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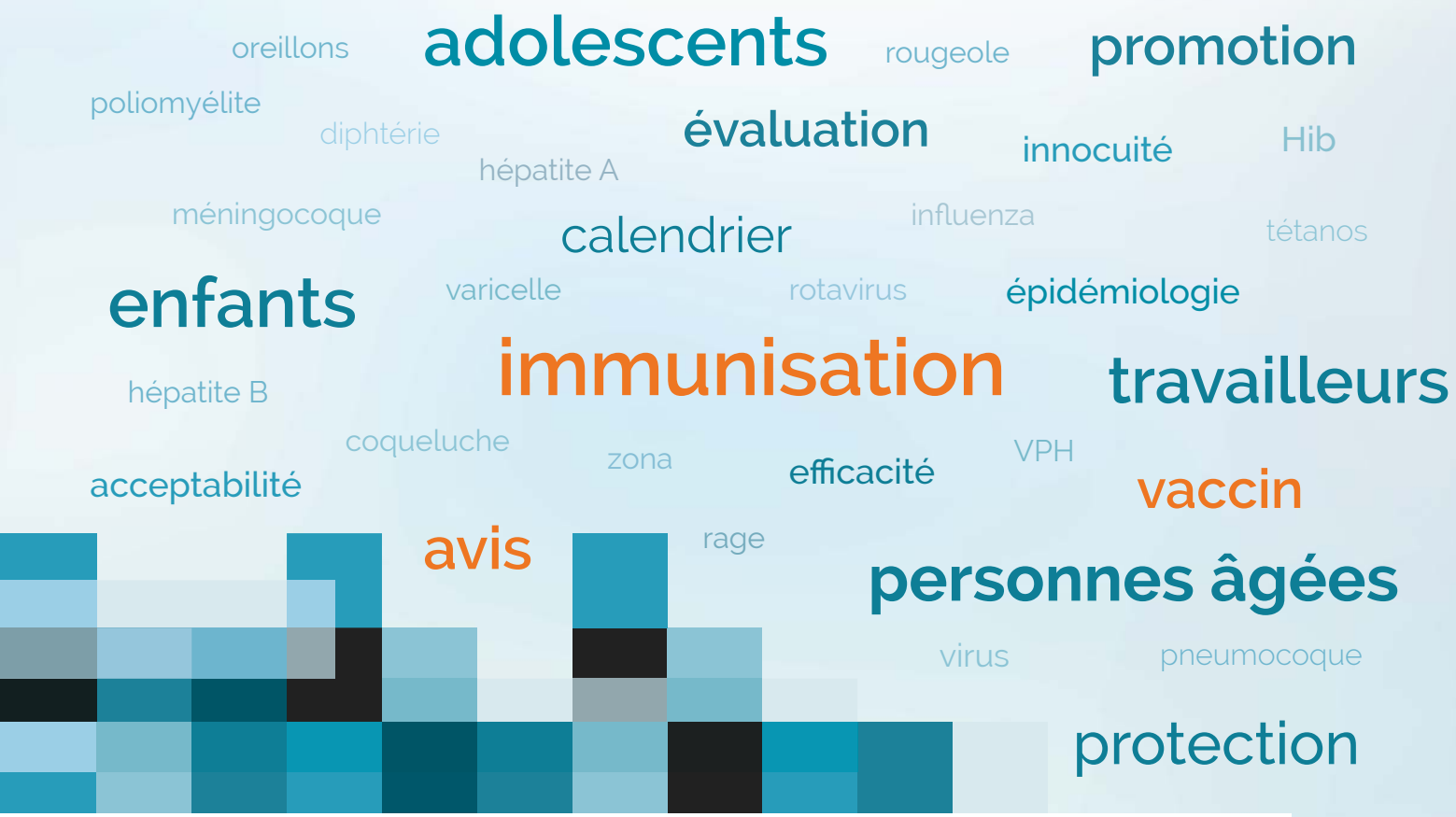

Revision of the *Programme d'immunisation contre l'influenza au Québec*

COMITÉ SUR L'IMMUNISATION DU QUÉBEC

Québec

Revision of the *Programme d'immunisation contre l'influenza au Québec*

COMITÉ SUR L'IMMUNISATION DU QUÉBEC

Direction des risques biologiques et de la santé au travail

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Institut national de santé publique Québec

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
ARI	Acute respiratory infection
CI	Confidence interval
CIQ	Comité sur l'immunisation du Québec
CIRN-SOS	Canadian Immunization Research Network, Serious Outcomes Surveillance Network
CLSC	Centre locaux de services communautaires (local community services centers)
ED	Emergency department
GDP	Gross domestic product
HALE	Health-adjusted life expectancy
HCW	Healthcare worker
IC	Intensive care
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ILI	Influenza-like illness
IMPACT	Canadian Immunization Monitoring Program, ACTive
IP	Influenza and pneumonia
LSPQ	Laboratoire de santé publique du Québec
LTCF	Long-term care facility
MSSS	Ministère de la Santé et des Services sociaux
NACI	National Advisory Committee on Immunization
NNV	Number needed to vaccinate
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
PIIQ	*Programme d'immunisation contre l'influenza du Québec*
QALY	Quality-adjusted life year
RAMQ	Régie de l'assurance maladie du Québec
RSV	Respiratory syncytial virus
SPSN	Sentinel Practitioner Surveillance Network
UIIP	Universal Influenza Immunization Program
VE	Vaccine effectiveness

Key messages

The last report issued by the Comité sur l'immunisation du Québec (CIQ) concerning the *Programme d'immunisation contre l'influenza du Québec* (PIIQ) [Québec's Influenza Immunization program] was published in 2007. An update became necessary, given the many scientific advances that have occurred in this field.

The primary objective of the PIIQ must be to reduce influenza-associated hospitalizations and deaths.

To attain this objective, the CIQ recommends maintaining a targeted vaccination strategy for individuals at high risk for hospitalization and death and giving priority to achieving vaccine uptake of at least 80% in these groups.

