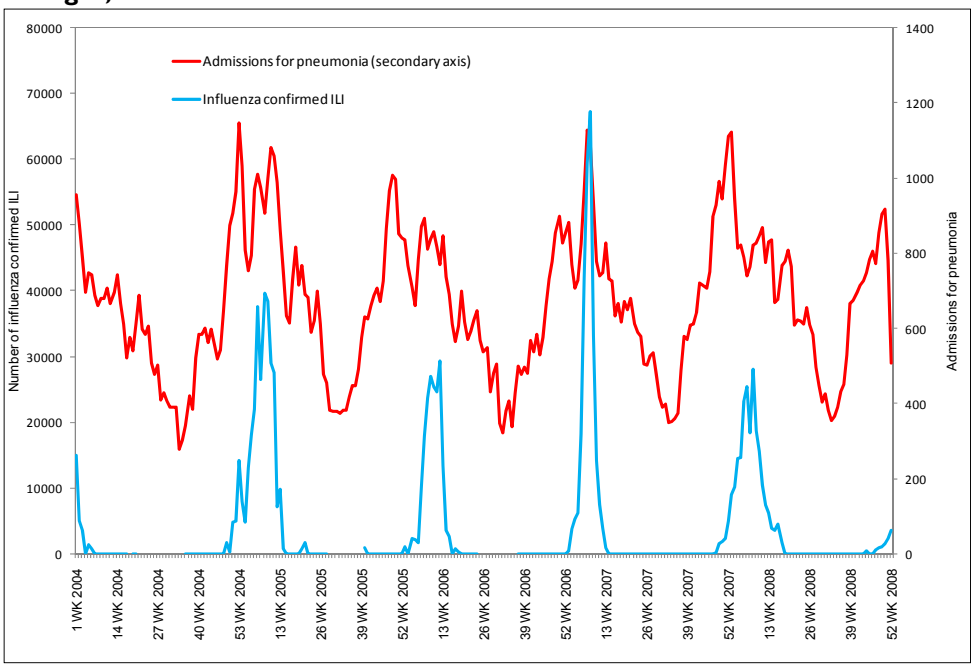
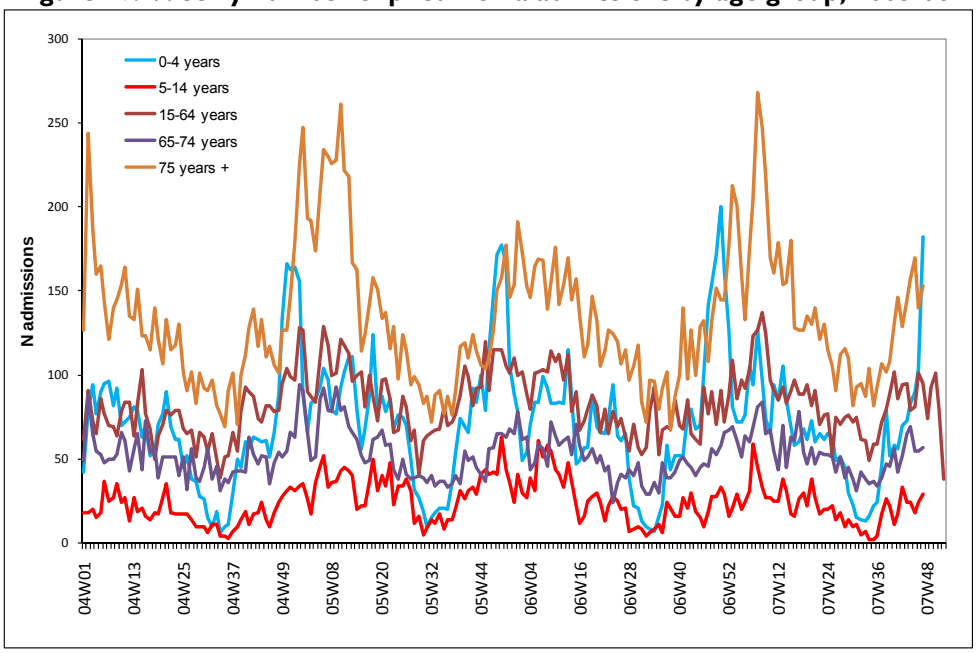


Figure 27: Weekly number of pneumonia admissions by age group, 2003-08



MCD data on pneumonia admissions also have data on causing pathogen (according to ICD9 codes). However, these data provide little information because 64% pneumonia admissions are coded as bronchopneumonia or pneumonia with organism unspecified, and an additional 21% as "other bacterial pneumonia". Among remaining admissions, 2% are coded as viral pneumonia, 7% as pneumococcal pneumonia, 2% as *H. influenzae* pneumonia and 3% as pneumonia due to *Mycoplasma pneumoniae*. These proportions stayed relatively stable over time.

9.4.2 Admission in healthy adults aged 15-75 years

Admissions in the healthy adults represent 74% and 38% of all admissions for influenza and pneumonia, respectively, but this proportion varies by age group. These account for a majority of admissions in the young adults (86% and 67%) but for a minority in the elderly 65-74 years, especially in pneumonia (40% and 19%), Table 44. Admission rates for P+I in this group accounted for 48, 54 and 85 per 100,000 in the 15-49, 50-64 and 65-74 years respectively for the last 3 seasons (2004-07), and little variations was observed from season to season. Data on admissions in the persons with co-morbidities are described below.

Table 44: Number of MCD admissions for influenza and pneumonia in the healthy adults, by age group and influenza season

	2000-2001	2001-2002	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	Mean	% all admissions in this age
Influenza (main)									
15-49 years	283	410	286	315	327	309	332	323	86%
50-64 years	37	74	32	66	55	48	54	52	55%
65-74 years	20	45	27	35	32	15	33	30	40%
Pneumonia (main)									
15-49 years	1,736	1,716	1,648	1,533	1,856	2,133	1,680	1,757	67%
50-64 years	729	734	686	770	815	833	828	771	32%
65-74 years	616	608	612	614	601	525	546	589	19%

MCD: Minimal clinical data.

9.4.3 Admissions in persons with co-morbidities

The number of influenza and pneumonia admissions in persons with at least one co-morbidity and in "healthy" persons is presented in Table 46 and Figure 28. Overall 20% and 55% of all influenza admissions were recorded in patients with at least one co-morbidity. This proportion increases with age, accounting for only 4-11% in children <15 years but reaching 85% for pneumonia admissions in the ≥75 years of age, while the proportion of the ≥75 years having reported at least one co-morbidity was 35% in 2008 (HIS 2008).

To compare Belgian data with published studies, we calculated the admission rates in the two groups, with and without co-morbidity, over 3 epidemic seasons (2004-05 to 2006-07 based on HIS 2008 denominator, Table 45 and Figure 29), and we calculated the relative risk (RR) of admission in persons with co-morbidity. In average, persons with co-morbidity have a 8-fold higher risk of admission for influenza and pneumonia. In the adults ≥50 years, the RR ranged 11-13.

Table 45: Admission rates (per 100,000) for influenza and pneumonia in persons with and without co-morbidity by large age group, mean of 3 influenza seasons (2004-05 to 2006-07)

	Influenza		Pneumonia		P+I		
	Co-morbidity		Co-morbidity		Co-morbidity		RR (95% CI)
	No	Yes	No	Yes	No	Yes	
0-14 years	50.4	40.4	377.0	482.8	427.4	523.2	1.2 (1.17-1.28)
15-49 years	7.0	13.2	41.0	223.4	48.0	236.6	4.9 (4.7-5.1)
50-64 years	3.2	17.6	50.9	572.3	54.1	589.9	10.9 (10.5-11.3)
65+	5.0	28.6	140.1	1,913.0	145.0	1,941.6	13.4 (13.1-13.7)
Total	14.0	22.6	117.9	998.8	131.9	1,021.5	7.7 (7.7-7.8)

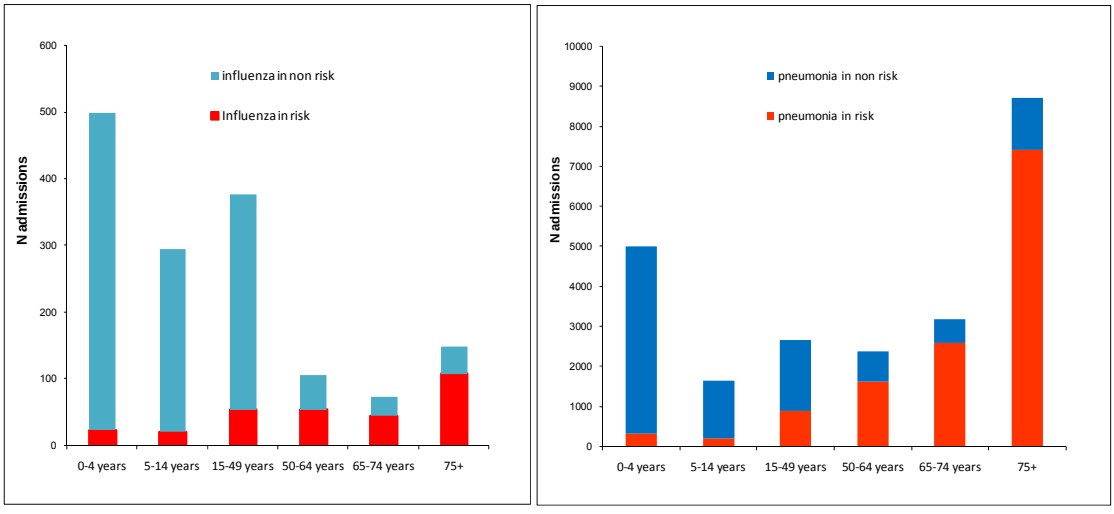
These RR were compared to those found in published studies using comparable outcomes (admission for influenza and pneumonia, ICD code) and risk group (persons with any co-morbidity). Few studies were including the same population and outcomes, and those retrieved found lower RR. Irwin estimated a RR for influenza admissions in all co-morbidities of all ages at 5.5[i] compared to 1.6 in our data, but few patients were >65 years of age.[56] Nichol showed an adjusted OR for influenza and pneumonia admissions in elderly (>65 years) at 3.3 (95% CI 2.8-3.9) for "high risk" co-morbidities (heart or lung disease) and 1.6 (95% CI 1.2-2.0) for "intermediate risk" co-morbidities (diabetes, renal disease etc.).[58]

One reason of the higher RR in our study may be due to an underestimation of the denominator for persons with co-morbidities (thus over-estimating the incidence), since the HIS 2008 data are missing immunodeficiencies and are based on self-report. However as outcomes, population, influenza seasons and vaccine uptake in the literature differed from our study, we decided to use the MCD data for parameters on admissions in persons with co-morbidities.

Table 46: Number of influenza and pneumonia admissions by co-morbidity status and age group, by influenza season (mean 2000-2007)

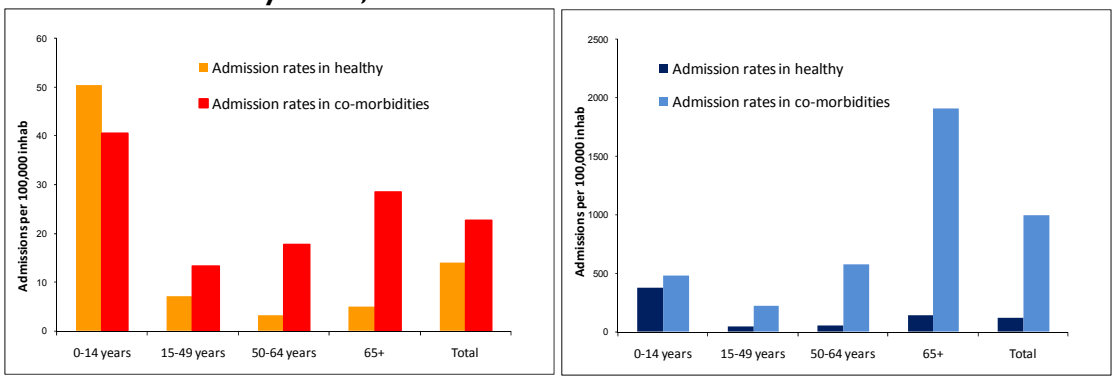
	Influenza			Pneumonia		
	Comorbidities[1]		% co-morbidity in admissions	Comorbidities[1]		% co-morbidity in admissions
	Yes	No		Yes	No	
0-4 years	22	475	4%	318	4668	6%
5-14 years	20	274	7%	186	1450	11%
15-49 years	53	323	14%	884	1757	33%
50-64 years	53	52	50%	1,604	771	68%
65-74 years	44	30	60%	2,578	589	81%
75+	107	41	72%	7,403	1,290	85%
Total	298	1195	20%	12,973	10,525	55%

Figure 28: Number of MCD influenza and pneumonia admissions (average/year) by age group and co-morbidity status, all influenza seasons 2000-01 to 2006-07



[i] No confidence interval or p value were provided

Figure 29: Admissions rates for influenza (left) and pneumonia (right) by co-morbidity status, mean of the seasons 2004-07



Experts suggested that many children may be admitted with a diagnosis of influenza for a 24-hour observation period and would not represent a true burden of influenza admissions. We thus analyzed the frequency of admissions with a length of stay of 1 day. For influenza as main diagnosis, these admissions represented 10% in children <5 years with a peak at 25% in the 15-49 years of age, and decreased with increasing age. For pneumonia as main diagnosis, these only account for 2-3% admissions in all age groups.

9.4.4 Admissions in pregnant women

We did not have MCD data on influenza admission during pregnancy, and we tried to approximate the risk of influenza admission during pregnancy by other methods. We first compared the rate of MCD admissions in women of children bearing age (in influenza season) with the rate in males from the same age group (comparing sex ratio across age cohorts), but no clear trend could be observed: the risk of admissions for influenza was similar in males and females (rate sex ratio=0.98) and was higher in males for pneumonia (rate sex ratio = 1.14), as observed in other age groups.

The literature showed an excess in respiratory admissions during pregnancy. However, studies compared the risk of influenza admissions in pregnant women to the risk in non pregnant (e.g. same women, previous year), while pregnancy in itself already increases the overall rate of admission. The relative risk of admission consistently increased with gestation trimester and the presence of co-morbidities, but the same trend was observed for admissions outside influenza periods.[51, 59, 114] Some studies also show conflictual results and very different estimates, which may be due to differences in methods, setting and assumptions of influenza-related hospitalization rates.[21]

In a large Canadian population-based study over 1990-2002, around 10% of pregnant women presented a co-morbidity that put them at increased risk of influenza morbidity, compared to 8% in the 15-49 years of age in Belgium, but anaemia (3% women) was included as co-morbidity in the Canadian study.[51] The rate ratio of admission for respiratory illnesses (ICD9 480-487 and other respiratory causes) in pregnant women without co-morbidity compared to non-pregnant ranged increased from 1.7 to 5.1 from the first to the third gestation trimester. When comparing influenza to non-influenza seasons in pregnant women, the rate ratio ranged 1.5-2.4 but was not significantly different in pregnant women with and without co-morbidities.

In Canada, Schanzer estimated the number of respiratory admissions that are attributable to influenza (using a regression model) over 1994 to 2000 at 150/100,000 (95% CI 140-170).[60] Admission rates were relatively constant across multiple influenza seasons of varying intensity. The rate ratio of admission in pregnant vs. non pregnant aged 20-34 years was 9 for all women and 18 for healthy women (no CI). The rate of influenza-attributed admissions for healthy pregnant women was similar to that estimated in adults 65-69 years of age in Canada, and 56% of admissions in pregnant women occurred in healthy women. However, influenza attributable admissions calculated by a regression model do not correspond to the outcome selected for this study.

In a US cohort study, hospital admissions for influenza and pneumonia (ICD9 codes) were extremely rare at 18.2/100,000 pregnancies.[61] However, this rate is much lower than the Belgian admission rate in the 15-49 years (60/100,000).

Overall, a significantly higher risk of hospitalization related to seasonal influenza was found in healthy women in the second half of normal pregnancy and earlier among women with select co-morbidities. In a recent review, Skowronski found no evidence for significantly higher risk of admissions due to seasonal influenza for the healthy woman in early pregnancy; the admission rate in healthy women in early pregnancy appears not significantly different from that of other healthy young adults.[21]

However, a substantial excess of admissions was described in the H1N1 2009 pandemic influenza and this strain is expected to circulate the next influenza seasons. Data from the CDC surveillance showed an excess of admission rates in pregnant women in the first months of the outbreak compared to the general population (RR=4.3, 95% CI 2.3-7.8).[62] However, no systematic review has been conducted on the topic. US data may not be completely applicable to the Belgian context, as for instance, obesity was an important risk factor and has a different prevalence in Belgium compared to the US.

As single estimate in pregnant women are not available for Belgium, we computed the numbers of influenza and pneumonia admissions in pregnant women based on several hypotheses described above. This number would vary from 22 to 103 by epidemic season, according to each hypothesis (Table 47). For this study, we opted for 2 scenarios: 1. Best case: same admission rate as in the 15-49 years; 2. Worst case: similar admissions rate as during the 2009 pandemic in the US.

Table 47: Estimated numbers of influenza and pneumonia admissions in pregnant women by influenza season, based on three hypothesis

Outcome	Study	Criteria	Admission rate estimated	Estimated admissions	Comments
ICD9 480-7	Belgian MCD data for age	Based on admission rates for 15-49 years	60.3/100,000 persons	73	Considered as realistic best case
ICD9 480-7	Black 2004	Observed rate	18/100,000 pregnancies	22	Same outcome
ICD9 480-7 + respiratory	Dodds 2006	RR=1.7 (1.02.8) RR= 7.9 (5.0-2.5) vs. non pregnant	52.2/100,000 242.6/100,000	Not calculable*	1st trimester, no comorbidities 3rd trimester, co-morbid Using 15-49 years
US admissions in H1N1 influenza	Jamieson 2009 (H1N1)	RR=4.3 for influenza admissions	85.2/100,000	103	Applying RR=4.3 on overall influenza admission rate

*: The denominator of pregnant women by trimester of gestation in not known. RR: Relative risk. MCD: Minimal clinical data.

9.4.5 Admissions in HCW

No study on the relative risk of admissions for influenza and pneumonia in HCWs was found. However, as HCW are not at higher risk of serologically-confirmed ILI than non-HCW and seem even better protected against influenza, we assumed that HCW have the same rate of influenza and pneumonia (P+I) admissions as the general population of the same age (Table 48).

Table 48: Estimated number of influenza and pneumonia admissions in HCW by influenza season

Total number HCW	Rate in BE	Estimated N admissions P+I	Comments
239.740	80.4	193	Based on rate in 15-64 years

9.5 DEATHS FROM INFLUENZA AND PNEUMONIA BY INFLUENZA SEASON

9.5.1 Deaths by age group

In both data sources, most influenza and pneumonia deaths are found in the elderly, while few deaths are reported in the children and adults <50 years. Our baseline analysis is based on the main diagnosis, but the sensitivity analysis includes a scenario using all causes of death (main and associated).