It is recommended to withdraw healthy children aged 6–23 months and healthy adults aged 60–74 years from the list of groups at high risk for influenza-associated hospitalization and death, but to maintain the other groups currently included in the PIIQ.

The CIQ recommends that all healthcare workers receive the vaccine.

A permanent infrastructure should be implemented to continually appraise influenza disease burden, vaccination effectiveness, vaccine uptake and program impact to be able to quickly make any necessary adjustments to the planning and implementation of the PIIQ.

Summary

Background

The last report issued by the Comité sur l'immunisation du Québec (CIQ) addressing the different dimensions of the *Programme d'immunisation contre l'influenza du Québec* (PIIQ) was published in 2007. Since that publication, additional information has become available and has permitted improved quantification of influenza disease burden and a demonstration of lower vaccine effectiveness than previously estimated and new data on the impact of repeated vaccination have also become available. As a result, questions have been raised about the utility and necessity for the PIIQ and its cost effectiveness. In December 2015, the Ministère de la Santé et des Services sociaux (MSSS) asked the CIQ to confirm or recommend changes to the current guidelines in the PIIQ. To reassess the PIIQ, the CIQ proposed to evaluate the scientific evidence by focussing on influenza disease burden and the populations targeted for vaccination by distinguishing individuals with a chronic condition and healthy individuals, and to perform an economic analysis of the program, which had never been done in Québec.

The strategy of the PIIQ is currently based on age and the presence of an underlying medical condition leading to a high risk for influenza-associated complications, with its main objective being to reduce complications and premature deaths among the vulnerable populations. The main groups currently included in the PIIQ are individuals with a chronic condition, children aged 6–23 months, seniors aged 60 years and older, and individuals susceptible to transmitting influenza to individuals at high risk for complications (such as those who have household contact with these risk groups, and healthcare workers).

Summary

Influenza Disease Burden

Influenza-attributable hospitalizations

The 2007 report mentioned the considerable burden of influenza morbidity and mortality, but it was not possible to quantify it precisely at that time. In Québec, the average annual estimate for the 2011–2012 to 2015–2016 influenza seasons is 6194 influenza-attributable hospitalizations, a rate of 76 per 100 000 population, 80% of them among individuals with a chronic condition. The rate of influenza-associated hospitalizations among healthy children is more than 10 times lower than that among children with a chronic condition. Fewer than 1 in 5 influenza-associated hospitalizations is detected among children and approximately half among individuals aged 75 years and older. Healthy individuals younger than 75 years are rarely hospitalized for influenza. For example, the rates of influenza-associated hospitalizations among individuals aged 60–64 years and 65–74 years are respectively 10 times and 6 times lower than the rate among healthy individuals aged 75 years and older.

Influenza-attributable deaths

An annual average of 417 deaths (rate of 5.2 per 100 000 population) is estimated in Québec for the same 5 influenza seasons. Among children, deaths are exceptional: only 2 influenza-attributable deaths were identified over the 5-year period in the Québec hospitals participating in the IMPACT network. According to the data in the literature, the death rate among children with a chronic condition is estimated to be approximately 1.5/100 000; it is approximately 10 times lower among healthy children, where it is instead in the order of 1–2 per million. The vast majority of influenza-

associated deaths in Québec is observed among individuals with a chronic condition (92%) and among individuals aged 75 years and older (88%). The rates of influenza-associated deaths among healthy individuals aged 60–64 years and 65–74 years are respectively 100 times and 12 times lower than the rate among healthy individuals aged 75 years and older. More than half of influenza-associated deaths occur among the residents of nursing homes and long-term care facilities (LTCF). Among more than one third of all deceased seniors with an influenza-confirmed infection, influenza was not the primary or contributing cause of death and could not have been averted by vaccination.

Influenza vaccine uptake

A downward trend in vaccine uptake in the Québec population has been observed over the past few years, especially among children aged 2 years, where it dropped from 29% in 2004–2005 to 17% in 2015–2016 for 2 doses. Vaccine uptake is higher among individuals with a chronic condition and among older adults. However, vaccine uptake exceeds 80% only among residents in LTCFs; it is far from optimal among individuals with chronic conditions (42%), and among the healthy individuals currently included in the PIIQ (21% among children aged 6–23 months and 43% among individuals aged 60 years and older).

Influenza vaccine effectiveness

The annual publication of influenza vaccine effectiveness values for each influenza season by several countries over several years has brought to light wide variability in vaccine effectiveness by season, circulation of specific influenza subtypes and strains, type of vaccine, frequency of vaccine administration, etc. Vaccine effectiveness is generally lower against the A(H3N2) subtype, compared with the other types and subtypes, and could also be lower among older adults. Compared with the vaccine effectiveness values of 70–90% estimated 10–30 years ago, several recently published systematic reviews and meta-analyses have shown vaccine effectiveness values on the order of 30–60% among the general public and of 10–30% among older adults. Even lower values of up to null effectiveness among older adults have also been reported for specific seasons. In addition, concerns about the potential negative effects of repeated vaccination have put into question the relevance of vaccination for individuals at low risk for complications.

Economic evaluation

An economic evaluation of the PIIQ was performed by comparing its cost and benefits by age group and presence or absence of a chronic condition against a scenario without an influenza immunization program, from a healthcare system perspective. The influenza-associated outcomes considered in that analysis were outpatient visits and emergency visits, hospitalizations and deaths. The PIIQ has been proven to be cost effective for the population groups with chronic conditions within the age extremes (6 months to 4 years and 65 years and older); it is not cost effective among the groups with chronic conditions aged from 5 to 64 years. The program has not been proven to be cost effective for any of the healthy groups, even the groups currently included in the program (6–23 months and 60 years and older). However, it approaches the cost-effectiveness threshold for healthy individuals aged 75 years and over.

Decision-making process

A strategy based on the Delphi method was used to reach a majority recommendation by the CIQ members for each of the groups considered in the program. A questionnaire developed according to age group and presence or absence of a chronic condition was designed to determine the level of agreement of the CIQ members on whether or not to include each group in the PIIQ, taking into account the weight of the criteria playing a role in their decision. Criteria based on the analytical framework by Erickson–De Wals were used, such as disease burden, vaccine effectiveness and safety, economic considerations, conformity, acceptability and feasibility. This Delphi process, which took place in 3 stages (2 online and 1 during a CIQ's meeting), helped the CIQ members reach consensus on the groups to include or not in the program.

Recommendations by the CIQ

In light of the appraisal of the scientific data available in early 2018 on influenza disease burden, vaccine effectiveness, and vaccine uptake, along with the results of the economic analysis and evaluation of the other elements considered, the CIQ formulated the following recommendations:

1) Confirm that the primary objective of the PIIQ is to reduce influenza-associated hospitalizations and deaths.
2) Maintain a targeted vaccination strategy for individuals at high risk for hospitalization and death, and give priority to achieving a vaccine uptake of at least 80% within these groups.
3) Withdraw healthy children aged 6–23 months and healthy adults aged 60–74 years from the list of groups at high risk for influenza-associated hospitalization and death, but maintain the rest of the groups currently included in the PIIQ. These withdrawals are certainly not intended to generate savings by cutting the cost of the program because it will be necessary to administer the same number of vaccines annually to increase vaccine uptake up to at least 80% in the risk groups.
4) Concentrate efforts on promoting and improving vaccine services for individuals at highest risk for influenza-associated hospitalization and death.
5) The CIQ recommends that all healthcare workers receive the vaccine. The vaccination offer should prioritize the healthcare workers who provide direct care to patients in hospitals and LTCFs.
6) The CIQ recommends that persons residing in the same household as, and caregivers for, individuals at high risk for influenza-associated hospitalization and death (including children younger than 6 months) receive the vaccine.
7) Put in place a permanent infrastructure to continually evaluate the important aspects of the PIIQ (burden, vaccine effectiveness, vaccine uptake and program impact) in order to be able to quickly make any necessary adjustments to the planning and implementation of the PIIQ. (Recommendation also formulated in 2007).

1 Introduction

In a letter dated December 4, 2015, the Ministère de la Santé et des Services sociaux (MSSS) asked the Comité sur l'immunisation du Québec (CIQ) to confirm or recommend changes to the current guidelines in the *Programme d'immunisation contre l'influenza du Québec* (PIIQ). In this letter, the MSSS mentioned that vaccine effectiveness often lower than previously estimated, lack of significant changes in the technology currently used to manufacture the vaccine, and the significant investment costs related to this program, including the increase in vaccine costs, all are increasingly raising questions about the program with regard to its utility, necessity and cost effectiveness.

The CIQ discussed this request during its meeting of December 10–11, 2015. The last report issued by the CIQ addressing all the dimensions of the PIIQ was published in January 2007(1). Since then, new scientific data have been published and have put into question the optimistic premises upon which the impact of this program had been estimated. Moreover, an economic analysis of the PIIQ had never been performed in Québec.

In reassessing the PIIQ, the CIQ proposed to evaluate the scientific evidence by focussing on influenza disease burden, the target populations and the economic analysis of the program.

This advisory report summarizes the process undertaken to answer these questions, as well as the CIQ's recommendations following the performed evaluation .

2 Current influenza immunization programs in Québec, Canada and elsewhere in the world

The *Programme d'immunisation contre l'influenza du Québec* (PIIQ) was introduced in 1971. Details regarding the evolution of this program, along with the results of the last revision of all of its components, including the additions of target groups since its introduction, can be found in the report published in French in 2007(1). Since its introduction, the PIIQ has aimed to reduce the complications and premature deaths among vulnerable populations, a strategy based on age and presence of health conditions leading to a high risk for influenza-related complications(1). The last health condition added to the program was morbid obesity in 2011, as a result of the identification of this new risk factor during the 2009 pandemic(2–4). As part of the current program, the vaccine is offered for free by the MSSS to the following groups (*Protocole d'immunisation du Québec* [PIQ][4]):

Individuals at high risk for complications due to their age or health, that is:

- Children aged from 6 to 23 months;
- Individuals aged 60 years and older;
- Individuals aged 6 months and older with a chronic illness or condition, according to the indications in the *Protocole d'immunisation du Québec (PIQ)*;
- Children and adolescents (younger than 18 years) receiving long-term acetylsalicylic acid therapy;
- Individuals of any age residing in nursing homes or long-term care facilities;
- Pregnant women presenting with a chronic illness or condition (the vaccine may be administered irrespective of the term of pregnancy);
- Healthy pregnant women in their 2nd or 3rd trimester (13 or more weeks);
- Individuals living in remote or isolated communities;
- Travellers presenting with a chronic illness or condition and who will go to a region with circulating influenza virus (tropical regions: year-round; Southern Hemisphere: April to September).

Individuals susceptible to transmitting influenza to those at high risk for complications, that is:

- Household contacts of individuals at high risk for complications (including children aged 0–6 months) and caregivers for individuals at high risk for complications (e.g., daycare staff);
- Individuals, particularly healthcare workers, who, through their work or activities, have frequent contact with individuals at high risk for complications.

In Canada, in September 2017, most provinces and territories had a universal influenza immunization program, except for British Columbia, New Brunswick and Québec. In contrast to the two other provinces without universal vaccination, healthy children aged 24–59 months are not included in the PIIQ (whereas individuals aged 60–64 years are included[5], see also Appendix 1A). Another difference from all the other provinces is the fact that in Québec, healthy pregnant women are included in the PIIQ only when they are in the 2nd or 3rd trimester of pregnancy.

In the United States, universal influenza immunization has been in place since 2006. In Europe, three countries recommended influenza vaccination for the entire population for the 2014–2015 season: Austria, Estonia and Poland(6). In most European countries (21 out of 30), influenza vaccination for children was not recommended for the same season. Different age subgroups among the children were included in the influenza vaccination programs in Lithuania (6–23 months), Slovenia (6–23 months), Finland (6–35 months), Malta (6–59 months), Slovakia (6 months–12 years) and the United Kingdom (different subgroups between the ages of 2 and 11 years, depending on the jurisdiction [7]).