1. Deaths recoded by the communities as influenza and/or pneumonia as main diagnosis account in average for 115 influenza deaths/year and 4006 pneumonia deaths/year. The main diagnoses represent 84% and 36% of all death codes (including associated) for influenza and pneumonia, respectively. Most deaths, i.e. 98% and 95% of influenza and pneumonia deaths respectively, are recorded in the elderly ≥ 65 years, and 87% and 86% in the ≥75 years.
2. The annual number of deaths recorded in MCD for pneumonia and influenza as main diagnosis accounts in average for 9 influenza deaths/year and 3493 pneumonia deaths/year. The main diagnoses represent 24% and 31% of all death coded for influenza and pneumonia, respectively, in the period 2000-07. 97% and 91% of influenza and pneumonia deaths, respectively, are recorded in the elderly ≥ 65 years, and this proportion amounts to 85% and 75% in the ≥75 years.

Annual MCD influenza and pneumonia deaths combined (main diagnosis) represent 85% of the annual deaths reported by death certificates (data from the communities) over the period 2000-07. However, this proportion varies widely by age and diagnosis:

1. Influenza deaths (main) recorded in the MCD represent a very small number of deaths and only 7% of influenza deaths based on death certificates, suggesting that most influenza deaths do not occur in hospitals and are not coded as influenza. MCD pneumonia deaths (main) represent in average 87% of community pneumonia deaths (main), but this ratio shows discrepancies across ages: MCD death numbers are higher than deaths based on certificates in all age groups under 75 years, while it drops to 76% in the 75 years and above. One possible explanation is that a MCD death represents a death during a hospitalization with influenza or pneumonia as main diagnosis, and not exactly the cause of death.
2. 97% of the difference between the number of P+I deaths reported by communities and the RCM (main diagnosis) is due to the pneumonia deaths, as the number of influenza deaths is very limited.

The proportion of MCD annual deaths (week 40 to week 39) recorded during influenza seasons was in average 87% for influenza (range 60-100% by year) and 66% for pneumonia deaths (range 64-70%). This proportion was relatively homogenous across seasons and age group, for each diagnosis.

To estimate the total number of deaths that occurred during the influenza season, we applied these proportions from the MCD dataset on the total numbers of deaths recorded by the communities, by age and season, Table 49.

Table 49: Number of influenza and pneumonia deaths (main diagnosis) by age and influenza season, extrapolated from community and MCD data

	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Mean
Influenza deaths (main)								
0-4 years	0	0	0	0	0	0	0	0
5-14 years	0	0	0	0	0	0	0	0
15-49 years	2	2	2	1	2	0	1	1
50-64 years	1	4	0	1	3	0	1	1
65-74 years	0	24	11	10	6	2	9	9
75 years +	51	141	34	125	151	34	106	92
Total	54	171	47	136	162	36	117	103
Pneumonia deaths (main)								
0-4 years	1	2	2	1	2	2	2	2
5-14 years	0	0	2	1	2	0	0	1
15-49 years	31	32	34	22	29	34	32	30
50-64 years	81	97	107	86	113	93	83	94
65-74 years	264	266	282	264	291	235	195	257
75 years +	2,180	2,267	2,385	2,418	2,576	2,361	2,051	2,319
Total	2,557	2,663	2,812	2,792	3,013	2,725	2,363	2,704

Death rates during the influenza season are presented in Table 50, and show very high rates in the elderly, as expected. Rates largely vary by season for influenza while they are relatively stable across seasons for pneumonia.

Table 50: Death rates per 100,000 for influenza and pneumonia, by age group and influenza season, 2000-07

	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Mean
Influenza deaths (main)								
0-4 years	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5-14 years	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15-49 years	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
50-64 years	0.1	0.2	0.0	0.1	0.2	0.0	0.1	0.1
65-74 years	0.0	2.5	1.1	1.0	0.6	0.2	0.9	0.9
75 years +	6.9	18.3	4.4	15.5	18.3	4.0	12.2	11.4
Total	0.5	1.7	0.5	1.3	1.5	0.3	1.1	1.0
Pneumonia deaths (main)								
0-4 years	0.2	0.3	0.4	0.2	0.3	0.3	0.3	0.3
5-14 years	0.0	0.0	0.2	0.1	0.2	0.0	0.0	0.1
15-49 years	0.6	0.6	0.7	0.4	0.6	0.7	0.6	0.6
50-64 years	4.7	5.5	6.0	4.8	6.2	5.0	4.3	5.2
65-74 years	27.1	27.4	29.2	27.3	30.1	24.6	20.8	26.7
75 years +	292.0	295.2	302.9	300.5	312.8	279.0	235.5	287.5
Total	24.9	25.9	27.2	26.9	28.9	26.0	22.4	26.0

9.5.2 Deaths by co-morbidity status (<75 years)

Deaths stratified by co-morbidity status are only available from MCD deaths. We calculated the deaths in co-morbid patients by using the proportion of co-morbid deaths from the MCD database (by diagnosis, season and age group) and applying it to all (community) deaths (Table 51). As this assumes that patients who died at home from influenza and pneumonia presented the same prevalence of co-morbidities than those dying in hospitals, we compared the relative risk of dying from influenza or pneumonia in co-morbid patients from our data to those found in the literature to assess this assumption (see Appendix 3).

Co-morbid patients accounted for 86% of MCD influenza deaths and 86% of MCD pneumonia deaths during influenza seasons. There was little variation in this proportion across seasons but a slight age trend (Table 51). Overall, most P+I deaths were due to pneumonia in persons with and without co-morbidity (99.7% for each).

Table 51: Number of deaths from influenza and pneumonia by co-morbidity status and age, in an influenza season (mean 2000-01 to 2006-07)

	Influenza			Pneumonia		
	Comorbidities[1]		% co-morbidity in admissions	Comorbidities[1]		% co-morbidity in admissions
	Yes	No		Yes	No	
0-4 years	0	0	NA	1	1	53%
5-14 years	0	0	NA	0	0	32%
15-49 years	1	0	100%	21	10	69%
50-64 years	1	0	100%	74	20	79%
65-74 years	7	2	80%	219	38	85%
75+	78	13	86%	2005	315	86%
Total	88	15	86%	2320	384	86%

1: Co-morbidities as defined in the recommendations for influenza vaccination in Belgium: all patients with a underlying chronic disease, even stabilized, involving lungs, heart, kidney, liver or metabolic and immune disorders. Defined in ICD codes in Appendix 1.

Death rates in the persons with and without co-morbidity and the relative risk (RR) of death in persons with co-morbidity over the three epidemic seasons from 2004-05 to 2006-07 are presented in Table 52. In average for all ages, the risk of death from pneumonia was 47-fold higher for persons with co-morbidity compared to those without co-morbidity. The relative risk could not be computed for influenza alone, as there were no influenza deaths in persons without co-morbidity in the period 2004-07.

Table 52: Death rates (per 100,000) for influenza and pneumonia by co-morbidity status and age, in an influenza season (mean 2004-05 to 2006-07)

	Influenza		Pneumonia		P+I		
	Comorbidity		Comorbidity		Comorbidity		RR P+I (95% CI)
	Yes	No	Yes	No	Yes	No	
0-4 years	0.0	0.0	3.3	0.1	3.3	0.1	43.6 (12.1-157.1)
5-14 years	0.0	0.0	0.0	0.1	0.0	0.1	NA
15-49 years	0.2	0.0	5.4	0.2	5.7	0.2	26.9 (20.2-35.8)
50-64 years	0.4	0.0	26.2	1.2	26.6	1.2	22.7 (18.6-27.8)
65-74 years	2.1	0.0	80.2	4.9	82.4	4.9	16.8 (14.4-19.5)
75 years +	33.5	0.0	714.9	46.6	748.4	46.6	16.1 (15.2-17.0)
Total	7.7	0.0	173.9	3.5	181.6	3.5	51.2 (49.4-53.2)

P+I: Pneumonia and influenza. RR: Relative risk.

These relative risks were compared to those found in published studies using comparable outcomes (deaths from influenza and pneumonia, ICD code) in Table 53. All published studies showed lower associations between co-morbidity status and risk of deaths from pneumonia or/and influenza than in our Belgian analysis. However, all these studies are older (all covered seasons before 2000), those using the same outcome (P+I) only involved diabetes – which is considered as a condition at low risk, and none of these studies involved persons with any co-morbidity. A Canadian study also suggested that there is a large hidden mortality burden due to influenza as it was determined to be the underlying cause of death in only 8% (and pneumonia in 15%) of influenza-attributable deaths calculated by a regression model.[60]

For this reason, it was decided to consider two scenarios, one low case (applying RR/OR from studies on diabetes, by age group) and one high case (applying Belgian data), that are computed in Table 54.

Table 53: Association between deaths from pneumonia and influenza and co-morbidity status from published studies

Study	Seasons	Patients	Deaths	RR/OR	95% CI
Valdez 1999[115]	1986	Diabetes 25-64	P+I (ICD)	4.0	2.2-7.5
		Diabetes 65+	P+I (ICD)	2.2	1.7-2.7
Hak 2001[116]	1996-97	COPD 18-64y	Admission + deaths P+I+bronchitis +diabetes, heart failure or myocardial infarction	15.6	2.1-120
Tierney 2001[117]	1992-96	Diabetes 65-74	P+I	2.3	1.6-2.9

P+I: Pneumonia and influenza. RR/OR: Relative risk or add ratio. COPD: Chronic obstructive pulmonary disease.

Table 54: Estimated number of deaths from influenza and pneumonia in persons with co-morbidity 1-64 years of age, by influenza season

Scenario	Criteria used	Estimated nbr deaths / season	Comments
Low case: Based on studies on diabetes	RR =4.0 in 25-64 years Rates by age group	18	RR applied to MCD rates in healthy, by age group
High case: Belgian data (mean)	MCD crude data in Belgium	99 mean (range 83-115)	MCD data

MCD: Minimal clinical data. RR: Relative risk.

9.5.3 Deaths in pregnancy

An extensive literature review on the subject revealed that no robust data showed an excess of mortality associated with seasonal influenza during pregnancy. However, mortality excess was shown with the H1N1 2009 pandemic influenza, and this strain is expected to circulate the next influenza season. No Belgian data on pregnant women deaths could be found. The most recent US CDC study on pregnant women with H1N1 reported 30 deaths on 692 reported pregnant women (4.3%) with mortality outcome known.[64] However, 39% of these deaths were among obese women. We thus also opted for 2 scenarios (Table 55):

1. Low case: same death rate as in the 15-49 years;
2. High case: same death rate as during the 2009 pandemic. As Belgian data are not available, we used US data on the proportion of pregnant suffering from influenza who died, although they likely represent a more severe situation than the one in Belgium, due to high prevalence of obese pregnant women.

Table 55: Estimated number of influenza and pneumonia deaths (average) in pregnant women and HCW by epidemic season

Group	Population (2008)	Criteria	Estimated Nbr deaths / season	Comments
Pregnant low case	121,500	Death rate P+I by 100,000: 0.6	0.8	Based on rate 15-49 years
Pregnant high case	121,500	4.3% deaths in influenza cases	144	Based on mortality from H1N1 in pregnant women
HCW	239.740	1.8	4.4	Based on rate in 15-64 years

P+I: Pneumonia and influenza. HCW: Health care worker.

9.5.4 Deaths in HCW

As the literature did not show an increased risk of dying from respiratory diseases among HCWs, we applied the mortality rate in the 15-64 years to the number of HCWs. The estimated number of deaths from influenza and pneumonia is provided in Table 55.

9.6 INFLUENZA BURDEN BY SEASON OF VIRAL ACTIVITY

The number of outcomes that occurred during the more specific seasons of viral activity (i.e. when the influenza virus was circulating) is described in Table 56. The proportion they represent on those occurred during an influenza season (i.e. week 40 to week 20) represent for all ages 87%, 95%, 84% and 94% of ILI, influenza outpatient cases, influenza admissions and influenza deaths, respectively. As expected, the majority of influenza outpatient cases and deaths occurred during this period. Surprisingly, 16% of influenza admissions occurred outside the activity season. A smaller proportion of pneumonia admissions and deaths were found in the activity period (62% and 64%, respectively), as these are also caused by other pathogens that have a different seasonality.

As no data are available on outpatient cases by week in persons with co-morbidities, nor on all outcomes in HCW and pregnant women, the same proportion of outcomes occurring in an activity season (compared to an influenza season) is used in the corresponding age group and season.

Table 56: Number of outcomes that occurred during the viral activity period, by age (% of mean)

	Outpatient		Admissions		Deaths	
	ILI	**Influenza**	**influenza**	**pneumonia**	**influenza**	**pneumonia**
0-4 years	39,949	20,794	438	2,955	0	1
5-14 years	86,767	57,780	255	1,041	0	1
15-49 years	224,832	131,039	295	1,610	1	20
50-64 years	86,230	45,770	76	1,438	1	58
65-74 years	17,102	9,183	58	1,955	9	161
75 years +	15,746	7,820	126	5,557	84	1,489
Total	470,626	272,385	1,248	14,556	96	1,729

ILI: Influenza like illness.

Table 57: Number of outcomes that occurred during the activity seasons in specific groups (mean of seasons)

	ILI outpatient	Influenza outpatient	Admissions P+I	Deaths P+I
HCW	10,779	6,191	120	2.8
Pregnant women	5,279	3,075	46 (low case) 70 (high case)	0.5
Co-morbidities <65 years	40,423	23,076	1,883	62.7

ILI: Influenza like illness. P+ I: Pneumonia and influenza. HCW: Health care worker.

9.7 VACCINE UPTAKE

As the HIS 2008 survey collected data on a representative sample of the population, we used this source for most uptake data, including HCWs. Results from several surveys among HCWs are also provided below for information, as they present partial results; they are however consistent with uptake values from the HIS 2008. We assumed that the uptake of pregnant women was at around 0% in 2008.

Table 58: Vaccine uptake (vaccinated in last season) in the different target groups and source

Group	Uptake in all	Uptake in co-morbidities	Uptake in healthy	Source
6 months-18 years	NA	1.0%	0%	HIS 2008[25]
18-49 years	11.4%	15.7%	10.8%	
50-64 years	27.9%	36.7%	25.2%	
All elderly 65+	66.0%	73.5%	58.1%	
All 65-74 years	49.6%			
All aged 75 years and above	70.9%			
Chronic diseases 1-64 years		22.2%		
HCW in Belgium (sample)	35.4%			
GPs in Wallonia	67%			CUMG, Semaille (2006)
HCW in Vlaanderen: - **Hospitals** - **Nursing homes**	36% 34% 40%			VIGEZ 2008-09
HCW in 20 nursing homes	40%			WIV-ISP surveillance, 2009
Pregnant women	0%			Assumption

HCW: Health care worker. GP: General practitioner.

10 APPENDIX 3: LITERATURE REVIEW ON BURDEN OF INFLUENZA IN SPECIFIC TARGET GROUPS

The objective of this literature review is to define the (excess) risk of influenza-like illness (ILI), hospitalizations for influenza and pneumonia and deaths from influenza and pneumonia in specific groups, for which no Belgian data were available – or if they exist, to assess their validity. Three groups were assessed: patients with underlying conditions (or co-morbidities), pregnant women and health care workers.

As absolute incidence and mortality from influenza cannot be compared across countries, due to differences in influenza burden, influenza detection and health care systems, we focused the literature search on the measures of (increased) risk in these specific target groups.

10.1 METHODS

Published studies by risk groups was searched in Medline and Embase in June 2010. The selection criteria were: English, French and Dutch language; publication date: 1995-June 2010.

Because a number of studies focused on a specific age group of persons with underlying conditions, we considered each outcome by age group: adults, seniors and children.

10.2 ADULTS WITH UNDERLYING CONDITIONS

10.2.1 Outpatient influenza in adults with underlying conditions

The risk of influenza in persons with underlying conditions is difficult to assess on the basis of the literature because the incidence of infections among people with underlying condition is rarely compared to a control group (without underlying conditions).

A number of publications focused on the proportion of underlying condition among the person with influenza infections and highlight the risk of complications in adults with co-morbidity. For example, in prospective cohorts in the U.S, Falsey et al found that among the patients with confirmed Influenza A infection, 42% required an outpatient visit, 8% an emergency room visit, and 33% an antibiotic if they were healthy. In the high-risk group (congestive heart failure or chronic pulmonary disease), the corresponding figures were 60%, 10% and 60% respectively.[118]

In an U.S. study, 23% of the influenza/ILI episodes had evidence of one or more co-morbid conditions occurring in the year before the influenza/ILI diagnosis.[56] Chronic lung disease was the most prevalent co-morbidity, observed in approximately 20% of the influenza/ILI episodes, at all ages. Chronic corticosteroid use, malignancy, chronic heart disease and diabetes were more frequent with advancing age. In approximately 2% of the influenza/ILI intervals of care, patients had evidence of multiple co-morbidities and this rose with age, reaching 21% in the males aged 65+ and 17% for females aged 65+. Patients with an underlying chronic illness, a recent complication, or a higher health care cost in the recent months had the highest risk of hospitalization and complications after a diagnosis of influenza/ILI.

In a population based study in the UK, influenza and ILI were defined as a clinical diagnosis recorded in the GP database.[57] A total of 141,293 subjects who had one or more diagnoses of influenza or ILI during the study period as well as the same number of age-, sex-, practice and calendar time-matched controls were identified. The risk of getting influenza was particularly increased for subjects with chronic respiratory conditions (odd ratio [OR] 1.65, 95% CI 1.60-1.70). This risk was only marginally increased in persons with chronic cardiovascular diseases (adjusted OR, 1.23; 95% CI, 1.17–1.29), diabetes (adjusted OR, 1.11; 95% CI, 1.04–1.18), or cancer (adjusted OR, 1.08; 95% CI, 1.03–1.11).

As compared to cases who did not have any pre-existing diseases, the relative risk estimates of developing clinical complications were highest in cases with chronic respiratory diseases (OR, 1.89; 95% CI, 1.80–1.99), Parkinson's disease (OR, 1.58; 95% CI, 1.02–2.46), and cardiovascular diseases (OR, 1.42; 95% CI, 1.29–1.58), after adjusting for age and gender. The adjusted relative risk estimate of developing clinical complications was not altered for subjects with diabetes (OR, 1.09; 95% CI, 0.93–1.28) or cancer (OR, 0.97; 95% CI, 0.89–1.06). Authors also suggest that this increased risk may be due to a higher likelihood of getting an influenza diagnosis recorded (diagnostic bias) because such patients are more likely to see the GP on a regular basis or because they are more careful about their health and more likely to report fever and cold symptoms to their GP.