For adults, in all European countries, influenza vaccination for individuals ≥ 65 years is recommended (threshold set at 60 years in Germany, Greece, Iceland and the Netherlands, 55 years in Malta, and 50 years in Belgium and Ireland[6]).

In Australia, influenza vaccination is recommended for individuals with a chronic condition starting at the age of 6 months, individuals aged 65 years and older, as well as Aboriginal individuals and pregnant women(8).

In all the countries with influenza immunization programs, vaccination for individuals with a chronic condition is recommended.

In its November 2012 position paper on influenza vaccination, the WHO recommended that national decisions be made by taking into account each country's specificities with respect to risk groups, disease burden, cost-benefit ratio and organizational aspects of the program(9).

3 Seasonal influenza vaccine uptake

3.1 Seasonal influenza vaccine uptake in Québec and Canada

3.1.1 Trends in seasonal influenza vaccine uptake in Québec

Trends in vaccine uptake in Québec and Canada over the past few years are presented in detail in Appendix 1B.

In short, according to the surveys on vaccine uptake among Québec children from 2006 to 2016, which are carried out every 2 years(10–15), a downward trend in vaccine coverage has been found over the years among children aged 2 years, from 36.7% in 2004–2005 down to 19.6% in 2015–2016 for one dose, and from 29.0% in 2004–2005 down to 17.4% in 2015–2016 for two doses.

The data on adults derive from Québec surveys on seasonal influenza and pneumococcal vaccination from 2001 to 2016, published every 2 years(16–23). In 2015–2016, 27% of the Québec population aged 18 years and older had been vaccinated. In the population targeted by the free vaccination program, owing to age or presence of a chronic condition, this proportion rose to 43%; among Individuals ≥ 65 years it was 59% overall and 66% among those with a chronic condition. Among healthcare workers, according to the same survey data, excluding the pandemic influenza season, vaccine uptake ranged from 37% to 58% by age and season.

In general, vaccine uptake is higher among individuals with a chronic condition, in all age groups, and also among older adults, but it is far from optimal. Overall, a general slight decrease has been observed in vaccine uptake since 2011 for all age groups, both in the general population and among individuals living with a chronic condition, excluding individuals aged 65 years and older with a chronic condition and healthcare workers aged 50–59 years (see Appendix 1B). Influenza vaccine uptake among the residents of LTCFs has exceeded 80% over the past few years (MSSS data).

3.1.2 Trends in seasonal influenza vaccine uptake in Canada

According to the adult National Immunization Coverage Survey (aNICS) conducted every two years or so since 2001, seasonal influenza vaccine uptake in Canada between 2001 and 2014 ranged from 33% to 40% in the adult general population, from 53% to 70% among individuals aged 65 years and older, from 35% to 59% among individuals aged 18–64 years with a chronic condition, and from 55% to 74% among healthcare workers. Further details can be found in Appendix 1B.

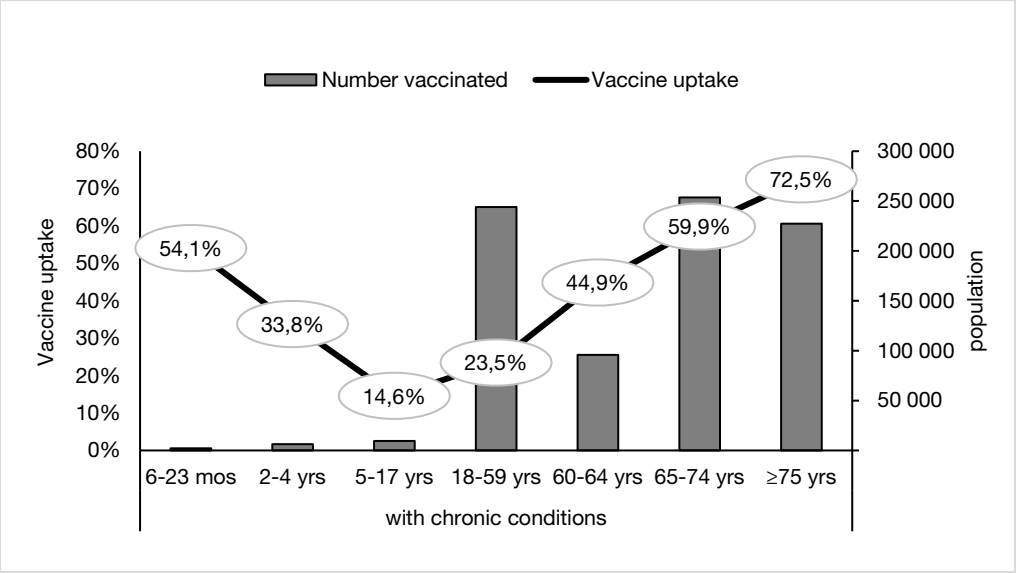
3.2 Estimation of seasonal influenza vaccine uptake, by age group and presence of a chronic condition, for the economic analysis

To estimate vaccine uptake among the different age groups according to the presence or not of a chronic condition, we used the data from the *Enquête québécoise sur la vaccination contre la grippe saisonnière et le pneumocoque de 2015–2016*(23) and from Manale Ouakki (personal communication). The sample size for the groups of healthy children aged 2–4 years and 5–17 years was too small to be able to estimate vaccine uptake. Among these children, the data were calculated based on an average calculated over 4 years (2012–2015) among children hospitalized for respiratory symptoms and negative for influenza in a prospective study conducted in Québec(24–28).