In a prospective nested case-control study in Netherlands, Hak found that influenza morbidity was highest in the older age group (45-64 years), in females and in those subjects who had COPD.[119]

10.2.2 Hospitalizations in adults with underlying conditions

The risk of admission is clearly higher in adults with co-morbidity than in healthy patients. For example, Falsey assessed that 20% high risk patients with influenza A required hospitalization compared to none of the healthy elderly group.[118] According to Arden, the estimated rates of influenza-associated hospitalization are higher among adults with high-risk than rates among healthy adults of the same age group, both for adults 15-44 years old and 45-64 years old.[120]

In a matched case-control study in the Netherlands involving 119 cases and 196 matched controls in the 1996-97 season, Hak found that presenting more than one co-morbidity was a prognostic factor for hospitalization or death due to influenza, bronchitis, pneumonia, diabetes, heart failure or myocardial infarction (adjusted OR 24.9; 95% CI 2.8-223) among the 18-64 years old. COPD was also a prognostic factor for these outcomes in the 18-64 years old (adjusted OR 15.6; 95% CI 2.1-120). These association were not significant in those aged 65 years and above. [116] Mulloly also showed that unvaccinated high-risk persons aged 50-64 years had significant excess of hospitalizations for pneumonia and influenza during the 1996/1997–1999/2000 influenza epidemics.[121] Baltussen estimated an excess hospitalization for pneumonia by regression analysis and found it higher in high-risk compared to low-risk groups.[122]

The risk of hospitalisation varies across co-morbidities. Irwin found a adjusted OR for influenza hospitalisation at 3.7 (95% CI 1.8-7.4) in malignancies, 3.2 (95% CI 1.7-6.0) in chronic heart disease, 2.2 (95% CI 1.1-4.5) in diabetes compared to 1.3 (95% CI 0.8-2.0) in chronic lung disease.[56]

In a U.S. retrospective cohort study, Griffin estimated an excess hospitalizations due to influenza in persons with chronic lung disease.[123] This excess was estimated at 8, 0, 3,13, and 23 per 1000 persons with chronic lung disease per year in the age groups < 5, 5-14, 15-49, 50-64, and 65 years or older, respectively.

Finally, some authors highlight the risk of underestimating the number of influenza-related hospitalizations.[122, 124] Baltussen found that among the 2700 hospitalizations that were attributed to influenza per year by a mathematical model, only 326 had a diagnosis of influenza. This suggests that a large proportion (88%) of all influenza-related hospitalizations were not recognized as such. However, all excess hospitalizations were diagnosed as pneumonia[122].

10.2.3 Mortality in adults with underlying conditions

Mortality attributed to influenza is also underestimating the burden of influenza due to the large 'hidden' mortality due to influenza. According to study of Schanzer using a regression model, influenza was identified as the underlying cause of death in only 8% (95% CI 6-10) of influenza attributable deaths; pneumonia was identified in 15%.[125]

Some authors provide assessment of influenza-related mortality in adults with co-morbidity but studies are often based on old data. In a retrospective cohort (1974-1993), Neuzil showed that influenza caused a seasonal excess of mortality in high risk women.[126] Among 488 deaths (due to selected cardiopulmonary causes) recorded during 19 influenza seasons, 79% occurred in high-risk women.

Valdez showed that people with diabetes had a higher risk to have pneumonia and influenza as an underlying or contributing cause of death than those without diabetes.[115] After adjustment for age and regardless of race, men with diabetes had a 2-fold risk of dying with pneumonia and influenza relative to men without diabetes. After adjustment for age, women with diabetes remained more likely to die with pneumonia and influenza than women without diabetes. These models indicate that, in the general population, regardless of sex and socioeconomic status, Whites and Blacks with diabetes in the 25- to 64-year age group were 4.0 times (95% CI = 2.2, 7.5) and 3.7 times (95% CI = 2.1, 6.6) more likely, respectively, to have pneumonia or influenza as a listed cause of death than their peers without diabetes. At 65 years and older, the relative risk diminished, but whites persons with diabetes were still 2 times more likely to die with P&I than were whites without diabetes.

More recently in an US study, Tierney showed that the relative risk of dying from pneumonia and influenza in diabetic patients compared to non diabetic adults patients varied with age: the age-adjusted RR was 2.3 (95% CI 1.6-2.9) in the 65-74 years of age and 1.5 (95% CI 1.1-1.8) in those aged 75 years and above.[117]

According to several authors, influenza mortality seems high among immunosupressed patients due to cancer, bone-marrow transplant or HIV but the group of patient is very small and the incidence complex to estimated.[127-129]

Key points on adults with underlying conditions:

- **The incidence of influenza and ILI in persons with underlying condition is difficult to assess. However, an excess of GP diagnosed influenza has been found in respiratory chronic diseases such as COPD in two studies. In other co-morbidities, no or only a mild increase in risk was found.**
- **All studies showed a higher risk of complications from influenza in adults with co-morbidity compared to those otherwise healthy. Indeed, the risk of hospital admission is clearly higher in adults with co-morbidity than in healthy patients.**
- **A number of studies showed an higher risk of influenza-attributed deaths in high-risk adults. But mortality codes as influenza is underestimating the mortality burden of influenza.**

10.3 ELDERLY WITH UNDERLYING CONDITIONS

10.3.1 Outpatient influenza/ILI in elderly with underlying conditions

Only few studies focused specifically on the ILI incidence among persons 65 years and older with co-morbidity, and we could not find any data in our the literature search.

10.3.2 Hospitalization in elderly with underlying conditions

Several authors underline the risk of hospitalization in elderly with co-morbidity during the influenza season. In a U.S. cohort study, Mullooly showed that high-risk elderly had significantly increased rates of influenza-associated hospitalizations for pneumonia and influenza, but no measure of risk was provided. [121]

In a U.S. adjusted cohort study, Hak assessed 20 hospitalizations for pneumonia and influenza or all cause-deaths in elderly ≥ 65 years of age, non institutionalized and non vaccinated, with or without underlying conditions. Rates of these outcomes were more frequent in elderly with underlying conditions (4.7-fold in 1996-1997 and 3.6-fold in 1997-1998), mainly among those with heart & lung diseases and immunosuppression.[99] In the same U.S. cohort study, Nichol found that subjects who had a diagnosis of cardiac or pulmonary disease (high-risk group) were at substantially increased risk for hospitalization for pneumonia and influenza when compared with subjects in the low-risk group.[58] While this high-risk group represented only 20.6% of all subjects in the study, they experienced 56% of the hospitalizations for pneumonia and influenza.

Nevertheless, intermediate (diabetes, renal disease, stroke and/or dementia, or rheumatologic disease) and low-risk senior citizens also experienced significant numbers of complications of influenza. The adjusted OR for hospitalization for pneumonia and influenza was 3.3 (95% CI 2.8-3.9) and 1.6 (95% CI 1.2-2.0) in high-risk and intermediate-risk subjects, respectively, compared to subjects with low-risk.

In a retrospective cohort US study, Nichol found hospitalization rates for pneumonia and influenza in elderly persons with chronic pulmonary disease >4 times higher than those of their HMO counterparts who did not have underlying lung disease.[130]

10.3.3 Mortality in elderly with underlying conditions

Carrat indicates the difficulty to quantify precisely the impact of influenza in the elderly, as they account for 90% of registered influenza deaths, but the more frequently underlying conditions found in this population can result in a misclassification of causes of death (infarctus of pneumonia).[131]

Using a model, Schanzer estimated influenza-attributed deaths in the Netherlands. He showed that this outcome was 20 times more frequent in persons aged 65 years and over with both chronic heart and chronic lung disease than for those without either of these conditions, and 12 and 5 times higher for elders with chronic lung disease and chronic heart disease, respectively.[125]

In his US cohort study, Nichol showed that subjects who had a diagnosis of cardiac or pulmonary disease (high-risk group) were at substantially increased risk for death when compared with subjects in the low-risk group.[58] While this high-risk group represented only 20.6% of all subjects in the study, they experienced 53% of the deaths. Intermediate (diabetes, renal disease, stroke and/or dementia, or rheumatologic disease) and low-risk elderly also experienced significant numbers of deaths. The adjusted OR for all-cause mortality was 3.3 (95% CI 2.9-3.8) and 2.7 (95% CI 2.3-3.2) in high-risk and intermediate-risk subjects, respectively, compared with low-risk.

Key points in elderly with underlying conditions

- **No data on outpatient ILI and influenza was available in the literature**
- **Hospitalisation for pneumonia and influenza was clearer higher in elderly with underlying condition compared to healthy elderly.**
- **The majority of influenza deaths is found is this age group, and particularly among those with high risk condition. However, there is a hidden mortality burden related to influenza in the elderly.**

10.4 CHILDREN WITH UNDERLYING CONDITIONS

According to several authors, an average of 10% of children are identified as high risk, and the most prevalent high-risk conditions is asthma.[132-135]

10.4.1 Outpatient influenza/ILI in children with underlying conditions

The risk of ILI in high risk children compared with healthy children is rarely described but the rate of outpatient visits is assessed.

In a U.S. prospective population based study, Miller found that children 6-59 months of age with asthma had approximately two-fold more influenza-attributable outpatient visits in 2003-2004 than did healthy children (despite their 3-4fold greater odds of having a parental report of influenza vaccination, compared with healthy children).[136] During the 2003-2004 season, influenza-attributable visit rates were significantly higher among children with asthma than among healthy children, that is, 316 vs. 152 cases/1000 children 6-23 months of age and 188 vs. 102 cases/1000 children 24-59 months of age ($p<0.05$ for both). During the 2002-2003 season, influenza-attributable outpatient visit rates were similar for children with asthma and healthy children, i.e. 60 vs. 61 cases/1000 children 6-23 months of age and 59 vs. 62 cases/1000 children 24-59 months of age.[136]

In an US study over 5 seasons (1994-2000), O'Brien found a rate of outpatient visits for acute respiratory disease during periods in which influenza predominated at 28.7/100 person-months (95% CI 26.6–30.9) among children aged 6-23 months who were at high risk for complications from influenza. In healthy children from the same age group, this rate was 14.5/100 person-months (95% CI 13.9-15.1). The difference in the rate of outpatients visits among high risk 6-23 month-old children that could be attributed to influenza compared with the rate during the summer baseline period was 16.1/100 person-month (95% CI 13.9-18.4).[135]

In a US retrospective cohort study (1974-1993), Neuzil found that an estimated 10-20% of high-risk children aged <15 years have an additional outpatient visit during an average influenza season vs 7-12% in the same population without high-risk conditions.[134]

Another issue concerns the implication of neurological and neuromuscular disease in the burden of influenza in children. These diseases were relatively recently found to be a risk factor for respiratory failure and other influenza-related complications.[137] This was demonstrated for the winter of 2003–2004 by Keren in a retrospective cohort study in which the likelihood for a child with a neurological or neuromuscular disease to develop respiratory failure was six times that of a previously healthy child (OR 6.0; 95% CI 2.7–13.5).[138] Furthermore, in the same year, a national US survey by Bhat of influenza-associated deaths demonstrated that chronic neurologic conditions, including developmental delay, seizure disorder and cerebral palsy, made up one third of the influenza-associated deaths in children aged under 18 years.[139]

Finally, we have to keep in mind that RSV has a substantially greater impact on young children than influenza.[140-145]

10.4.2 Hospitalization in children with underlying conditions

Several authors underline the higher risk of influenza-related hospitalisations for children with co-morbidity compared to healthy children. In a US study based on registers, the rate of hospitalization for acute respiratory illness during periods of influenza was 44.6/10 000 person-months (CI 19.0-88.0) among high-risk children and 10.4/10 000 person-months (CI 6.0-17.0) in healthy children in the same age group.[135] During a lower-than-usual season (2000-2001) in the U.S., Iwane showed a rate ratios of 4.0 (CI 1.1-10.0) between high risk and low risk children <5 years of age hospitalized with laboratory-confirmed influenza infection.[142] That season, the overall rate of hospitalization was 3.5/1000 for RSV, 1.2/1000 for parainfluenza and 0.6/1000 for influenza virus. In a US retrospective study in 19 consecutive years (1974-1993), Neuzil found an excess influenza-associated hospitalization rates of 2 to 4 times higher for children with high-risk than for healthy children of comparable age from the same population. These rates was comparable to those reported for older persons with high-risk medical conditions.[134] According to Arden also, the estimated rates of influenza-associated hospitalization among high risk children 0-4 years old were higher than rates among healthy children in the same age group (500/100,000 versus 100/100 000). The estimated rates of influenza-associated hospitalization among high risk children 5-14 years old were five-fold to ten-fold higher than rates among healthy children of the same age group (200/100,000 vs. 20 to 40/100,000) and higher than rates among high-risk individuals 15 to 44 years old (40 to 60/100,000).[120]

A number of studies focused on asthma and respiratory diseases, as this represents the most frequent high-risk condition in children. According to Miller, children of 6 to 59 months of age with asthma had approximately fourfold more influenza-attributable hospitalizations in 2000-2004 than did healthy children (despite their greater odds of being vaccinated compared to healthy children).[136] The influenza attributable hospitalization rates were higher among children with asthma in all seasons, except 2001-02. From 2000 to 2004, the average annual influenza-attributable hospitalization rate for children 6 to 59 months of age with asthma was 1.0 case per 1000 children (range: 0.3–1.8 /1000 children), compared with 0.4 case per 1000 children (range: 0.1–0.6 case per 1000 children) among healthy children. The average annual rates of influenza-attributable hospitalization for children with asthma and healthy children were 2.8 and 0.6 cases per 1000 children 6 to 23 months of age, respectively ($p<0.05$), and 0.6 and 0.2 case per 1000 children 24 to 59 months of age ($p<0.05$).

In a German study, Weigl found that having asthma gave a RR of 4.1 (95% CI 1.7-9.9) and 2.1 (95% CI 0.9-5.1) respectively.[145] Given the prevalence of cardiac conditions of 0.6% in the paediatric population, the RR for hospitalization was 9.8 (95% CI 4.3-23.1) for influenza A and 8.5 (95% CI 4.5, 15.9) for RSV. He concluded that asthma and cardiac diseases are special risk factors for hospital admission for laboratory-confirmed influenza infections.

The very young children with co-morbidity appear to be particularly at risk of hospitalisation during influenza season. Izurieta showed that the hospitalization rate for acute respiratory disease was 4 to 5 times higher for children aged less than 2 years with co-existing chronic illnesses (and prematurity) than those without, but this was 13 to 21-fold for children 2-17 years.[133]

Several studies showed a proportion of high-risk children around 30-50% among those with an influenza-associated hospitalisation. Coffin in a U.S. academic tertiary hospital found that 49% of children<21 years old had a medical condition associated with an increased risk of influenza among those hospitalised with laboratory confirmed influenza.[146] Rojo in an tertiary universitary hospital in Madrid found that 40% of hospitalized children with lab-confirmed influenza have underlying disease, mostly asthma, bronchopulmonary dysplasia and congenital heart disease.[147] Moore found that 42% only of children admitted in 9 tertiary care hospitals in Canada were previously not healthy. The proportion who were healthy decreased with age[148]. Pulmonary disease (asthma, bronchopulmonary dysplasia, cystic fibrosis, other chronic lung disease, etc.) was most frequent, occurring in 18% of all children, followed by neurologic disease in 12%, immune deficiencies in 11%.

Ampofo in a retrospective study in U.S. found that 37% of hospitalized children <18 years old with laboratory confirmed influenza had a high risk medical condition. The most common was pulmonary disease, accounting for 64% of these conditions.[132] Quach showed that 30% of the children hospitalized with laboratory-confirmed influenza at the Montreal Children's Hospital were not healthy.[149] This proportion is lower in those below 6 month of age.

However, in a prospective hospital-based cohort study in Australia, Iskander found that the majority of children <1 year admitted with influenza had no high-risk conditions, besides an overrepresentation of ex-premature children with 29% of the children admitted born prior to 37 weeks.[141] In an active prospective surveillance in Canada among children admitted to hospital with influenza A infection, 90% of <6 months age were healthy, 42% of 6-23 month and 19% >2 years ($p<0.001$).[150] In a US academic tertiary care hospital, Coffin found that the proportion of healthy children hospitalized for confirmed laboratory influenza was highest in children <6 months but decreases to be lower than the proportion of high risk from 2-4 years old children.[146] Meury found that less than 30% of children and adolescent hospitalized with influenza infection had underlying conditions.[151] Zerr found approximately 15% of children <18 years hospitalized with influenza and 21% of those hospitalized with influenza or a respiratory illness had a comorbidity.[152]

Other studies showed the higher risk for hospitalization for other or all causes in children with underlying conditions. In a US retrospective cohort study, Bender found that high-risk medical conditions were a factor associated with hospitalization (as respiratory distress, pneumonia and influenza B infection) in children <18 years old with laboratory-confirmed influenza infection seen at emergency department.[153] Coffin examined risk factors for prolonged hospitalization among children with influenza in U.S. and found that underlying conditions were the only independent predictors.[146] However Loughlin found that there is a trend towards a higher rate of complications in 'at-risk' children, but for most complications the increased rate is generally slight and the confidence intervals included 1.0.[154] The greatest difference in incidence rate in the 0-4 year age group was for asthma (incidence rate ratio 8.7, 95% CI 5.2-14.4), and in the 5-14 year age group for asthma (incidence rate ratio 8.5, 95% CI 5.2-13.7) and acute sinusitis (incidence rate ratio 2.7, 95% CI 1.2-5.4). This study also had a relatively high incidence of complications among children considered healthy before the onset of the ILI.

10.4.3 Mortality in children with underlying conditions

The US reported a high rate of mortality among children in the season 2003-04 (Fujian strain). Bhat reported 153 influenza-associated deaths from 40 state health departments in U.S. during the season 2003-04.[139] The overall influenza related mortality rate among children was 0.21 death/100,000. The rate was highest among those younger than 6 month of age and generally declined with increasing age. A 33% of children had underlying conditions known to increase the risk of influenza-related complications, and 20% had other chronic conditions. Chronic neurologic or neuromuscular conditions were present in 33%. 47% were previously healthy. During this season, 16% had received at least one dose of vaccine. During the same season, the Centres for Disease Control and Prevention received (CDC) reported 93 influenza-associated deaths among children <18 years: 59% aged <5 years and 39% have had underlying chronic medical conditions (44% no and 18% unknown).[155]

In a retrospective cohort study during 19 consecutive years (1974-1993), Neuzil identified 194 deaths from selected cardiopulmonary causes in children below 15 years of age with high-risk conditions; 96 deaths (49%) occurred among children younger than 1 year. Although rates of death from cardiopulmonary causes for all ages combined were higher during influenza season (14.8 deaths per 10,000 person-years) than during peri-influenza (12.3 deaths per 10,000 person-years) and summer seasons (7.5 deaths per 10,000 person-years), the difference between influenza and peri-influenza seasons was not statistically significant (2.5 deaths per 10,000 person-years, 95% CI –2.3 to 7.3).[134]

Key points in children with underlying conditions

- **No prospective study provided data on ILI incidence in high-risk children compared to healthy children. Some authors suggested that influenza illness is more severe in this group, but not necessarily more frequent compared to low-risk children.[134]**
- **The very young high-risk children appear to be particularly vulnerable to influenza outcomes.**

10.5 PREGNANT WOMEN

10.5.1 Outpatient influenza/ILI in pregnant women

Only few studies focused on ILI in pregnant women but the usual focus was on influenza complications. According to Skowronski, the influenza incidence (range 1–22% per year) is not higher in pregnant women, but immunological and physiologic changes imply that any developing pneumonia can culminate in greater morbidity, especially toward the later stages of pregnancy.[21] The disease burden for healthy women in early pregnancy does not appear significantly different from that of other healthy young adults.

Based on a retrospective population-based cohort study in Canada, Dodds found that 25.2% of pregnant women visited their physician at least once because of a respiratory illness (during any season from 1990-2002).[51] Among women without co-morbidities, the rate of physician office visits during the influenza season did not differ significantly during pregnancy from the rate in the year before pregnancy (500/10,000 women month). However, among women with co-morbidities, the rate of physician visits during the influenza season was 20% higher in the third trimester than in the year before pregnancy.

In a US cohort study, Lindsay found that approximately 8.3% of healthy pregnant and post-partum women experienced ILI that resulted in health-care utilization.[59] The risk of influenza was not statistically different during influenza-exposed week versus non-exposed weeks for the first and second trimester. This risk becomes statistically higher in the 3rd trimester and in post partum. Moreover, the proportion of severe ILI episodes increased with the pregnancy stage (3.1%, 4.0% and 6.2% for the 1st, 2d and 3rd trimester and 10.9% for the postpartum period). Black noted that 4.7% of pregnant women had at least one outpatient visit for influenza or pneumonia during the influenza season of delivery (1997-2002) but these were concentrated on the end of the pregnancy.[61]

The incidence of pneumonia seems similar in pregnant and in non pregnant women, at 0.78-2.7/1000.[156] The problem of pneumonia diagnosis, which prevails in pregnant and non pregnant population, is that the etiological agent is not identified in 40–61% of cases of community-acquired pneumonia. Viral pneumonia contributes to 5% of identified pathogens in pneumonia during pregnancy, with varicella and influenza being the most common viral pathogens.[157]

10.5.2 Hospitalisation in pregnant women

Several authors noted that influenza during pregnancy is synonymous of increased hospitalizations for ILI, cardiopulmonary or respiratory outcomes. A review found that these outcomes affect 1-9/1000 pregnant women (and 1 à 2.3% of episode with fever or ILI required hospitalization). But these outcomes are rarely laboratory-confirmed.[21] In addition, Mak noted that, the precise level of risk and the extent that risk varies by trimester are unclear because of varying outcome definitions and difficulty in controlling for unknown underlying morbidity.[158]

A large population-based study over 1990-2002 in Canada showed that women at all stages of pregnancy are at increased risk of hospitalization during the influenza season compared with the year before pregnancy, even in the absence of pre-existing co-morbid conditions known to increase the risk of influenza-associated morbidity.

The rate ratio of admission for respiratory illnesses in pregnant women without co-morbidity compared to non-pregnant increased from 1.7 to 5.1 from the first to the third gestation trimester. The same rate ratio in pregnant women with co-morbidity increased from 2.9 to 7.9. However, the rates of hospitalization increase also with the gestational age in pregnant women in non-influenza season. Dodds also found that the rate of excess admissions observed in healthy pregnant women in their third trimester (68/100,000) is comparable to observed rates among American 15-44 years of age with co-morbid conditions (56-110/100,000). [51]

In Canada, Schanzer found a higher rate of attributed influenza hospitalisation in healthy pregnant women (104/100,000 pregnant women per influenza season) compared to not pregnant (6/100,000).[60]. This rate varies according to the type of co-morbid conditions (1500/100,000 in pregnant women with chronic respiratory conditions). The rate ratio of attributed influenza hospitalisation in pregnant versus non pregnant women was 9 for all women,18 for healthy women, 4 for women with asthma and 10 for those with other chronic respiratory condition.

In a nested case control study in US, Neuzil found an increased hospitalisation rate for influenza and pneumonia during influenza period as pregnancy progressed.[114] But this increase was also observed in peri-influenza and non-influenza period.

In a US cohort study, Black found only few hospital admissions with a principal diagnosis of influenza and pneumonia (18.2 hospitalizations for pneumonia/100,000 pregnant women,[61] but in another US cohort study, Hatert found 510 hospitalization for respiratory disease in pregnant women during influenza season/100,000.[159] This also illustrates the difficulty to assess the true influenza-attributable risk because of the lack of laboratory-confirmed influenza data.

10.5.3 Mortality in pregnant women

Excess mortality was noted among pregnant women in both the 1918 and 1957 influenza pandemics. Skowronski considers that these data are the only robust evidence of an increased influenza related fatality in pregnancy.[21] However, Ayoub noted that citing studies from 1918 and 1957 epidemics are irrelevant now that pneumonia can be easily diagnosed and treated with modern technology.[160]

Callaghan found 78 "respiratory" deaths in pregnant women during 7 years in all US with 40 occurred during an influenza season (from 2 to 14 per year).[161] The mean mortality rate was 3.1 death/million live birth (range 1.5-5.9). Black found no death from influenza or pneumonia during 5 influenza seasons in Northern California, in a population of 49,585 women.[61] In its nested case control study, Neuzil found no death from cardiopulmonary causes during influenza season in 4369 pregnant women.[114]

In conclusion and according to Dodds, although fatal and near-fatal influenza has been reported in pregnant women during pandemic influenza seasons, the true impact of influenza on pregnant women during non pandemic influenza seasons is not clear.[51]

10.5.4 Outcome of the foetus

Available evidence suggests a lack of clear evidence for an association between maternal influenza infection and congenital abnormalities.

According to Skowronski, influenza virus can cross the placenta but viraemia for human strains is rare. In this review, no consistent association between influenza and adverse pregnancy outcomes (pre-term delivery, low birth weight, low Apgar scores, delivery complications), or specific congenital defects has been found, though several, notably neural tube defects, have been proposed.[21] Evidence for subsequent childhood neoplasm following maternal influenza is also considered weak. On the basis of ecologic observations around the 1957 pandemic and subsequent patterns of seasonality, a link between early-to-mid-gestation maternal influenza and subsequent schizophrenia decades later in offspring has long been debated.

Key point in pregnant women

- **Several studies show that influenza is associated with an excess risk of hospitalization during pregnancy, which is increasing with co-morbidities and gestational age. However, the same trend was observed for admissions outside influenza periods. Additionally, the precise level of risk is unclear because of different outcome definitions and difficulties to control for unknown underlying morbidity.**
- **No robust data show an excess of mortality associated with influenza during pregnancy**

10.6 HEALTH CARE WORKERS

10.6.1 Definition of health care workers

According to Tabarani, a health care providers includes anyone who may interact with patients during the work day.[162] As such, HCPs might include (but are not limited to) physicians, nurses, nursing assistants, therapists, technicians, emergency medical service personnel, dental personnel, pharmacists, laboratory personnel, autopsy personnel, students and trainees, contractual staff not employed by the healthcare facility ant those such administrators, office assistants, dieticians, housekeeping and catering staff, maintenance workers and volunteers not directly involved in patient care but potentially exposed to influenza in their work environment. The definition of a healthcare facility is also quite broad, including hospitals, long-term care facilities, off-site clinics and private offices.

10.6.2 Outpatient influenza/ILI in health care workers (HCW)

Data on ILI in health care workers are scarse. In a Belgian retrospective cohort study, Michiels showed that general practitioners (GPs) were more protected against upper respiratory tract infection compared to their patients, excepted for young GPs.[63] The author suggested that GPs may suffer from milder signs and symptoms, mostly without high fever. In a trial among Belgian GPs, Michiels measured influenza antibody titres during two influenza seasons, and found a high basic immunity among GPs. Seroprotection rate against the circulating A/H3N2 influenza virus amounted to 80% and 42% in the unvaccinated group in 2002 and 2003 (when the virus was antigenically slightly different from the previous strains).[53] The frequent and close contacts of GPs with influenza cases may explain these results.

In a cohort study in Germany, Williams showed that HCW were not at higher risk of serologically-confirmed ILI than non-HCW (RR=1.09, p=0.70).[55] HCW were less susceptible to the previous and current influenza viruses than non-HCW. Interestingly, household contact with children was the main significant risk factor for confirmed ILI, with a strong dose-response relationship. This finding is similar to that in meningitis – which is also a droplet-transmitted infection.

Attack rates for health care workers during nosocomial influenza outbreaks have been shown to reach 14 to 23% of HCW.[163, 164] However, without the inclusion of a comparison group of non HCW, neither study could demonstrate an increased risk.[55]

ILI-syndrome appears to be a poor marker for influenza infection, suggesting that HCWs cannot rely on this syndrome to protect their patients.[55]

10.6.3 Mortality in health care workers

Based on US death registers, Franck showed that white male physicians were less likely to die from chronic obstructive pulmonary disease, pneumonia/influenza or liver disease than were other professional white men, but this study dated from 1984-1995.[165]

10.6.4 Transmission in vulnerable patients

Many nosocomial influenza outbreaks have been reported in paediatric wards, nursing home, intensive care units, and studies discussed the likely transmission role of HCW.[166, 167] The contributing factors are:

- Possible transmission by asymptomatic HCWs. According to Stott, half of infected HCWs are likely to be asymptomatic or to have minimal symptoms that may not be attributed to true influenza.[167] Tabarani considers that staying home from work when ill is an insufficient strategy for preventing nosocomial transmission of influenza because an individual can transmit infection to susceptible contacts for at least 24 hours before the acute onset of fever, headache and chills.[162]
- Rare absenteeism. According to several authors, many HCW continue to work despite being ill with influenza, potentially putting patients at risk.[162, 164, 168, 169]

Key points in health care workers

- **The influenza morbidity and mortality in HCW appears similar or lower to non-HCW.**
- **The role of HCW in nosocomial outbreak is widely debated but not clearly described.**

11 APPENDIX 4: SELECTION OF PARAMETERS ON INFLUENZA VACCINE EFFICACY AND EFFECTIVENESS

11.1 METHODS

11.1.1 Inclusion criteria for IVE studies

A systematic literature review has been conducted and is described in Appendix 3. Not all retrieved studies were relevant for the determination of parameters. We used the following selection criteria to apply to the studies extracted through literature search:

1. Study design.
   - RCT and quasi RCT.
   - For groups in which RCT are no longer conducted for ethical reasons (elderly and persons with co-morbidities), observational prospective studies that control for the most important confounding factors (including presence of underlying diseases and its severity).
2. Outcome of interest: ambulatory ILI, ambulatory laboratory confirmed ILI, influenza admissions (based on ICD), pneumonia admissions (based on ICD), deaths from influenza, and deaths from pneumonia.
   - For laboratory confirmed influenza: we restricted to studies that confirmed influenza based on culture and/or PCR, not by serology, to fit with the Belgian data. We restricted to IVE against influenza all influenza strains, not only those matched to the vaccine strains.
3. Date: data covering seasons from 2000 onwards to fit with the period of influenza burden data (2000-08). This is important because influenza seasons before 2000 had a higher intensity (severity has decreased across time in recent decades)[38], and higher seasons result in higher IVE. For outcomes for which no or only few data are available after 2000, we retrieved studies pooling several seasons in 1990-2000.
4. Setting: Northern hemisphere, EU, US or Canada. The rationale is to limit discrepancies in the prevalence of other seasonal pathogens causing ILI and pneumonia.
5. Studies in the elderly were limited to the community-dwelling elderly, as in our study.
6. Intervention: trivalent inactivated vaccine (TIV) only, non adjuvanted.
7. Comparator: placebo or nothing.
8. ILI definition is provided

11.1.2 Data analysis

When relevant, IVE estimates from RCTs were pooled as risk ratios (RR) and 95% confidence intervals were calculated, using Review Manager 5. We used random-effects models to take into account the between-study variance in our findings, as there are unpredictable systematic differences between trials regarding the circulating strains and the levels of immunity presented by different population in different settings.

Influenza vaccine efficacy (IVE) was expressed as a percentage using the formula:

VE= 1-RR or VE=1-OR or VE=1-HR.

11.2 IVE PARAMETERS

Several Cochrane systematic reviews have been published on influenza vaccine efficacy (IVE) in different groups and several of them have been updated in 2010. The last Cochrane reviews cover IVE in healthy adults,[13] in the elderly,[12] in persons with chronic lung disease [9-11, 65] and in health care workers working with the elderly.[14]

However, these reviews have many limitations for the determination of IVE parameters.

1. Many analyses involved other vaccines, other outcomes or did not adjust for important confounders. For instance, none of the 4 reviews on chronic lung disease involved the outcomes of our study.
2. Literature search for primary studies revealed that many eligible studies had been missed, likely because they were not retrieved by the search strategy (not because of exclusion). For instance in healthy adults, at least three recent RCTs fitting the selection criteria and published before the search date have not been included.[66-68] In the elderly, at least two quality studies were also not retrieved by the search.[69, 70]
3. The two Jefferson reviews tended to over-estimate the current IVE:[12, 13]
   - They included mostly old studies, dating from periods with higher intensity: pooled estimates included studies from the 1968-69 pandemic period showing higher IVE; in healthy adults, 25/50 RCTs measuring IVE dated before 1980; in the elderly, very few studies involved data from 2000-2008. Indeed, pooled IVE was lower when the studies carried out during 1968-69 pandemic were excluded.
   - In the elderly, Jefferson has only included data restricted to higher viral circulation when primary studies were presenting data according to different levels of viral circulation.[12]
   - Adjuvanted vaccines were pooled with TIV (e.g. in the elderly).
4. Some meta-analyses pool different outcomes and populations, and this could impact on IVE results. In the elderly, a meta-analysis on IVE in preventing deaths from pneumonia or influenza included data on influenza deaths only[170] to data on deaths from influenza and pneumonia.[171] As no statistical heterogeneity was detected, Jefferson pooled these data though the outcomes were different.[12] For instance, IVE against influenza outcomes is obviously higher than against pneumonia which is a less specific outcome.
5. The meta-analyses from Jefferson pool studies covering seasons with poor or unknown matching with vaccine strains; the extent to which these seasons can be considered as presenting poor match is unknown.
6. Though adjusted observational studies are presented separately, the Jefferson reviews did not specify criteria for adjustment. However, we now know that some essential confounders need to be taken into account (e.g. severity of underlying disease).
7. Cochrane updates published one year after each other by the same team, updating studies with only 2 new studies, have drastically changed their conclusions though the new studies did not change substantially the main effect measures.[13, 71]
8. The definitions for epidemic periods differ across studies, and data were pooled regardless of the definition of epidemic period used in the primary study. Definitions and are not described in the analyses.

For these reasons, the results of the Cochrane meta-analyses are not used in this study as parameters. Primary studies included in Cochrane reviews and fitting with selection criteria were retrieved, and additional literature searches were conducted to identify primary studies involving efficacy and effectiveness data collected from 2000 onwards in these groups. In general, only few primary studies included in the Cochrane reviews could be selected as they were older, involved other vaccines, other outcomes or did not adjust for important confounders.

11.2.1 Healthy adults

A Cochrane systematic review has included RCTs and quasi-RCTs published up to June 2010.[13] However, 3 recent RCTs conducted in the US have not been retrieved,[66-69] and only 2 primary eligible studies were conducted after 2000. The literature search performed only found eligible RCTs involving laboratory confirmed ILI (Influenza). As no recent RCT involved hospitalization or mortality for pneumonia and influenza (P+I) as outcomes, the search also included observational studies (cohort or case control) conducted after 2000, adjusting for the main confounding factors and including the above outcomes.

11.2.1.1 Influenza (influenza laboratory confirmed ILI)

The 6 retrieved RCTs are presented in Table 59. [67, 68, 72-74, 172] All involved laboratory confirmed ILI (Influenza). However, the range of estimates was wide (16-75%). VE pooled estimates tended to be higher in seasons with good matching than in seasons with poor matching, but Table 59 indicate that IVE estimates were also influenced by season intensity, and high intensity systematically resulted in highest IVE.

We thus categorized study seasons by matching (good, relative and poor) and by season intensity (high, moderate, low and very low). We pooled IVE estimates by category of season as in Table 61 and Table 60, merging seasons with high to moderate intensity because descriptions were not always concordant across sources and values were very close. For all pooled estimates, no heterogeneity was detected and a minimum of 1800 subjects was included in each category. Figure 30 show an example of the pooled analysis for one season category (low intensity and good match). As expected, pooled IVE was significantly higher in good matching seasons (56%) compared to poor matching seasons (22%, NS). But pooled IVE was also significantly higher in high/medium seasons (65%) compared to low intensity season (39%), Table 60. Table 61 shows the IVE estimates by the season categories that are considered for Belgian data.