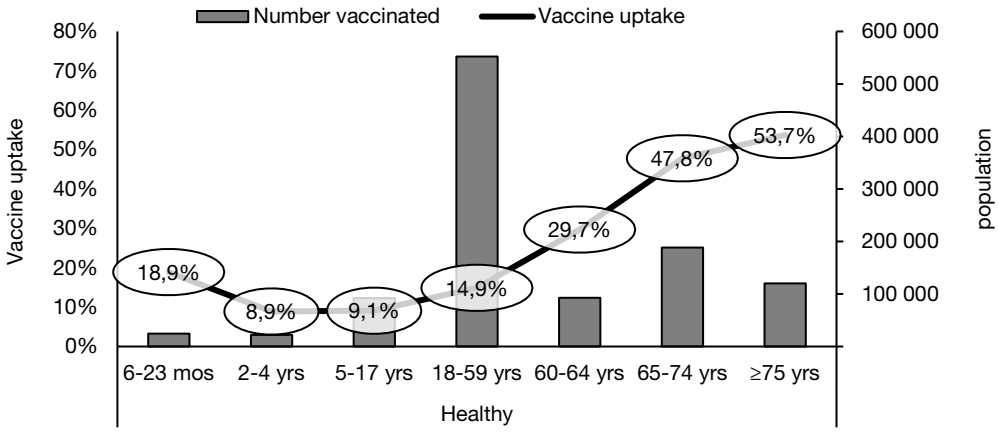
Figure 1 presents the vaccine uptake, population and number of individuals vaccinated, by age group and presence or not of a chronic condition. Among the children, the proportion of those with a chronic condition was estimated from case-control studies conducted in 2010, as reported in telephone interviews(29,30) by the parents of children randomly selected from the Québec population. Among the adults, the proportion of chronic conditions in the different subgroups was calculated from the data on the presence of chronic conditions reported in the *Enquête québécoise sur la vaccination contre la grippe saisonnière et le pneumocoque de 2015–2016* (Manale Ouakki, personal communication). Vaccine uptake was found to be better among older adults, and among individuals with a chronic condition, compared with healthy individuals. Further details can be found in Appendix 6.1A.

Figure 1 Vaccine uptake, population and number of individuals vaccinated against influenza, by age group and presence of a chronic condition

A) Population with a chronic condition



B) Healthy population



4 Influenza disease burden

4.1 Method used

A recent literature review was performed in order to estimate the burden of influenza among different groups of individuals. Given the large extent of the literature on this subject, we reviewed, for the most part, recent articles, dating from 2006 to 2016. We gave priority to the sources cited most frequently in the literature and those used by the governments of Canada and the United States to evaluate the burden of influenza in their countries(31–37). In addition, we focussed on the publications presenting data on Western populations (North America, Europe, Australia), where health services and vaccine uptake may be comparable to those in Québec. The studies that did not present population-based rates were excluded, given that the data could not be used for comparison purposes.

Two main approaches were used to evaluate the burden of influenza. First, prospective studies directly measure influenza-attributable morbidity and mortality, using laboratory data (confirmation of influenza by different tests) collected from the patients who are followed-up, in accordance with the objectives pursued (with respiratory symptoms, with influenza-like illness [ILI], consulting a physician or hospitalized). Population-based rates were then calculated from the results obtained, by using corresponding multipliers to extrapolate the results. This approach is used less often, because it is costly. The limitations of this method include the difficulties involved in capturing patients who consult late with influenza-related complications for cardiovascular events or loss of autonomy, and patients who may die from influenza without having been tested, as well as the fact that even very sensitive tests are not perfect. The underestimation of influenza disease burden is reduced when sensitive tests are systematically used for patients susceptible to presenting with influenza and when information on the entire source population is available. The recent use by the surveillance networks of data on outpatient visits and hospitalizations with laboratory-confirmed influenza to estimate the burden of influenza could be considered a variant of the direct method. This method extrapolates surveillance data by using population-based multipliers that take into account several probabilities (outpatient visits, hospitalizations, deaths, testing for the influenza virus), as well as the sensitivity of laboratory tests(38,39).

Second, indirect methods for estimating disease burden are the second approach and are more common. These ecological studies use surveillance data from administrative databases (e.g., hospitalizations or deaths). Traditionally, detection of influenza-attributable hospitalizations involves looking at influenza and pneumonia diagnoses (influenza/pneumonia – IP) and respiratory and cardiovascular disease diagnoses. Based on these figures, excess cases during seasonal influenza epidemics are calculated relative to the number of cases during the period in which the influenza virus is not circulating. The same applies for deaths, where the cases of mortality due to IP, respiratory and cardiovascular diseases and all-cause influenza-attributable mortality are evaluated. Given that these methods are based on several assumptions that are not necessarily valid, and on several statistical manipulations, interpretation of the results obtained is often difficult. Furthemore, comparison of the results obtained using the two methods (prospective vs ecological studies) often reveals significant discrepancies(40–44). For example, the results of a prospective study with systematic virological confirmation in Québec were compared with the results obtained following application of indirect statistical methods(45). The preliminary results of the comparison of three influenza seasons showed that, in general, indirect measures allow the capture of relative changes in influenza-attributable hospitalizations, but are less appropriate for estimating specific rates of hospital morbidity by age group and season. A recent meta-analysis of 103 publications presenting

influenza-associated mortality estimates using different methods concluded that it was not possible to calculate a single "average" measure of influenza-associated mortality, given the substantial heterogeneity, and the fact that the different study designs used represented one of the variables associated with the variation in the estimates(46). In a publication estimating the relationship between respiratory hospitalizations, circulation of influenza and respiratory syncytial virus (RSV) infections, and several environmental factors (ambient temperature, humidity and other covariates) in London, England, the number of influenza-associated hospitalizations decreased substantially when covariate adjustments were added to the model, and was from 7 to 9 times lower in the model adjusted for all the covariates of interest (seasonality, trend, days of the week, public holidays and several environmental factors), compared with the unadjusted model(47). In light of current knowledge, we could believe that, most often, indirect methods present the highest estimates of influenza-attributable morbidity and mortality, while prospective methods allow us to measure the minimum values of influenza disease burden.