Table 59: VE for laboratory confirmed ILI (culture or culture + PCR) in RCT

Reference	Season and match	Study design	Level of evidence	Study group, years	IVE	95% CI	Remark / limitations
Ohmit 2006	2004-05 Moderate season Relative match	RCT (US)	High	18-49	75%	42–90	Nov- April
Beran 2009[2]	2005-06 Low season Poor match	RCT (Czech)	High	18-64	22.3% (NS)	-49.1–58.5	AR <1%. From week with 2 confirmed cases to week with 1 case.
Ohmit 2008	2005-06 Low season Good match	RCT (US)	High	18-49	16% (NS)	-171–70	Viral activity: Jan-Apr. Only 4.6% ILI were +
Beran 2009[2]	2006 -07 Medium season Good match	RCT (Czech , Finland)	High	18-64	61.6%	46.0–72.8	Sept-May. Culture confirmed. From week with 2 confirmed cases to week with 1 case.
Jackson 2010[1]	2005-06 & 06-07 Low seasons Good match (75.5% match)	RCT (US)	High	18-49	49% [3] 66.8% if fever	1-sided 20.3	Nov-April, culture confirmed.
Monto 2009	2007-08 High season Relative/good match	RCT (US)	High	18-49	68%	46–81	Jan-April

1: ILI = symptoms that interfered with normal daily activities and that included cough, and at least 1 additional symptom from among fever (oral temperature >37.7°C/99.9°F), headache, myalgia and/or arthralgia, chills, rhinorrhea/nasal congestion, and sore throat. 2: ILI: at least 1 systemic symptom [fever (oral temperature, _37.8_C) and/or myalgia] and at least 1 respiratory symptom. 3: calculated. IVE: influenza vaccine effectiveness/efficacy

Figure 30: Pooled analysis for TIV vaccination against influenza in low season and good match (Rev Man 5)

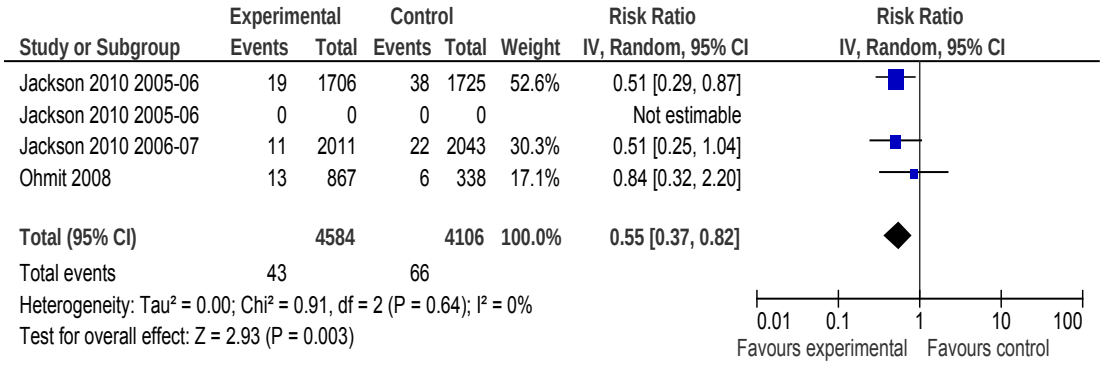


Table 60: Pooled IVE estimates for influenza by type of season

Season characteristics	N subjects	Pooled IVE (95% CI)
High/medium intensity, any matching[66, 67, 72]	9,518	65% (55-73%)
Low intensity, any matching[68, 73, 74]	14,893	39% (15-56%)
Good match, any intensity[68, 72, 74]	16,342	56% (43-65%)
Poor match, any intensity[73]	6,203	22% (-40 to 57%), NS
High/medium season and good match[72]	7,652	62% (47-72%)
High/medium season and relative match[66, 67]	1,866	70% (55-80%)
Low season and good match[68, 74]	8,690	45% (18-63%)
Low season and poor match[73]	6,203	22% (-40 to 57%), NS

NS: non-significant; IVE: influenza vaccine effectiveness/efficacy; RR: risk ratio, as calculated by Rev Man 5.

The pooled IVE estimates fit relatively well with the data from recent adjusted case-control studies, ranging 46-70% in season with good or relative match, Table 62.[75-79] The gradient of IVE in seasons with poor to good matching was also confirmed in adjusted case-control studies.[80] The Cochrane 2010 review calculated an IVE of 73% (54% to 84%) against influenza symptoms in matching seasons, and 44% (95% CI 23% to 59%) when there was no matching, which are higher than our recent estimates.[13] However, these pooled estimates included studies from 1970-1978 with much higher intensity, and whose IVE amounting to 93% in matching seasons. Pooled IVE was lower when the studies carried out during 1968-69 pandemic were excluded.[13]

Table 61: Pooled VE estimates for influenza, by season categories

Season	Medium and high	Low	Total (pooled)
Good	62%	45%	56%
Relative	70%	NA	Not calculated
Poor	NA	Not defined (NS)	Not defined (NS)
Total (pooled)	65%	39%	NA

Table 62: VE for laboratory confirmed ILI (culture or culture + PCR) in adjusted case control (CC) studies

Reference	Season, match	Study design	Level evidence	Study group	VE	95% CI
Skowronski 2010	2008-09, pandemic year	Adjusted CC (Canada)	Low	All ages	56%	41-67%
Skowronski 2007	2005-06, poor match, low intensity	Adjusted CC (Canada)	Low	All ages	61%	26-79%
Skowronski 2009	2006-07, relative match	Adjusted CC (Canada)	Low	All ages	46%	17-65%
CDC 2010	2007-08, relative match, high intensity	Adjusted CC (US)	Low	5-49y	54%	12-76%
Belongia 2009	2004-05, poor match 2005-06 poor, low 2006-07, good match	Adjusted CC (Canada)	Low	Groups eligible for vaccination	10% 21% 52%	NS NS 22-70%
Fleming 2009	2005-08 (3), medium intensity, good or relative match	Adjusted CC (England)	Low	0-64y	70%	57-78%

11.2.1.2 ILI

Data on IVE for not laboratory confirmed ILI were heterogeneous, depended on the epidemiology of concomitant aetiologies of ILI, and were mostly not statistically significant or statistics were not clear. For this reason, we decided to work with VE for influenza only and derive corresponding impact on ILI from the impact on those ILI that are laboratory positive. However, IVE data for ILI are given in appendix for information (Table 72).

11.2.1.3 Hospitalization for influenza and pneumonia

Very few studies have evaluated IVE for this outcome because it is rarely observed in healthy adults. Only one observational study which fitted with the selection criteria involved this outcome in healthy adults (Table 63): an US adjusted cohort study has estimated the VE in adults aged 50-64 years over 10 influenza seasons (1997-2007) at 12.4% (95%CI 1.6-22.0%).[81] This study has used a different and new method for adjusting for unknown confounders ("difference of difference"),[81] and only covered adults ≥50 years of age. However, this estimate is close to the results of other observational studies. Jackson found an effectiveness of 15% (non significant) against community acquired pneumonia admissions validated by medical file review.[69] Older studies included in the Cochrane review did not provide IVE for P+I hospitalization but hospital admissions for respiratory causes were evaluated in 4 (mostly old) trials, and pooled IVE was estimated at 11% [95% CI -20 to 35%].[13] As the IVE was not significant, the review concluded that vaccination had no effect on hospital admissions rates. However, this is likely due to the very low number of admissions in healthy adults in all studies.

Table 63: Adjusted cohort studies estimating IVE for admissions for pneumonia or influenza

Reference	Season	Population	Study design	Level evidence	N	IVE	Remark / limitations
Baxter Vaccine 2010[81]	1997-2007 All together	Adults ages 50-64 years	Cohort, adjusted (US, California)	Low	68,000 admis-sions	12.4% (1.6-22.0%)	Adjusted by computing difference with non-influenza periods (difference of difference)

IVE: Influenza vaccine effectiveness/efficacy.

11.2.1.4 Mortality for influenza and pneumonia

No study involved mortality outcomes in this group, which is likely due to the very low influenza mortality in healthy adults.

11.2.2 Patients 15-64 years with co-morbidities

The 4 Cochrane systematic reviews covered influenza vaccination in chronic lung disease (asthma, bronchiectasis, cystic fibrosis and COPD) but did not cover our selected outcomes and search dates covered dates up to 2006-2007.[9-11, 65] Two small primary RCTs were conducted in other settings (Thailand and Korea).[93, 94] A small open-label RCT in heart transplant recipients was conducted in Italy but the IVE was not calculated and the outcome not clearly defined.[95] These RCT could thus not be selected. An adjusted US retrospective cohort study involved end-renal stage patients over 2 seasons, just before our inclusion period (1997-99).[96] However, the study included all ages with high proportions of elderly (29-45% were ≥65 years of age) and IVE estimates were not stratified by age.

Other observational studies included all patients with any co-morbidity and are presented under the respective outcomes.

11.2.2.1 Influenza

In most studies estimating IVE against GP attended influenza, the presence of co-morbidity had a low confounding effect but no recent studies stratified for the presence of co-morbidities.[77, 78, 87] We assumed that the VE against influenza is similar in patients with and without risk factors, and parameters from Table 61 are selected.

11.2.2.2 Admissions for influenza and pneumonia

A Dutch adjusted cohort study in co-morbid adults showed a IVE for hospitalisation due to influenza or pneumonia at 63% in 1999-2000 (CI provided by the author at 16-80%).[50] Other studies involved other hospitalization outcomes.[95, 97, 98]

Table 64: Studies estimating IVE in persons with high risk of complications

Reference	Season	Design	Patients	Level evidence	Outcome	IVE	95% CI
Hak 2005, NL	1999-2000, high season, good match	Case control	18-64 years with co-morbidities	low	Adm. P+I	63%	16-80%

IVE: Influenza vaccine effectiveness/efficacy.

11.2.2.3 Deaths from influenza and pneumonia

No eligible study included deaths from influenza and pneumonia as outcome. Most studies only assessed IVE on winter all-cause mortality, which is prone to bias. We thus selected two scenario for IVE parameters:

1. Best case, same IVE as for admissions for P+I (63%)
2. Worst case: same IVE as for deaths P+I in elderly 65-74 years of age with co-morbidities (29%).

11.2.3 Elderly (65 years and above)

We mainly consider here community-dwelling elderly and did not include studies on nursing homes.

One recent Cochrane review was identified covering the literature until October 2009.[12] This review included 5 RCTs, 51 cohort studies and 12 case-control studies. Only one RCT in the 65-74 years, three adjusted cohort studies and no case control study were eligible for study period, vaccine and outcome.[82]

We retrieved five adjusted cohort studies including at least the year 1999, including three from the Cochrane review.[81, 83-86]

In case-control studies published after the Cochrane search date, only a pooled analysis of 5 recent case-control studies has been selected.[87] A Romanian case control study also fitted with the criteria but was included in the above pooled analysis.[89] Other case control studies covered 2005-08 but included all age groups and did not provide stratified estimates for elderly or lacked power, or did involve other outcomes.[69, 75-79]

Results are provided in Table 65 and parameters were checked against values from older case control studies.[12, 173]

Table 65: Retrieved IVE studies for elderly all ages and all outcomes

Reference	Outcome	Season	Design	Patients	IVE	95% CI
Kissling 2009	Influenza	2008-09, good match, high/medium	5 adj. case control pooled	All elderly	59%*	15.3-80.3%
Baxter 2010	Admissions P+I	1997-2007, all	Adjusted cohort	All elderly	8.5%	3.3-13.5%
Nordin 2001	Admissions P+I	1996-97 (good, medium) 1997-98 (poor, medium)	Adjusted cohort	All elderly	20% 24%	5-31% 14-34%
Nichol 2003	Admissions P+I	1998- 99 (good, medium) 1999-00 (good, medium)	Adjusted cohort	All elderly	32% 29%	22-40% 20-38%
Nichol 2007 (pooled)	Admissions P+I	1998-99 (good, medium) 1999-00 (good, medium)	Adjusted cohort	All elderly	27%*	23-32%
Mangtani 2004	Deaths P+I +bronchitis	1989-99, good match, all	Adjusted cohort	All 65+	12%*	8-16%

*: Selected for parameter; IVE: Influenza vaccine effectiveness/efficacy; P+I: Pneumonia and influenza.

11.2.3.1 Influenza in all elderly

Only the Kissling pooled case control study provided IVE value, during a season with good matching and moderate to high intensity (depending on the country).[87] It involved all elderly (healthy and with co-morbidities) and adjusted data for important confounders. IVE was 59.1% for all elderly, and estimates stratified by age are provided in the next sections (Table 65). This value is close to those from the three older RCT in the Jefferson review, with an overall IVE of 58% (95%CI 34-73%) against laboratory-confirmed influenza cases in three matching seasons.[12]

Data for other season categories are not available so far. The same value is assumed in high and low risk (see above).

One English RCT involved ILI in healthy elderly aged 65-74 years (see Table 67), but IVE for ILI is not used as parameter.[82]

11.2.3.2 Hospitalization for influenza and pneumonia in all elderly

Four recent adjusted (cohort) studies were included. Older but well adjusted cohorts were also retrieved for additional information on specific groups.

In US cohorts, IVE against P+I admissions in all elderly were significant and ranged 20-32% over 4 consecutive seasons (1996-2000), Table 65.[83, 84] A later publication pooled results from the 1998-2000 seasons, with a VE at 27% (95% CI 23-32%).[86] This was similar to a pooled IVE estimates from older adjusted cohorts by Jefferson at 27% (95% CI 21-33%) for all seasons, and close to another US cohort study on admissions for influenza, pneumonia and bronchitis (IVE at 21%, 95% CI 17-26%).[12, 85]

However, a more recent cohort study estimated at 8.5% (95% CI 3-14%) the VE against admissions for P+I in all elderly over 10 influenza seasons (1997-2007), using a new and different method (difference of difference) to adjust for unknown confounders. It found much lower values than all previous cohort studies.[81] The lower value found in this study may be due to differences in methods, population and diagnosis (Table 66).

These studies and other cohort studies brought two other interesting findings for parameter determination:

1. IVE for hospitalization for P+I were similar in healthy elderly and those with co-morbidities in both Nichol and Mangtani cohorts, and this was supported by other studies (Table 69).[58, 83, 85, 99]
2. IVE estimates in seasons with poor match did not differ from seasons with good match in US cohorts, including in the analysis of 10 influenza seasons.[84, 86]
3. In a UK cohort, VE for hospitalization were lower in mild seasons (ranged 3-7% in 3 mild seasons and were not significant) but no pooled estimates was provided.[85]

Results from pooled analyses suggest that adjusted case control studies yield systematically higher values than adjusted cohort studies, with pooled estimate at 32% in Jefferson et al (95% CI 14-46%) and 33% in an Italian non-included study (Table 69).[173]

We thus selected the pooled IVE from the US cohort (27%; 95% CI 23-32%) as it met all selection criteria. The same IVE value is considered for healthy elderly and those with co-morbidities, and in poor and good matching seasons (Table 66). As the adjustment method used by Baxter has not been validated yet, we did not consider it for parameter determination.

Table 66: Comparison Nordin-Nichol vs. Baxter cohorts

Reference	Season	Population	Method	Uptake	Age/risk	Outcome	IVE
Baxter	1997-2007 (10 years) Nov-May	Kaizer permanente California	Adjusted cohort, with difference of difference	65% in 65+	65+ No % risk 75+ No % risk	Admissions P+I (ICD 480-487, primary) (+ Other causes H)	8.5% in 65+
Nordin / Nichol	1996-2000 (4 years, 3 papers)	3 HMOs: Minnesota, Oregon, NY	Adjusted cohort	56-60% in 65+	65+ 43% risk 75+ 47% risk	Admissions P+I (ICD 480-487)	19-32% in 65+

IVE: Influenza vaccine effectiveness/efficacy.

11.2.3.3 Mortality for influenza and pneumonia in all elderly

The effectiveness of TIV vaccination to prevent deaths in the elderly is a subject of debate. Many observational studies have showed an impressive effect of TIV vaccines to prevent all cause mortality (~50%).[12] However, further research showed that these results were flawed by important selection biases and confounding factors; after adjustment, no significant effect was observed - or sometimes a detrimental effect.[18, 91, 92] An obstacle to gain further insight in this issue is that RCTs in the elderly are no longer conducted for ethical concerns.

No IVE studies against death from P+I, adjusting for confounders and involving TIV, covered periods after 2000. The most recent study meeting the criteria is a UK adjusted cohort study, involving deaths from pneumonia, influenza and chronic bronchitis, over the 10 seasons 1989-1999.[85] It showed a 12% significant VE in all elderly above 65 years. Residual confounding was suggested in the high risk groups and the 85+. Little effect of vaccination was found in the non-epidemic years, with VE ranging -4 to 13% in the three mild years, but no pooled estimate was provided.

We thus selected the same IVE at 12% for all elderly, in persons with or without co-morbidities.

Two older adjusted studies involving TIV vaccines and P+I deaths were also included in Jefferson and are presented in Table 69.[170, 171] However, Ahmed only involved deaths from influenza, not from pneumonia. The Cochrane review from Jefferson pooled them (as no statistical heterogeneity was detected) and found similar IVE (26%) but the outcomes were different. In these studies, VE estimates were higher, in the same range than VE for admissions for P+I. Two older adjusted studies involving TIV vaccines and P+I deaths were also included in Jefferson and are presented in Table 69.[170, 171]

11.2.3.4 Elderly 65-74 years of age

Table 67: Retrieved IVE for elderly 65-74

Reference	Outcome	Season	Design	Patients	Level evidence	IVE	95% CI
Allsup 2004	ILI (no fever)	1999-00 good, high	1 RCT UK	Healthy 65-74 years	moderate	20% NS	-310–84%
Kissling 2009	Influenza	2008-09 good, medium?	5 case control adjusted	All 65-74 years	low	65.4%	16-86%
Baxter 2010	Admissions P+I	1997-2007, all	Adjusted cohort + diff. of diff.	All 65-74 years	low	16%	7-24%
Nichol 2003	Admissions P+I	1998-2000, good match, high	Adjusted cohort	All 65-74 years	low	~35%	~20-45%
Mangtani 2004	Deaths P+I +bronchitis	1989-99, good match, all	Adjusted cohort	Healthy 65-84y	low	21%	11-29%
Mangtani 2004	Deaths P+I +bronchitis	1989-99, good match, all	Adjusted cohort	65-84 y at risk	low	29%	22-34%

IVE: Influenza vaccine effectiveness/efficacy; P+I: Pneumonia and influenza.

Influenza in the 65-74 years olds

The Kissling adjusted pooled case-control measured IVE in the 65-74 years at 65.4% in a season with good match and medium intensity (Table 67).[87]

IVE against ILI was measured in one RCT in a season with good matching and high intensity in healthy elderly aged 65-74 years.[82]

Hospitalization for influenza and pneumonia in the 65-74 years olds

The Nichol and Nordin cohort studies provided no quantitative IVE for P+I admissions by age group but IVE figures by age group show overlapping confidence intervals, and IVE are consistent among the age subgroups:[83, 86] in the 1998-2000 seasons, IVE in the 65-74 years was around 35% vs. 29 and 32% by season for all ages. We thus selected the same parameters for younger and older elderly.

Mortality for influenza and pneumonia in the 65-74 years olds

In the Mangtani cohort (10 seasons 1989-1999), IVE against deaths was only estimated in the 65-84 years, by risk group, and no pooled estimate was provided.[85] we thus selected the IVE for high and low risk as parameter.

11.2.3.5 Elderly ≥75 years of age

Most recent studies did not provide stratified IVE estimates by age group.

Influenza in the ≥75 years of age

The Kissling case control provided estimates for the 75 years and above, at 60% (Table 68).[87]

Hospitalization for influenza and pneumonia in the ≥75 years of age

No estimate of IVE against P+I admissions was provided for the 75 years and above. However in all adjusted cohort studies, IVE was generally consistent across age groups and ranged 20-50%. Even in the ≥85 years, VE estimates were significant and ranged around 20-40%.[83, 85, 86] The exception was for the ≥85 or 90 years with high risk, in which no IVE could be shown against P+I admissions, but this group is not considered separately.[85] The same parameter is thus applied to both age groups (IVE 27%).

Mortality for influenza and pneumonia in the ≥75 years of age

In the Mangtani cohort, IVE in the 85 years and above showed point estimates at around -30% in low risk and 0% in high risk for P+I mortality (values not provided).[85] No parameter could thus be defined.

Table 68: Retrieved IVE for elderly > 75 years

Reference	Season	Design	Patients age	Level evidence	Outcome	IVE	95% CI
Kissling 2009	2008-09 good, medium?	5 case control adjusted	All 75+	low	Influenza	59.6%	-73–91%
Nichol 2003	1998-2000, good match, high	Adjusted cohort	75-84 85+	low	Admissions P+I	~ 25% ~ 40%	~ 15–40% ~ 18–37%
Mangtani 2004	1989-99, good match, all	Adjusted cohort	All 85+	Low	Deaths P+I +bronchitis	-30% or 0% [1]	NA

1. Residual confounding. IVE: influenza vaccine effectiveness/efficacy. P+I: pneumonia and influenza

Table 69: Older studies 1990-2000 and studies included in Jefferson et al (for validation)

Outcome	Studies	Patients	Season	Results (range)	95% CI
Admissions P+I + chronic bronchitis	Adjusted cohort Mangtani, UK	All 65+	1989-1999, good match, all	21% (3-34% ~season)	17-26%
Admissions P+I + chronic bronchitis	Adjusted cohort Mangtani, UK	65-84 years low risk	1989-1999, good match, all	22%	9-29%
Admissions P+I + chronic bronchitis	Adjusted cohort Mangtani, UK	65-84 years high risk	1989-1999, good match, all	21%	22-34%
Admissions P+I	Jefferson 2010, 4 adjusted cohorts	All 65+	Good match, high	29%	23-35%
Admissions P+I	Jefferson 2010, 4 adjusted cohorts	All 65+	All	27%	21-33%
Admissions P+I	Crocetti 2001. adjusted case control	All 65+	1994-95 (relative)	33%	5-52%
Admissions P+I	Jefferson 2010, 1 adjusted case control	All 65+	All	32%	14-46%
Deaths I	Ahmed 1995, adjusted case control	All 65+	1989-90, good match, high	24%*	3-40%*
Deaths P+I	Mullooly 1994, adjusted case control	Elderly at high risk	1981-89, all	33%	-7%–58%, NS
Deaths P+I	Jefferson 2010, meta-analysis of Ahmed and Mullooly	«all elderly» but incorrect	High, good or poor match	26%	8-40%

NS: Non significant. P+I: Pneumonia and influenza. I: Influenza.

11.2.4 Pregnant women and infants

A literature review and 4 primary studies were identified, including one RCT and 3 observational studies, but few studies involved the same outcomes.[21, 61, 174-176]

11.2.4.1 IVE in pregnant women

The RCT was conducted in Bangladesh, where influenza viruses circulate most of the year with limited seasonal effect.[174] IVE was significant at 36% against respiratory illness with fever. However, the control (pneumococcal) vaccine also aimed at reducing respiratory illnesses and no case definition was provided. In a US large retrospective cohort study over 5 influenza seasons, no IVE against pneumonia or influenza hospitalisation in mothers could be calculated due to the low burden of admissions in this group; no IVE against ILI visits could be demonstrated.[61] Other studies using other outcomes (acute respiratory tract illnesses) also failed to achieve significance.[175, 176] The literature review has concluded that TIV protection against serious outcomes in pregnant women (hospitalization and deaths) has not yet been shown.[21]

11.2.4.2 IVE in infants

In infants, the RCT in Bangladesh found a significant IVE against influenza at 63%.[174] However, the setting cannot be compared to Belgium. A recent cohort study in mother-infant pairs showed a significant 41% IVE for laboratory-confirmed influenza and a significant 39% IVE for ILI hospitalization in infants.[177] In the Black cohort over 5 influenza seasons, adjusted IVE against pneumonia or influenza hospitalisation in infants was not significant at 38%.[61] The duration of protection is not clear in these studies; Eick had a 6-months follow up and other studies did not describe it clearly.[175, 176] Munoz and France could not identify a reduced risk of influenza-related episodes in infants but outcomes were non-specific.

A recent matched case control study revealed much more favourable 92% IVE against admissions for influenza in infants of vaccinated mothers (when pregnant) in the first 6 months of life.[178]

Table 70: IVE for pregnant women

Reference	Season	Design	Patients	Level evidence	Outcome	IVE (95% CI)
Zaman 2008 Bangladesh	No season (tropical country)	RCT	340 pregnant	High	Mothers: RTI Infants: infuenza	36% (4-57%) 63% (5-85%)
Black 2004 US	5 seasons 1997-2002	Retrospective adjusted cohort	49,585 pregnant	Low	Mothers: ILI Infants: adm. P+I	-15%, NS 38% (-29%–60%)
Eick 2011 Navajo and Apache	3 seasons 2002-05	Prospective adjusted cohort	1169 mother-infant pairs	Low	Infants: influenza Infants: adm. I	41% (7-63%) 39% (16-54%)
Benowitz 2010, US	9 seasons 2000-09	Matched adjusted case control	247 infants	Low	Infants: admission for influenza	92% (62-98%)

NS: Non significant. IVE: Influenza vaccine effectiveness/efficacy. P+I: Pneumonia and influenza. I: Influenza. Adm.: admission. RTI: Respiratory tract infections.

In conclusion, the IVE estimated in pregnant women seem comparable to those in non-pregnant adults and are concordant with results from immunogenicity studies that show that the influenza vaccine in pregnancy reach similar antibody responses than in nonpregnant adult women.[100, 101] As a result, the same IVE are considered for pregnant women than for healthy adults aged 15-64 years (Table 61).

11.2.5 Health care workers

11.2.5.1 IVE to protect health care workers (direct effect)

A systematic review evaluated both the direct and indirect effects.[179] One RCT found a very high 88% IVE but the outcome was seroconversion of influenza A(H3N2) regardless of symptoms; it also reported a non-significant IVE at 29% for cumulative days of febrile RTI.[164] Two other RCTs reported no significant IVE, although in one there was a poor vaccine match, the incidence of influenza was low in the other, and outcomes were less specific.[180, 181] In a Belgian non-randomized controlled trial, IVE was estimated in 122-140 GPs in Flanders during two seasons (2002-04). Non adjusted IVE for laboratory confirmed RTI was non significant at 41% but adjusted IVE decreased with age: IVE was highest (87%) and significant at 30 years of age, non significant above 36 years of age and even negative above 48 years of age, see Table 71.[52] Authors suggest that GPs who have been working for more than 20 years in full time practice and who have enough yearly contact with influenza patients do not need to be vaccinated.

Table 71: Direct IVE for health care workers

Reference	Season	Design	Patients	Level evidence	Outcome	IVE (95% CI)
Michiels 2006 Belgium	2002-03 2003-04	Non randomized trial	122 and 140 GPs	Moderate	Positive RTI (PCR) Sero-conversion (no symptoms)	30 yrs adj.: 87% (25-99%) 50 yrs adj.: -41% (-476–65%) Non adjust. 41% (-24% - 72%) Non adjust.72% (25-90%)
Wilde 1999 US	1992-93 1993-94 1994-95	RCT	264 hospital staff	High	Sero-conversion (no symptoms) Days febrile RTI	A(H3N2): 88% (47-97%) B: 89% (14-99%) 29% (-22% to 59%)
Saxen 1999 Finland	1996-97	RCT	428 paediatric hospital staff	High	Self reported RTI	Not calculated, IVE ~10%, NS
Weingarten 1988, US	1985-86	RCT	179 hospital staff	High	ILI	25%, p=0.07

IVE: Influenza vaccine effectiveness/efficacy. RTI: Respiratory tract infection. PCR: Polymerase chain reaction. ILI: Influenza like illness.

These studies did not find significant IVE for less specific outcomes but were also mostly underpowered. Though IVE seem to be lower in older GPs, results are in line with those from other healthy adults. We thus assume that the IVE against the different outcomes are similar than those estimated in other healthy adults aged 15-64 years, and parameters for this group are selected.

11.2.5.2 IVE to protect patients (indirect effect)

Two systematic reviews involved indirect effect from vaccination HCW and no new primary studies were identified.[14, 179] Evidence is inconclusive. Thomas et al concluded that there is no evidence that vaccinating only HCW prevents influenza and death from pneumonia in elderly residents in long-term care facilities. Most IVE were not significant, except for the prevention of ILI if patients were vaccinated too (86%; 95% CI 40-97%). Burls et al. included 2 old cluster RCTs that looked at overall mortality; one trial showed a significant 44% IVE for overall deaths but the analysis did not take clustering into account;[182] the other trial did find a non-significant 39% reduction in overall mortality when adjusting for confounders.[183]

This lack of demonstrable indirect effect may be due to the inability of TIV to prevent virus replication. Michiels et al. suggested that virus replication and subclinical influenza infections are not countered enough by an inactivated vaccine.[54] More evidence emerges that LAIV vaccines administered locally (e.g. in the nose) will be more effective in preventing virus replication, but these vaccines are not yet available in Belgium (as of May 2011) and thus not considered in this study.

No parameter for indirect effect is selected from this literature review, and this effect is not included in the model.

11.3 ADDITIONAL DATA VACCINE EFFECTIVENESS/EFFICACY FOR OUTCOME ILI

These data are given for information, as the IVE on lab confirmed cases is more accurate and less biased by the differences in other etiologic agent prevalence in the study settings. Only the IVE for lab confirmed cases will be used as parameter for the model.

Table 72: IVE estimates on ILI (not laboratory confirmed)

Reference	Season	Study design	Level evidence	N	IVE	CI, n/N (vaccine vs. placebo)	Remark / limitations
Beran BMC 2009	2005-06, poor match	RCT (Czech) 18-64y	High	6203 18-64y	-6.1% NS	-33.8–15.5%	AR <1%. From week w/ 2 confirmed cases to week with 1 case.
Beran JID 2009	2006-07, good match	RCT (Czech R, Finland) 18-64 y	High	7652 18-64y	17.9% ITT 25.6% PPC	No CI but SS. 746/5103 vs. 459/2549	Low attack rate (3%). From week w/ 2 confirmed cases to week with 1 case. ILI = fever or myalgia.
Jackson 2010	2005-06 2006-07 Good match	RCT	High	7611 18-49y	NA, calculated at 14% PPC	362/3714 vs. 427/3768	See 1, Nov-April

Note: fever is not compulsory in the ILI definition of Monto and Jackson. PPC: Per-protocol cohort. IVE: Influenza vaccine effectiveness/efficacy.

12 APPENDIX 5: LITTERATURE REVIEW ON EFFICACY AND EFFECTIVENESS OF INFLUENZA VACCINATION

12.1 SEARCH STRATEGY

12.1.1 Research question

What is the efficacy and effectiveness of influenza vaccination in:

Group 1: Persons at high risk of complications:

1. elderly aged 65+
2. patients with chronic disease;

Group 2: Staff involved in health and nursing care;

Group 3: Pregnant women;

Group 4: Healthy adults (15-49 and 50-64 years separately);

Group 5: Persons in institutions (regardless of age); and

Group 6: Healthy children (6 months - 18 years).

Table 73: PICO of research question

Patients	Persons at high risk of complications: a) elderly aged 65+ and b) patients with chronic disease Staff involved in health and nursing care Pregnant women Healthy adults (15-49 and 50-64 years separately); Persons in institutions (regardless of age)
Intervention	Influenza vaccination
Comparator	No influenza vaccination
Outcomes	Prevented influenza and pneumonia deaths Prevented hospital admissions for influenza and pneumonia Prevented laboratory-confirmed influenza cases and influenza like illness (ILI) in outpatient setting

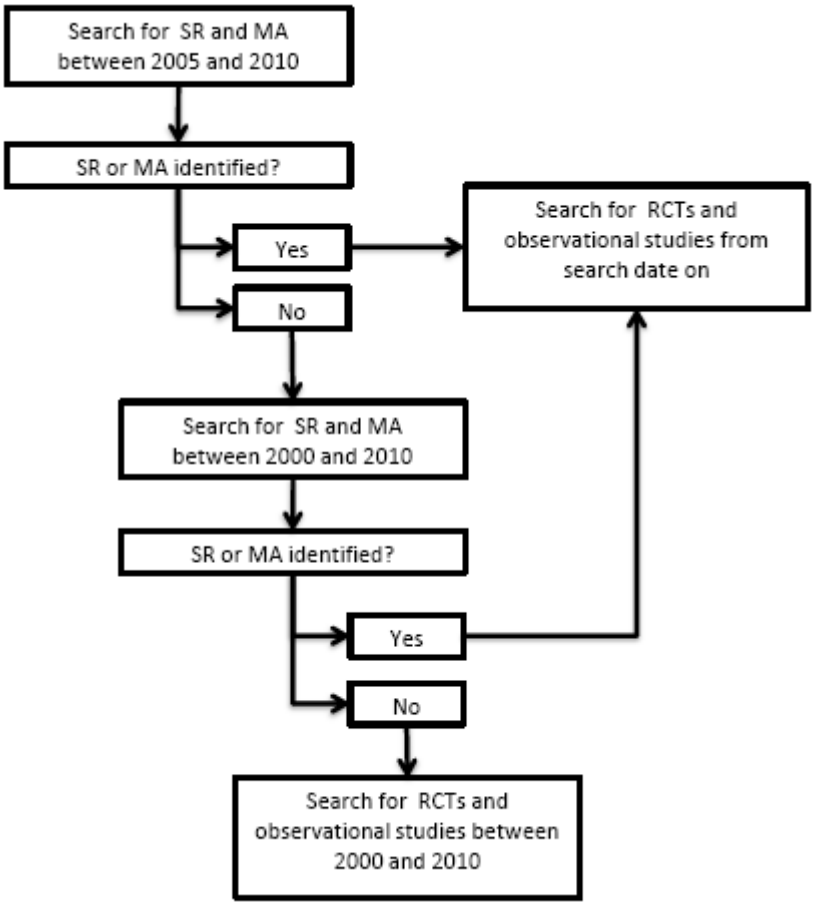
12.1.2 Searched databases

An iterative and pragmatic search strategy was chosen. First, systematic reviews (SR) and meta-analyses (MA) were searched between 2005 and 2010. If a good study was found, an additional search for randomised controlled trials (RCT) and observational studies was done, starting from the search date of the identified SR. In the absence of relevant SR and MA for a certain patient group, the search for SR and MA was extended to 2000 for this particular patient group. If no SR and MA was identified at all, a search for RCT and observational studies that adjusted for the major confounding factors was done between 2000 and 2010.

Depending on the study design, the following databases were searched:

- SR and MA: Cochrane Database of Systematic Reviews, OVID Medline, Embase, DARE
- RCT: CENTRAL, OVID Medline, Embase
- Observational studies: OVID Medline, Embase

Figure 31: Search strategy



12.1.3 Search strings and limits

For the first phase of the search, no population-related search terms were used to increase the sensitivity of the search. All searches were limited to humans and to articles published in English, French or Dutch. The syntax of the searches can be found in appendix.

12.1.4 Inclusion criteria

We only included studies from Europe and North America (US and Canada), to limit discrepancies in the prevalence of other seasonal pathogens causing ILI and pneumonia, and those involving trivalent inactivated vaccines (TIV). For observational studies, we only included studies that adjusted for the major (known) confounding factors. We did not include VE studies involving the pandemic H1N1 2009 strain.

12.1.5 Quality appraisal and data extraction

Methodological quality of the included studies was assessed using the checklists of the Cochrane Collaboration.

For each included study, data were extracted using a standard template. Data extraction was primarily focused on the outcomes pre-specified in the research question (Table 73).

12.2 HEALTH CARE WORKERS

Two eligible systematic reviews were identified.[14, 179] An additional search for RCTs and observational studies was done from June 2004 onwards (i.e. the search date of the Burls review). No new primary studies measuring the indirect effect were identified. A non-randomized controlled trial measuring the direct vaccine effectiveness was identified.[52]

The most recent review, a Cochrane review with search date until March 2006, focused on the indirect effects of vaccination of health care workers (HCW) on elderly,[14] while the review of Burls et al. evaluated both the direct and indirect effects.[179]

12.2.1 Indirect effect on patients

In total, 4 cluster RCTs and 1 cohort study were identified by the Cochrane review.[14] Meta-analysis of 3 RCTs (involving 7031 patients) found a vaccine effectiveness (VE) of 86% (95%CI 40-97%) for the prevention of cases of influenza-like illness (ILI) if patients were vaccinated too. The overall VE for the prevention of cases of ILI was 29% (95%CI 10-45%). The pooled OR (adjusted for clustering) for the prevention of influenza cases (confirmed by viral isolation and/or serological supporting evidence, plus a list of likely respiratory symptoms) was non significant at 0.87 (2 RCTs involving 752 patients; 95%CI 0.38-1.99, p=0.74). The VE for the prevention of deaths from pneumonia was non significant at 18% (2 RCTs involving 4459 patients; 95%CI -51% - 55%). The conclusions of the authors were that there is no evidence that only vaccinating HCW prevents laboratory-proven influenza and death from pneumonia in elderly residents in long-term care facilities.[14] In contrast, the conclusions of Burls et al. were more positive, but these were based on the 2 oldest cluster RCTs, selected according to unclear quality criteria.[179] The conclusion of Burls was that both trials showed a reduction in patient mortality after vaccinating HCWs; but in both studies, the analysis of cluster effect was inadequate or not reported.

12.2.2 Direct effect on HCW

In the review of Burls et al., the direct effects of HCW vaccination were also discussed.[179] One RCT reported a statistically significant reduction in rates of serologically confirmed influenza infections regardless of symptoms (VE 88%, 95%CI 47-97%) for influenza A(H3N2) and 89% (95% CI 14-99%) for influenza B, over 3 seasons.[164] A non-significant IVE was reported for cumulative days of febrile RTI (29% 95% CI -22% to 59%. Two other RCTs reported no difference, although in one there was a poor vaccine match and in the other the incidence of influenza was low.[179] Weingarten did not show any significant IVE for ILI and severity of illness.[180] Saxen involved other outcomes (respiratory infections and absenteeism).[181] Michiels et al. also evaluated the benefits of influenza vaccination on respiratory tract infection (RTI) in respectively 122 and 140 general practitioners (GPs) in Flanders during two consecutive winter periods, 2002-03 and 2003-04.[52] During the two influenza periods, 8.6% of the vaccinated and 14.7% of the unvaccinated GPs had RTI with positive swabs for influenza (non adjusted VE 41%; RR 0.59, 95%CI 0.28-1.24). The IVE adjusted for season was 58% (-42 to 87%). Non adjusted VE against respiratory tract infections was 7% (RR 93%, 95%CI 0.66-1.32). Adjusted IVE for positive RTI decreased with age: it was highest at 30 years of age (87%, 95% CI 25-99%), and non significant above 36 years of age and even negative above 48 years of age. However, the study was slightly under-powered.