The following chapters present a summary of the literature review, surveillance data and the prospective data found in Québec, as well as the approach used for selecting the parameters for the economic analysis with respect to influenza-associated visits, hospitalizations and deaths.

4.2 Influenza-associated visits

4.2.1 Data from the literature

The population-based rates of influenza-associated outpatient visits published in the literature present wide variations, depending on age and season. The highest rates are reported among children, especially the age group of 6–23 months (ranging from 5200 to 15 000/100 000), while the lowest rates are reported for individuals aged 65 years and older (ranging from 89 to 337/100 000)(48–56).

A prospective study conducted over three months in winter 2011 in the United States among 6492 randomly selected individuals presented a cumulative incidence of acute respiratory infection (feverishness or cough in the last 7 days), medically attended or not, of 52% in Rochester and 35% in Marshfield(57). An influenza virus was detected in 4% of the cases, for an overall cumulative incidence of 1.74% for the two areas. Given that 20% of the patients had seen a doctor, the frequency of medically attended influenza would be 0.35% in the population of all ages in 2011. A recent publication presents the global population-based rate in Germany calculated by using indirect statistical methods for the period between 2001–2002 and 2014–2015. The rate of influenza-attributable medically attended acute respiratory infection for all the population ranged from 0.7% (700/100 000 in 2003–2004) to 8.9% (8900/100 000 in 2012–2013)(58). A recent article presents the incidence of ILI (fever and at least one respiratory symptom) reported by individuals aged 60 years and older in the Netherlands during two influenza seasons (2011–2012 and 2012–2013), with or without an outpatient visit(59). The incidence of influenza-confirmed ILI, medically attended or not, was 1.3% in 2011–2012 and 3.8% in 2012–2013; the A(H3N2) subtype was predominant during the two seasons. In the United States, the rate of medically attended influenza infection estimated in the general population from a surveillance network during 3 seasons (2013–2014 to 2015–2016) ranged from 1.4% to 5.4%(60). Thus, the proportion of the population with medically attended influenza infection ranged from 0.35% to 8.9% in the literature.

The studies used to estimate medically attended influenza infection for the economic analysis are presented in detail below.

4.2.2 ESTIMATION OF MEDICALLY ATTENDED INFLUENZA INFECTION USED FOR THE ECONOMIC ANALYSIS

Medically attended influenza infection

The literature sources selected for the base-case scenario in the economic analysis were studies in which medically attended influenza infections were confirmed by a polymerase chain reaction (PCR), information on the source population was provided, population-based rates were provided or could be calculated by age group, and the country's healthcare system and economic conditions were comparable to Québec's. If several estimates were available for the same age group, the highest one was selected.

The only recent study presenting population-based medically attended influenza infection confirmed by PCR in different age groups is a prospective study conducted in the United States (Influenza Incidence Surveillance Project [IISP] by Fowlkes et al.(53,54). The other advantages of this study are (1) the use of both a definition of ILI, which may be more limited, and a broader definition; and (2) it was conducted over several seasons, which makes it possible to take into account the variability of influenza seasons. This study was based on 104 medical clinics covering a population of about 400 000 residents. The number of patients with medically attended respiratory symptoms was reported over four years (October 2009 to July 2013); a population sample was tested for a range of respiratory viruses, including influenza, using PCR(53,54). The incidence of medically attended influenza infection was calculated for the entire population by extrapolating the proportion of virus-positive patients each week. The results for ILI (fever with cough or sore throat) were reported for the 4 seasons. The results for patients with acute respiratory infection (ARI) (defined as at least two of the following symptoms: fever, cough, sore throat, nasal congestion or rhinorrhea) were reported only for the 2010–2011 season(53). The results for the 2010–2011 season show that the frequency of influenza-confirmed ARI was about two times greater than that of influenza-confirmed ILI, in all the age groups examined. Table 1 presents the average incidence for the three seasons (2010–2011 to 2012–2013), excluding the pandemic season, calculated from the article by Fowlkes et al.(54), and multiplied by 2, to take into account the greater frequency of influenza-confirmed infections among the patients with medically attended ARI compared with patients with medically attended ILI.

Given that Fowlkes's team presents aggregate results for children younger than 2 years, the results of two other prospective studies(50,55) were used, in order to derive the rates of medically attended influenza infection in the age groups of 0–5 months and 6–23 months. For the age group of 24–59 months, results were available in all these articles, but the aggregate rate based on the studies by Poehling et al.(50) and Simpson et al.(55) were selected for the base-case scenario, given the higher rates (Table 1). The overall annual rate of influenza-attributable outpatient visits for the entire Québec population is estimated to be 1.3%, which is higher than the rate of 0.35% estimated from the prospective study in the United States(57) and lies between the extremes of 0.7% and 8.9% in the German study using indirect statistical methods(58).

Table 1 Estimates of the rates/100 000 of influenza-attributable medically attended infections used in the base-case scenario in the economic analysis

Age groups	Fowlkes et al.(54)			Poehling et al.(50)		Simpson et al.(55)	Weighted average, Poehling et al and Simpson et al (50,55)
	Variations by season (2010–2011 to 2012–2013)		Aggregate rates from 3 seasons (2010–2011 to 2012–2013) x 2*	Variations by season (2002–2003 and 2003–2004)		Aggregate from 2006–2007 to 2008–2009	
	Min.	Max.					
0–5 months	NA		NA	2 800	5 900	NA	**4 350**
6–23 months	NA		NA	5 200	12 500	6 230	**7 336**
24–59 months	500	2 740	2 639	5 300	8 800	7 433	**7 271**
5–17 years	420	2 550	**2 827**	NA	NA	NA	NA
18–59 years	120	650	**752**	NA	NA	NA	NA
60–64 years	90	490	**429**	NA	NA	NA	NA
≥ 65 years	50	350	**337**	NA	NA	NA	NA

* To take into account all the acute respiratory infections, based on Fowlkes et al.(53).