12.3 PERSONS AT HIGH RISK OF INFLUENZA-RELATED COMPLICATIONS

12.3.1 Chronic respiratory diseases

Four recent Cochrane reviews were identified evaluating the use of influenza vaccination in persons with asthma,[9] bronchiectasis,[10] cystic fibrosis[11] and chronic obstructive pulmonary disease (COPD).[65] Although these reviews were of moderate to high quality, little information could be retrieved for the above pre-specified outcomes. Cates et al. identified 9 RCTs, of which the majority included asthmatic children only.[9] The most important reported outcomes were asthma exacerbations and differences in symptom score. According to the authors, uncertainty remains about the degree of protection vaccination affords against asthma exacerbations that are related to influenza infection.

Chang et al. did not identify RCTs involving patients with bronchiectasis.[10]

Dharmaraj et al. included 4 RCTs, but did not report on outcomes of our interest.[11] Above this, about 80% of the participants were children. The author's concluded that there is no evidence showing that regular influenza vaccine is beneficial to people with cystic fibrosis.

Poole et al. identified 11 RCTs evaluating the benefit of at least one annual influenza vaccination in adults with COPD.[65] No difference was found between vaccination and placebo with respect to the number of patients having at least one exacerbation or acute respiratory illness (OR 0.89, 95%CI 0.49-1.62). However, there was a significant reduction in the number of patients with an acute respiratory illness subsequently documented as influenza-related (OR 0.19, 95%CI 0.07-0.48) but not significant for hospitalisations due to influenza-related exacerbations (OR 0.41, 95%CI 0.09-1.89).

No eligible primary studies were identified for this population. A recent RCT included ILI and pneumonia, but was not retrieved because it was conducted in Thailand. [94]

12.3.2 Diabetes

Only one eligible observational study was identified involving patients with diabetes.[97] In this large nested case-control study (the PRISMA study) involving persons younger than 65 years with high-risk medical conditions (including diabetes), 192 diabetic cases were compared to 1561 controls. Adjusted VE for hospitalisations due to influenza, pneumonia, other acute respiratory disease, myocardial infarction, congestive heart failure, stroke or diabetes event was 70% (95%CI 39-85%) in the 18-64 years. Unfortunately, separate point estimates for influenza and pneumonia were not provided, and most of the hospitalizations were due to diabetes.

12.3.3 Cardiovascular disease

In the above-mentioned PRISMA study, also patients with myocardial infarction, congestive heart failure or stroke were included.[50] Unfortunately, no separate outcomes were presented for these subpopulations.

In a small Italian open-label RCT, 42 heart transplant recipients were randomised to two different influenza vaccines, while 16 additional heart transplant recipients were used as a control group.[95] Patients randomised to influenza vaccination had a significantly lower incidence of influenza-related symptoms compared to the 16 patients of the control group (33% vs. 29% vs. 63%, p=0.03). However, a clear definition of these symptoms was not provided and the IVE was not calculated.

12.3.4 Other high-risk populations

In the above-mentioned PRISMA study,[50] among all high-risk adults aged between 18 and 64 years (N=24928) and after adjustments, vaccination prevented 78% of all-cause deaths (95%CI 39-92%), 87% of hospitalizations for acute respiratory disease (ARD) and cerebro-vascular disease (CVD) (95%CI 39-97%) and 26% of GP visits for ARD and CVD (95%CI 7-47%).

Song et al. randomised 311 cirrhotic patients to influenza vaccination or no vaccination in Korea.[93] No significant difference was found in the incidence of ILI (OR 0.55, 95%CI 0.287-1.045), although the incidence of laboratory-confirmed influenza was lower in influenza-vaccinated patients (OR 0.24, 95%CI 0.07-0.82). Importantly, significant methodological limitations were present (unclear allocation concealment, high drop-out rate, baseline differences between study populations).

Finally, in a retrospective cohort study, the benefits of influenza vaccination were evaluated in patients with end-stage renal disease.[96] In patients undergoing hemodialysis, influenza vaccination resulted in less hospitalisations for influenza or pneumonia (1997-1998: OR 0.88, 95%CI 0.80-0.97; 1998-1999: OR 0.84, 95%CI 0.77-0.92). However, in patients undergoing peritoneal dialysis this was not confirmed (1997-1998: OR 0.95, 95%CI 0.67-1.37; 1998-1999: OR 0.85, 95%CI 0.59-1.21). The study did not provide IVE but the calculated 1-OR against admissions for influenza and pneumonia amounted to 12-16% in hemodialysis patients and was not significant in patients undergoing peritoneal dialysis. However, the study included all ages, without stratification by age, and high proportions of elderly (29% and 45% ≥65 years in hemodialysis and peritoneal group, respectively).

12.3.5 Patients with any co-morbidities

The above-mentioned PRISMA adjusted cohort study,[50] involving all high-risk adults aged between 18 and 64 years (N=24928), found a VE for hospitalisation due to influenza or pneumonia at 63% (95%CI provided by the author: 16-80%).

An adjusted Canadian case control study measured IVE among all ages (8% elderly patients). On a total of 841 participants, 115 (14%) had a chronic condition. IVE on laboratory confirmed ILI was not estimated in persons with chronic conditions but did not show significant difference in IVE when data were adjusted for chronic conditions (unadjusted: 61% [43 to 74]); adjusted for chronic conditions 58% [38 to 72].[78]

An adjusted case control study conducted in the US among patients 50-64 years of age at high risk (according to ACIP guidelines) measured IVE against laboratory confirmed ILI in a season with poor matching (2003-04). However, it included all providers, thus involved also admissions for ILI (not only GP visits). Adjusted IVE in high risk patients was 48.2% (95% CI 21-66%) for all influenza-related outcomes and 36% (95% CI 0-63%) for laboratory-confirmed hospitalizations, but adjustment was limited to 2 covariates and the outcome differed from influenza ICD code.[98]

12.4 PREGNANT WOMEN

Four primary studies were identified, including one RCT and 3 observational studies.[61, 174-176]

Zaman et al. randomised 340 women in the third trimester of pregnancy to receive a 23-valent polysaccharide pneumococcal vaccine or an inactivated influenza vaccine.[174] Among infants of mothers who received influenza vaccine, there were fewer cases of laboratory-confirmed influenza than among infants in the control group (6 vs. 16 cases; VE 63%, 95%CI 5-85%). The incidence of respiratory illness with fever was lower in the influenza-vaccine group (110 vs. 153 infants; VE 29%, 95%CI 7-46%). Among the mothers, there was a reduction in the rate of respiratory illness with fever of 36% (95%CI 4-57%). However, the study was conducted in Bangladesh, which is difficult to compare to a European setting because influenza viruses circulate most of the year, with limited seasonal effect. Furthermore, the control vaccine also aimed at reducing respiratory illnesses, and no case definition was provided.

Black et al. evaluated the effects of maternal influenza vaccination in a retrospective cohort study covering 5 influenza seasons (1997-2002).[61] A total of 49585 women with 48639 live births were included. Overall, influenza vaccination coverage was 7.5% across the five seasons. The risk of an outpatient visit for ILI, adjusted for women's age and week of delivery, did not differ between vaccinated and unvaccinated women (HR 1.151, 95%CI 0.979-1.352). Furthermore, no difference in risk of pneumonia or influenza hospitalisation was found between infants of vaccinated and unvaccinated women (adjusted HR 0.625, 95%CI 0.302-1.293).

Also, no differences were found in the adjusted risk of caesarean section (exact data not provided in article) or in the preterm delivery rate (7.37% in vaccinated women vs. 6.72% in unvaccinated women, p=0.136).

In another retrospective adjusted cohort study, the effects of maternal influenza vaccination were evaluated in 41129 infants.[176] The overall vaccination coverage was 7.7%. The incidence rate for acute respiratory illnesses did not differ significantly between infants exposed and unexposed to maternal influenza vaccination during the peak influenza weeks (incidence rate ratio 0.90, 95%CI 0.80-1.02).

In a case-control study involving 1051 mother-infant pairs, the incidence of acute respiratory tract illnesses did not differ between vaccinated and unvaccinated women (22.6% vs. 18.9%, p=0.24).[175] No significant difference was found in the preterm delivery rate (OR 0.67, 95%CI 0.32-1.32).

In a prospective adjusted cohort study in the Navajo and White Apache children, Eik et al included 1160 mother-infant pairs.[177] The ILI incidence rate was 7.2 and 6.7 per 1,000 person-days for infants born to unvaccinated and vaccinated women, respectively. There was a 41% reduction in the risk of laboratory-confirmed influenza virus infection (relative risk, 0.59; 95% confidence interval, 0.37-0.93) and a 39% reduction in the risk of ILI hospitalization (relative risk, 0.61; 95% confidence interval, 0.45-0.84) for infants born to influenza-vaccinated women compared with infants born to unvaccinated mothers. However, these results were not adjusted as the analysis found no statistically significant association between potential confounders and the occurrence of any outcome.

12.5 PERSONS AGED 65 OR MORE

12.5.1 Systematic reviews

One recent Cochrane review was identified covering the literature until October 2009.[12] This review included 5 RCTs, 51 cohort studies and 12 case-control studies. The 5 RCTs were characterised by a heterogeneous nature of vaccines tested (monovalent, trivalent, live, or inactivated aerosol vaccines), setting, follow up and outcome definition. Based on a meta-analysis of 4 RCTs, the overall VE (irrespective of vaccine nature, setting, adjustment etc.) against ILI was 41% (95% CI 27-53%). Overall VE against laboratory-confirmed influenza cases was 58% (95% CI 34-73%) in 3 RCTs during matching seasons.

Jefferson et al. included 30 datasets in long-term care facilities.[12] VE against ILI during outbreaks or periods of high viral circulation and in case of vaccine matching was 23% (95%CI 6-36%). VE against hospitalisation for ILI or pneumonia in these circumstances was 45% (95%CI 16-64%). No point estimates were available for ILI or pneumonia separately. VE against deaths from flu or pneumonia during outbreaks or periods of high viral circulation and in case of vaccine matching was 42% (95%CI 17-59%). Again, no separate point estimates were available. In addition, most studies were old and only 3 were published in 2000-2010.

Twenty datasets evaluated inactivated influenza vaccines in community-dwelling elderly, with only seven studies adjusting for confounders.[12] In adjusted studies, VE against hospitalisation for influenza or pneumonia was 27% (21-33%) for all seasons, amounted to 29% (23-35%) in matching seasons, was non significant at 10% (-38 to 42%) in a non-matching and non-epidemic season and was 18% (2-32%) in an epidemic and poor matching season. In non adjusted cohorts, VE was lower in elderly at risk of influenza complications (26%, 95%CI 14-37%) than in elderly without risks of influenza complications (50%, 95%CI 37-60%). No VE against laboratory confirmed influenza was provided in adjusted studies.

Finally, Jefferson et al. also included 12 case-control studies (14 datasets), including 7 studies assessing the effects of inactivated influenza vaccines on community-dwelling elderly.[12] The adjusted VE against death from influenza or pneumonia was estimated 26% (95%CI 8-40%) in epidemic years (vaccine matching or not), from meta-analysis of 2 studies. However, Ahmed only involved deaths from influenza.[170] Jefferson pooled the 2 studies, as no statistical heterogeneity was detected, but the outcomes were different.

In these seasons, the adjusted VE against hospitalisation for influenza or pneumonia was 45% (95%CI 15-64%) in one study involving data from 1989-90.

12.5.2 Primary studies

Since no separate reporting was done for the age categories 65-74 years and 75+, an additional search for primary studies stratifying by age was done between 2000 and 2010. Eight observational studies adjusting for confounding factors were identified of which 4 were already included in the Cochrane review.[83-85, 184]

Voordouw et al. compared 8911 elderly having received influenza vaccination to unvaccinated matched controls in a cohort study adjusting for major confounders.[184] However, results by age category were only presented for an aggregate outcome of death, pneumonia cases and influenza cases (outpatient and inpatient).

An European study pooled the results of 5 small case-controls studies from 5 different European countries.[87] In contrast to the previously cited studies, adjustment of the data was also done for functional status. VE for laboratory-confirmed influenza was overall 59% (95% CI 15.3-80.3%) for all elderly, amounting to 65% (95% CI 16-86%) in the age category 65-74 years and not significant at 60% (-73–91%) in the 75+ population. A Romanian case control study was also retrieved but was included in the above pooled analysis.[89]

Four US adjusted cohorts studies also estimated IVE for admissions for pneumonia and influenza (P+I), from which 2 were not included in Jefferson et al. (one excluded due to duplication and one published after search date). In 2 publications from the same study group, IVE against P+I admissions in all elderly ranged 20-32% over 4 consecutive seasons (1996-2000);[83, 84] the last study pooled results from the 1998-2000 seasons, with a VE at 27% (95% CI 23-32%).[86]. Analysis was stratified by age group, but no quantitative VE for P+I admissions by age group was provided (only graphically). However, VE values by age group show overlapping confidence intervals, and VE were consistent among all age subgroups:[83, 86] in the 1998-2000 seasons, VE in the 65-74 years was around 35% vs. 29% and 32% by season for all ages. A more recent cohort study estimated at 8.5% (95% CI 3-14%) the VE against admissions for P+I in all elderly ≥ 65 years over 10 influenza seasons (1997-2007), with 16% (95% CI 7-24%) in those 65-74 years of age and non significant at 5% (95% CI -1 to 11%) in the 75 years of age and older. However, it used a special method (difference of difference) to adjust for unknown confounders and found much lower values than all previous cohort studies.[81] This methodology has not been validated yet.

The most recent study on deaths from influenza and pneumonia is a UK adjusted cohort study, involving deaths from pneumonia, influenza and chronic bronchitis, over the 10 seasons 1989-1999, though it did not stratify exactly on the same age groups (65-84 and 85+).[85] It showed a 12% significant VE (95% CI 8-16%) in all elderly above 65 years, 21% (95% CI 11-29%) in those 65-84 years of age, and 29% (95% CI 22-34%) in those 65-84 years of age with co-morbidities. For the 65-84 years without co-morbidities, no VE was found outside influenza seasons, indicating that the analysis was well adjusted. Residual confounding was suggested in those ≥85 years of age, and no protective effect could be demonstrated. Little effect of vaccination was found in the non-epidemic years, with VE ranging -4 to 13% in the three mild years, but no pooled estimate was provided.

Several other observational studies were included in the Cochrane review but they are not included in this review because they did not adjust for confounders,.[185-187] Other case control studies covered 2000-10 but included all age groups and did not provide stratified estimates for the elderly or lacked power.[75-79]

12.6 HEALTHY ADULTS AGED 18-64 YEARS

One Cochrane review evaluated the effectiveness of influenza vaccination in healthy individuals aged 16 to 65 years.[13]. The authors included 40 RCTs, 8 quasi-RCTs and 2 safety studies published up to June 2010. Vaccination with an inactivated parenteral vaccine resulted in a VE against ILI of 30% (95%CI 17-41%) in case of vaccine matching. VE against laboratory-confirmed influenza was 73% (95%CI 54-84%) when the vaccine strain matched circulating strains but decreased to 44% (95% CI 23-59%) when vaccine matching was absent or unknown. Efficacy was lower (74%, 95% CI 45-87%) when the studies carried out during 1968-69 pandemic were excluded. However, this review has many limitations:

- The review includes mostly very old studies (25/50 dated before 1980) and only 2 primary efficacy studies on inactivated vaccines conducted after 2000.
- Four recent US RCTs were not identified by the search strategy (not within the included nor the excluded studies)
- The definition for influenza case is mixing laboratory confirmation and clinical picture
- The definitions for epidemic periods differ across studies and are not described in the analysis.

The meta-analyses pool studies covering seasons with poor or unknown matching with vaccine strains; the extent to which these seasons can be considered as presenting poor match is unknown.

For these reasons, the results of the meta-analyses are not reported in this review. An additional literature search has thus been conducted to identify primary studies involving efficacy data collected from 2000 onwards. Six RCTs and one non-randomised controlled trial fitting the selection criteria have been retrieved, and only the first 2 were included in the Jefferson review.[66-68, 72-74] All involved laboratory confirmed ILI (influenza). As no recent RCT involved hospitalization or mortality for pneumonia and influenza (P+I) as outcomes, the search also included observational studies (cohort or case control) conducted after 2000, adjusting for the main confounding factors and including the above outcomes.

In the 2006-07 season, Beran et al. randomised 7652 healthy individuals aged 18-64 years to a trivalent inactivated split-virus influenza vaccine or placebo.[72] VE against culture-confirmed influenza was 61.6% (95% CI 46.0-72.8%) for any strain and 67% (95%CI 52-77%) for influenza due to strains antigenically matched to the vaccine. In this study, the vaccine matching was good, but the attack rate low (culture-confirmed placebo attack rate: 3.2%). In another RCT from the same authors conducted in the 2005-06 season, 6203 healthy individuals aged 18-64 years were also randomised to a trivalent inactivated split-virus influenza vaccine or placebo.[73] VE against culture-confirmed influenza was non significant, at 22% (95%CI -49 – 59%). In contrast to the previous study, the vaccine matching was low and the attack rate even lower (culture-confirmed placebo attack rate: 0.9%).

A RCT conducted over a 4-year period in Michigan (US), beginning in 2004, evaluated the VE of the inactivated and live attenuated influenza vaccines in preventing laboratory-confirmed influenza.[66-68] In the 2004-05 influenza season (moderate matching), 1247 persons aged 18-48 years were randomized. VE was 75% (95% CI 42-90%) for laboratory confirmation by PCR or culture.[67] In the 2005-06 influenza season (good match and low season), 2058 persons aged 18-48 years were randomized. VE was 16% and non-significant for laboratory confirmation by PCR and/or culture (95% CI -171% to 70%).[68] In the 2007-08 influenza season (high season and relative match), 1952 subjects aged 18-49 years were randomized. VE was 68% (95% CI 46-81%) for culture and/or PCR endpoints.[66] When using positive serology as end points, VE was higher.

Another RCT sponsored by GSK was conducted in different areas of the US and involved 7219 subjects aged 18-49 years in the two influenza seasons 2005-06 and 2006-07 (low intensity and good march).[74] VE was 49.4% (lower bound 20.3%) for culture confirmed influenza over the two seasons. VE by season was not provided in the publication but was estimated at 49% (95% CI 13-61%) in 2005-06 and not significant at 49% (95% CI -4 to 75%) in 2005-06, using Review Manager 5. VE was higher (63.2%) when considering serology and positive culture endpoints.