Rates used in the base-case scenario in the economic analysis are shown in **bold.**

Emergency department visits

There are only limited data available on influenza-attributable emergency department visits (ED). In addition, the probability of ED visits may be different in different countries, depending on their organization of healthcare services. Kwong et al.(51) present the average annual rates of office visits, and of ED visits for influenza and pneumonia in Canada, by age group and province, from 1997 to 2004. The ratio of office visits to ED visits by age group presented in this study was used to extrapolate the rates of influenza-attributable ED visits in Québec. The overall annual rate of influenza-attributable office visits and ED visits for the entire Québec population is estimated to be 1.6%.

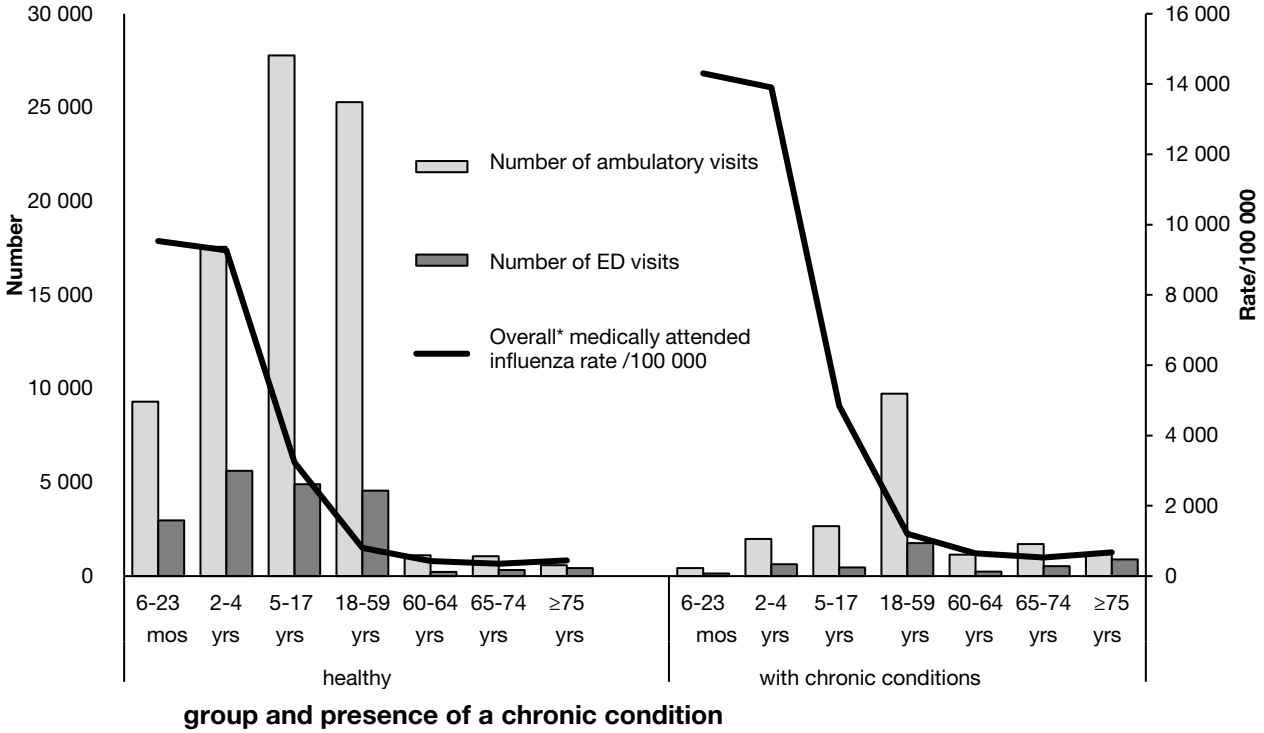
Medically attended influenza infections based on the presence of chronic conditions and complications

Data on population-based influenza rates based on the presence of chronic conditions are rarely available. However, several articles have quantified the relative risk of medically attended influenza infection based on the presence or not of chronic conditions. Although some variability exists, depending on the region, season, age or methodology used, the probability of a medically attended influenza infection is approximately 1.5 times higher for individuals with an underlying medical condition than for healthy individuals(61,62). This multiplier of 1.5 was used to calculate the rates of influenza-attributable office visits and ED visits for individuals with a chronic condition and healthy individuals, based on the overall rate by age group estimated using the method described in detail above. Figure 2 presents the estimation of the number and rates of medically attended influenza infections in Québec, by age group, used for the economic analysis.

According to the literature, the most common influenza-associated complications are acute otitis media (AOM) (mainly in children), lower respiratory tract infections (bronchitis, pneumonia), and upper respiratory tract infections (e.g., sinusitis)(63). It is estimated that between 5% and 29% of influenza-confirmed outpatient visits involve patients presenting with a disease complication(63–68). Young

children (< 2 years) are generally the most affected (29%)(66,69), along with those presenting with a chronic condition (26% among adults)(67,70). Given that the estimates of the rates of influenza-attributable office visits and ED visits include visits for complications resulting from an influenza virus infection, complications were not taken into account in the economic analysis. The sensitivity analysis took into account the possibility of an increase in the rates of medically attended influenza infections due to complications, among other things.

Figure 2 Number and rate of medically attended influenza infections in Québec, by age group and presence of a chronic condition



* The overall medically attended influenza infection rate includes office visits and emergency department visits.

4.2.3 Estimation of medically attended influenza infections in Québec for the sensitivity analyses in the economic analysis

To take into account the uncertainty in the estimates of medically attended influenza infections, we multiplied the base-case rate of medically attended influenza infections by factors ranging from 0.2 to 3, in the sensitivity analyses. These multipliers correspond to the lowest and highest confidence intervals for the medically attended influenza infections rates reported in the literature, irrespective of method or age group.

4.2.4 Medications used following medically attended influenza infections

In Québec, individuals without private prescription drug insurance are covered by the Public Prescription Drug Insurance Plan, administered by the Régie de l'assurance maladie du Québec (RAMQ). It is calculated that approximately 36% of the Québec population, all ages, was covered by the public plan in 2012.