12.7 SEARCH SYNTAXES

12.7.1 OVID Medline

Systematic reviews and meta-analyses

1	exp Influenza, Human/co, ep, im, mo, pc, tm [Complications, Epidemiology, Immunology, Mortality, Prevention & Control, Transmission]
2	exp Influenza Vaccines/
3	exp Vaccines/
4	exp Vaccination/
5	exp Immunization/
6	exp Disease Outbreaks/pc [Prevention & Control]
7	exp Disease Transmission, Infectious/pc [Prevention & Control]
8	or/3-7
9	(influenza or flu).ti,ab.
10	8 and 9
11	((influenza or flu) adj (vaccin$ or immuni$ or innoculat$ or efficacy or effectiveness)).ti,ab.
12	1 or 2 or 10 or 11
13	limit 12 to (humans and (dutch or english or french))
14	meta-analysis.mp,pt. or review.pt. or search:.tw.
15	13 and 14

Primary studies

General search

1	exp Influenza, Human/co, ep, im, mo, pc, tm [Complications, Epidemiology, Immunology, Mortality, Prevention & Control, Transmission]
2	exp Influenza Vaccines/
3	exp Vaccines/
4	exp Vaccination/
5	exp Immunization/
6	exp Disease Outbreaks/pc [Prevention & Control]
7	exp Disease Transmission, Infectious/pc [Prevention & Control]
8	or/3-7
9	(influenza or flu).ti,ab.
10	8 and 9
11	((influenza or flu) adj (vaccin$ or immuni$ or innoculat$ or efficacy or effectiveness)).ti,ab.
12	1 or 2 or 10 or 11
13	limit 12 to (humans and (dutch or english or french))
14	randomized controlled trial.pt.
15	controlled clinical trial.pt.
16	randomized.ab.
17	placebo.ab.
18	clinical trials as topic.sh.
19	randomly.ab.
20	trial.ti.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	exp animals/ not humans.sh.
23	21 not 22
24	Comparative studies/
25	Follow-up studies/

26	Time factors/
27	chang$.tw.
28	evaluat$.tw.
29	reviewed.tw.
30	prospective$.tw.
31	retrospective$.tw.
32	baseline.tw.
33	cohort.tw.
34	case series.tw.
35	or/24-34
36	23 or 35
37	13 and 36
38	limit 37 to yr="2000 - 2010"

Specific search for pregnant women

1	exp Influenza, Human/co, ep, im, mo, pc, tm [Complications, Epidemiology, Immunology, Mortality, Prevention & Control, Transmission]
2	exp Influenza Vaccines/
3	exp Vaccines/
4	exp Vaccination/
5	exp Immunization/
6	exp Disease Outbreaks/pc [Prevention & Control]
7	exp Disease Transmission, Infectious/pc [Prevention & Control]
8	or/3-7
9	(influenza or flu).ti,ab.
10	8 and 9
11	((influenza or flu) adj (vaccin$ or immuni$ or innoculat$ or efficacy or effectiveness)).ti,ab.
12	1 or 2 or 10 or 11
13	exp Pregnancy/
14	exp Pregnancy Complications, Infectious/pc [Prevention & Control]
15	exp Pregnancy Trimester, Second/ or exp Pregnancy Outcome/ or exp Pregnancy Trimester, Third/ or exp Pregnancy Trimesters/
16	exp Prenatal Care/
17	13 or 14 or 15 or 16
18	12 and 17
19	limit 18 to (female and humans and (dutch or english or french))
20	limit 19 to yr="2000 - 2010"

Specific search for health care workers

1	exp Influenza, Human/co, ep, im, mo, pc, tm [Complications, Epidemiology, Immunology, Mortality, Prevention & Control, Transmission]
2	exp Influenza Vaccines/
3	exp Vaccines/
4	exp Vaccination/
5	exp Immunization/
6	exp Disease Outbreaks/pc [Prevention & Control]
7	exp Disease Transmission, Infectious/pc [Prevention & Control]
8	or/3-7
9	(influenza or flu).ti,ab.
10	8 and 9
11	((influenza or flu) adj (vaccin$ or immuni$ or innoculat$ or efficacy or effectiveness)).ti,ab.
12	1 or 2 or 10 or 11
13	exp Health Personnel/
14	((health or healthcare or (health adj care)) adj (personnel or worker$ or provider$ or practitioner$)).mp.
15	health employee$.mp.

16	medical staff.mp.
17	(doctor$ or physician$).mp.
18	(allied health adj (staff or personnel)).mp.
19	paramedic$.mp.
20	nursing staff.mp.
21	nurse$.mp.
22	nursing auxiliar$.mp.
23	hospital personnel.mp.
24	hospital staff.mp.
25	hospital worker$.mp.
26	exp HOSPITALS/
27	exp Long-Term Care/
28	exp Residential Facilities/
29	nursing home$.mp.
30	or/13-29
31	12 and 30
33	limit 31 to (humans and yr="2004 - 2010" and (dutch or english or french))
34	randomized controlled trial.pt.
35	controlled clinical trial.pt.
36	randomized.ab.
37	placebo.ab.
38	clinical trials as topic.sh.
39	randomly.ab.
40	trial.ti.
41	34 or 35 or 36 or 37 or 38 or 39 or 40
42	exp animals/ not humans.sh.
43	41 not 42
44	Comparative studies/
45	Follow-up studies/
46	Time factors/
47	chang$.tw.
48	evaluat$.tw.
49	reviewed.tw.
50	prospective$.tw.
51	retrospective$.tw.
52	baseline.tw.
53	cohort.tw.
54	case series.tw.
55	or/44-54
56	43 or 55
57	32 and 56

Specific search for diabetes and cardiovascular disease

1	exp Influenza, Human/co, ep, im, mo, pc, tm [Complications, Epidemiology, Immunology, Mortality, Prevention & Control, Transmission]
2	exp Influenza Vaccines/
3	exp Vaccines/
4	exp Vaccination/
5	exp Immunization/
6	exp Disease Outbreaks/pc [Prevention & Control]
7	exp Disease Transmission, Infectious/pc [Prevention & Control]
8	or/3-7
9	(influenza or flu).ti,ab.
10	8 and 9
11	((influenza or flu) adj (vaccin$ or immuni$ or innoculat$ or efficacy or effectiveness)).ti,ab.
12	1 or 2 or 10 or 11
13	randomized controlled trial.pt.

14	controlled clinical trial.pt.
15	randomized.ab.
16	placebo.ab.
17	clinical trials as topic.sh.
18	randomly.ab.
19	trial.ti.
20	13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp animals/ not humans.sh.
22	20 not 21
23	Comparative studies/
24	Follow-up studies/
25	Time factors/
26	chang$.tw.
27	evaluat$.tw.
28	reviewed.tw.
29	prospective$.tw.
30	retrospective$.tw.
31	baseline.tw.
32	cohort.tw.
33	case series.tw.
34	or/23-33
35	22 or 34
36	exp diabetes mellitus/
37	IDDM.tw.
38	NIDDM.tw.
39	((typ* 1 or typ* 2) and diabet*).tw.
40	((typ I or typ* II) and diabet*).tw.
41	or/36-40
42	12 and 35 and 41
43	exp cardiovascular diseases/
44	myocardial.tw.
45	angina.tw.
46	coronary.tw.
47	heart.tw.
48	cardiac.tw.
49	cardiovascular.tw.
50	or/43-49
51	12 and 35 and 50
52	42 or 51
53	limit 52 to (humans and yr="2000 - 2010" and (dutch or english or french))

12.7.2 EMBASE

Systematic reviews and meta-analyses

'influenza vaccine'/exp OR 'influenza vaccination'/exp OR ('vaccine'/exp OR 'immunization'/exp OR 'disease transmission'/exp AND ('influenza virus'/exp OR 'pandemic influenza'/exp OR 'seasonal influenza'/exp OR influenza:ab,ti OR flu:ab,ti)) AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [humans]/lim AND [embase]/lim

Primary studies – general search

'comparative study'/exp OR 'controlled study'/exp OR 'experimental study'/exp OR 'observational study'/exp OR 'quasi experimental study'/exp OR 'validation study'/exp OR 'clinical study'/exp AND ('influenza vaccine'/exp OR 'influenza vaccination'/exp OR ('vaccine'/exp OR 'immunization'/exp OR 'disease transmission'/exp AND ('influenza virus'/exp OR 'pandemic influenza'/exp OR 'seasonal influenza'/exp OR influenza:ab,ti OR flu:ab,ti))) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [humans]/lim AND [embase]/lim AND [2000-2010]/py

Pregnant women

'influenza vaccine'/exp OR 'influenza vaccination'/exp OR ('vaccine'/exp OR 'immunization'/exp OR 'disease transmission'/exp AND ('influenza virus'/exp OR 'pandemic influenza'/exp OR 'seasonal influenza'/exp OR influenza:ab,ti OR flu:ab,ti)) AND ('pregnancy'/exp OR 'pregnancy complication'/exp OR 'pregnancy outcome'/exp OR 'second trimester pregnancy'/exp OR 'third trimester pregnancy'/exp OR 'prenatal care'/exp) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [female]/lim AND [humans]/lim AND [embase]/lim AND [2000-2010]/py

Health care workers

'influenza vaccine'/exp OR 'influenza vaccination'/exp OR ('vaccine'/exp OR 'immunization'/exp OR 'disease transmission'/exp AND ('influenza virus'/exp OR 'pandemic influenza'/exp OR 'seasonal influenza'/exp OR influenza:ab,ti OR flu:ab,ti)) AND ('health care personnel'/exp OR ((health OR healthcare) NEAR/3 (personnel OR worker* OR provider* OR employee* OR staff)):ab,ti OR ((medical OR hospital) NEAR/2 (staff OR employee* OR personnel OR worker*)):ab,ti OR doctor*:ab,ti OR physician*:ab,ti OR clinician*:ab,ti OR 'allied health staff':ab,ti OR 'allied health personnel':ab,ti OR 'allied health worker':ab,ti OR 'allied health workers':ab,ti OR paramedic*:ab,ti OR nurse*:ab,ti OR (nursing NEAR/2 (staff OR personnel OR auxiliar* OR assistant*)):ab,ti OR 'hospice'/exp OR 'assisted living facility'/exp OR 'hospital'/exp OR 'nursing home'/exp OR 'residential home'/exp OR (institution* NEAR/3 elderly):ab,ti OR 'aged care':ab,ti OR 'nursing home':ab,ti OR 'nursing homes':ab,ti)

Diabetes and cardiovascular disease

'influenza vaccine'/exp OR 'influenza vaccination'/exp OR ('vaccine'/exp OR 'immunization'/exp OR 'disease transmission'/exp AND ('influenza virus'/exp OR 'pandemic influenza'/exp OR 'seasonal influenza'/exp OR influenza:ab,ti OR flu:ab,ti)) AND ('cardiovascular disease'/exp OR myocardial:ab,ti OR angina:ab,ti OR coronary:ab,ti OR heart:ab,ti OR cardiac:ab,ti OR cardiovascular:ab,ti)

12.7.3 Cochrane database of systematic reviews and DARE (through Cochrane library)

#1	MeSH descriptor Influenza, Human explode tree 1 with qualifiers: CO,EP,IM,MO,PC,TM
#2	MeSH descriptor Influenza Vaccines explode all trees
#3	MeSH descriptor Vaccines explode all trees
#4	MeSH descriptor Vaccination explode trees 1, 4 and 5
#5	MeSH descriptor Immunization explode trees 1, 4 and 5
#6	MeSH descriptor Disease Outbreaks explode all trees with qualifier: PC
#7	MeSH descriptor Disease Transmission, Infectious explode all trees with qualifier: PC
#8	(#3 OR #4 OR #5 OR #6 OR #7)
#9	(influenza OR flu):ti,ab,kw
#10	(#8 AND #9)
#11	(vaccin$ or immuni$ or innoculat$ or efficacy or effectiveness):ti,ab,kw
#12	(#9 AND #11)
#13	(#1 OR #2 OR #10 OR #12)
#14	(#13), from 2000 to 2010

12.7.4 CENTRAL (through Cochrane library)

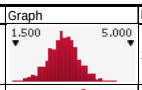
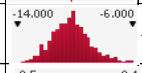
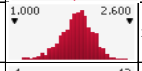
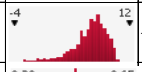
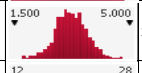
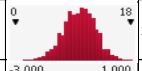
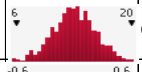
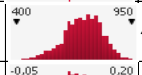
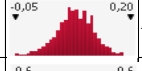
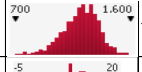
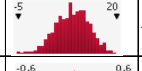
#1	MeSH descriptor Influenza, Human explode tree 1 with qualifiers: CO,EP,IM,MO,PC,TM
#2	MeSH descriptor Influenza Vaccines explode all trees
#3	MeSH descriptor Vaccines explode all trees
#4	MeSH descriptor Vaccination explode trees 1, 4 and 5
#5	MeSH descriptor Immunization explode trees 1, 4 and 5
#6	MeSH descriptor Disease Outbreaks explode all trees with qualifier: PC
#7	MeSH descriptor Disease Transmission, Infectious explode all trees with qualifier: PC
#8	(#3 OR #4 OR #5 OR #6 OR #7)
#9	(influenza OR flu):ti,ab,kw
#10	(#8 AND #9)
#11	(vaccin$ or immuni$ or innoculat$ or efficacy or effectiveness):ti,ab,kw
#12	(#9 AND #11)
#13	(#1 OR #2 OR #10 OR #12)
#14	(#13), from 2000 to 2010

13 APPENDIX 6: DISTRIBUTION OF INPUT PARAMETERS FOR AND RESULTS FROM THE UNCERTAINTY ANALYSIS

13.1 DISTRIBUTION OF INPUT PARAMETERS

	Distribution	Mean	95% CI		Source
			2,50%	97,50%	
Healthy 50-64 years					
Influenza best	Normal	49612	42155	57074	Weekly sample
VE influenza best	Normal	0,62	0,47	0,72	Pooled
VE deaths best	Normal	0,124	0,016	0,22	Baxter 2010
VE influenza worst	Normal	0,22	-0,40	0,57	Pooled
VE deaths worst	Normal	0	-	-	Scenario
Healthy 15-49 years					
Influenza best	Normal	152185	140369	163341	Weekly sample
VE influenza best	Normal	0,62	0,47	0,72	Pooled
VE deaths best	Normal	0,124	0,016	0,22	Baxter 2010
VE influenza worst	Normal	0,22	-0,40	0,57	Pooled
VE deaths worst	Normal	0	-	-	Scenario
1-64 years comorbid					
Influenza best	Gamma	30605	29681	32652	Weekly sample
VE influenza best	Normal	0,62	0,47	0,72	Pooled
VE deaths best	Normal	0,63	0,16	0,80	Hak 2005
VE influenza worst	Normal	0,22	-0,40	0,57	Pooled
VE deaths worst	Normal	0,29	0,22	0,34	Mangtani 2004
65-74 years					
Influenza best	Normal	21311	17769	24854	Weekly sample
VE influenza best	Normal	0,62	0,47	0,72	Pooled
VE deaths best	Normal	0,29	0,22	0,34	Mangtani 2004
VE influenza worst	Normal	0,22	-0,40	0,57	Pooled
VE deaths worst	Normal	0,21	0,11	0,29	Mangtani 2004
75+ years					
Influenza best	Normal	17188	12544	21834	Weekly sample
VE influenza best	Normal	0,60	-0,73	0,91	Kissling 2009
VE deaths best	Normal	0,12	0,08	0,16	Mangtani 2004
VE influenza worst	Normal	0,60	-0,73	0,91	Kissling 2009
VE deaths worst	Normal	0	-	-	Scenario
Health care worker					
Influenza best	Normal	7842	7428	8355	Weekly sample
VE influenza best	Normal	0,62	0,47	0,72	Pooled
VE deaths best	Normal	0,124	0,016	0,22	Baxter 2010
VE influenza worst	Normal	0,22	-0,40	0,57	Pooled
VE deaths worst	Normal	0	-	-	Scenario
Pregnant women					
Influenza best	Normal	3985	3684	4286	Weekly sample
VE influenza best	Normal	0,62	0,47	0,72	Pooled
VE deaths best	Normal	0,124	0,016	0,22	Baxter 2010
VE influenza worst	Normal	0,22	-0,40	0,57	Pooled
VE deaths worst	Normal	0	-	-	Scenario

13.2 RESULTS OF THE MONTECARLO SIMULATIONS

Name	Worksheet	Cell	Graph	Min	Mean	Max	2,5%	97,5%
impact influenza best	healthy 50-64 years	N5		1584.185	3013.153	4514.213	2180.839	3776.927
impact deaths best	healthy 50-64 years	R5		-0.1319186	0.3014257	0.6508913	0.02164332	0.5378705
impact deaths worst	healthy 50-64 years	X5		0	0	0	0	0
impact influenza best	healthy 15-49 years	N5		-13423.48	-10187.36	-6198.592	-12264.76	-7761.765
impact deaths best	healthy 15-49 years	R5		-0.4706642	-0.1998621	0.09391758	-0.3729336	-0.01634631
impact deaths worst	healthy 15-49 years	X5		0	0	0	0	0
impact influenza best	1-64 years comorbid	N5		1172.825	1878.185	2524.029	1448.607	2212.883
impact deaths best	1-64 years comorbid	R5		-2.195199	6.607594	10.26101	1.49229	9.4812
impact deaths worst	1-64 years comorbid	X5		0.3004805	0.4770506	0.6203218	0.3653533	0.5802258
impact influenza best	65-74 years	N5		1877.599	3253.45	4715.654	2343.301	4081.708
impact deaths best	65-74 years	R5		13.88089	20.87471	27.37616	16.34556	25.17919
impact deaths worst	65-74 years	X5		1.866975	10.08322	17.87049	5.527181	14.18801
impact influenza best	75+ years	N5		-2684.467	323.7713	839.7608	-567.8146	673.8776
impact deaths best	75+ years	R5		6.158157	13.16683	19.87226	8.438196	17.60875
impact deaths worst	75+ years	X5		0	0	0	0	0
impact influenza best	HCW	N5		446.2185	720.5009	936.4532	554.6067	860.9203
impact deaths best	HCW	R5		-0.03890091	0.08134494	0.1783172	0.007723059	0.1478307
impact deaths worst	HCW	X5		0	0	0	0	0
impact influenza best	Pregnant	N5		737.1577	1216.512	1562.008	955.1451	1436.105
impact deaths best	Pregnant	R5		-4.133839	8.914658	19.17384	1.160078	16.25187
impact deaths worst	Pregnant	X5		0	0	0	0	0

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