To evaluate the healthcare system expenditures related to the use of medications following a medically attended influenza infection, we asked the RAMQ to provide us with statistics on the medications prescribed in Québec. Refer to Appendix 2 for a description of the process for estimating the use of neuraminidase inhibitors (oseltamivir or zanamivir), antibiotics and inhalers (bronchodilators and inhaled corticosteroids), all potentially related to the treatment of the main influenza-associated complications (acute otitis media, sinusitis, bronchitis, pneumonias) in the Québec population covered by the Public Prescription Drug Insurance Plan.

It is estimated that, among the individuals covered by the public plan and having had a medically attended influenza infection, 32% received antibiotics (23% for children aged 0–4 years, 10% for ages 5–17 years and 35% for ages 18 years and older), 31% received inhalers (10% for ages 0–17 years and 34% for ages 18 years and older), and 9% received neuraminidase inhibitors (< 0.5% for ages 0–17 years, 1% for 18–59 years, 6% for 60–64 years, 12% for 65–74 years, and 32% for 75 years and older).

4.3 Influenza-attributable hospitalizations

4.3.1 Data from the literature and surveillance programs

According to data in the literature, pediatric hospitalization rates attributable to seasonal influenza estimated using indirect statistical methods ranged from 15–21/100 000 among children aged 15–17 years to 180/100 000 among those aged 6–23 months(32,49,71–73). The prospective studies including the use of laboratory tests provide lower rates: from 3–19/100 000 among children aged 5–17 years to 30–110/100 000 among ages 6–23 months(48,50,74–76). The rates estimated from surveillance network data in the United States ranged from 14 to 57/100 000 for children < 18 years(39), from 20 to 31/100 000 for children aged 0–4 years, and from 3 to 8/100 000 for children aged 5–19 years(38).

According to data in the literature, the rates of influenza-attributable hospitalizations estimated using indirect statistical methods ranged from 5 to 31/100 000 among adults aged < 65 years, from 63 to 340/100 000 among those aged 65 years and older, and from 202 to 559/100 000 among individuals aged 75 years and older(32,33,36,56,73, 77–79). A limited number of prospective studies including the use of laboratory tests among adults generally present lower rates: from 3 to 23/100 000 among adults < 65 years, from 14 to 182/100 000 among adults 65 years and older(80), and from 22 to 117/100 000 among adults 75 years and older(81). The rates estimated from surveillance network data in the United States ranged from 3 to 74/100 000 for adults < 65 years, and from 14 to 1033/100 000 for adults 65 years and older(38,39).

Influenza-confirmed hospitalizations, admissions to intensive care and deaths are reported each year to the Public Health Agency of Canada (PHAC) by a majority of the provinces and territories and are available on the Canadian government's website each week during influenza seasons(82). British Columbia, Québec and Nunavut do not report influenza-attributable hospitalizations to the PHAC. Case selection criteria may vary across provinces. Since 2011, between 736 and 1508 influenza-attributable hospitalizations have been reported annually among those aged < 20 years, and approximately 4500 among those aged ≥ 20 years. Few hospitalizations were reported during the 2011–2012 season (n = 1137), while the 2014–2015

season was the most severe in recent years with close to 7000 hospitalizations reported by the provinces among adults only. Of these, 80% were individuals aged 65 years and older.

Since 2012, the CIRN-SOS network (Canadian Immunization Research Network, Serious Outcomes Surveillance Network, composed of some 15 hospitals across 5 provinces) annually reports an average of approximately 1800 influenza-confirmed hospitalizations among adults (≥ 16 years). For children, the Canadian Immunization Monitoring Program, ACTive (IMPACT), including 12 Canadian pediatric hospitals, has annually reported an average of 849 influenza-attributable hospitalizations among those aged < 16 years since 2011–2012.

The number of hospitalizations reported by the provinces and territories, by the CIRN-SOS network and by the IMPACT network represents a sample of all the hospitalizations potentially associated with influenza among children and adults in Canada, and it is difficult to extrapolate these data to the entire population.

In the annual reports on influenza vaccination, the Public Health Agency of Canada (PHAC) presents estimates of the influenza burden in Canada based on indirect statistical methods using administrative databases and influenza circulation data from Schanzer et al.(35,36,79), which permit calculations extrapolated to the entire Canadian population. According to these calculations, the annual average of influenza-attributable hospitalizations in Canada is 12 200(83).

4.3.2 Influenza-attributable hospitalizations based on the Québec data used for the base-case scenario in the economic analysis

A prospective study with systematic specimen collections among patients presenting with respiratory symptoms has been conducted since 2011–2012 in 4 regional hospitals in Québec. For further details, refer to the reports for the 2011–2012, 2012–2013, 2013–2014, 2014–2015 and 2015–2016 seasons on the INSPQ website(24–28) and to a published article(84). In short, all the patients presenting with respiratory symptoms during the influenza season in the 4 hospitals participating in the study (representing close to 10% of hospitalization cases for respiratory diagnoses in the province) automatically provided nasal swabs tested by multiplex PCR at the Laboratoire de santé publique du Québec (LSPQ). For the patients who underwent specimen collections but who were not recruited (missed by the nurses due to logistical reasons or the impossibility of obtaining consent [incapacitated, confused patients, or others]), the laboratory test results were available only in aggregate form by age group.

The prospective study was conducted during the peak influenza period defined as the period in which the 15% threshold for weekly influenza-positive specimens was achieved by the Québec hospital laboratories participating in provincial surveillance (data from the LSPQ). The peak influenza periods included in the project corresponded to > 70% of positive influenza tests reported by the province's sentinel laboratories during the annual influenza circulation period.

To estimate the burden of influenza-attributable hospitalizations in Québec, we extrapolated the number of influenza-positive patients in the 4 hospitals included in the prospective study, for each age group, to the whole province of Québec, taking into account the following factors:

1) The proportion of patients hospitalized with an influenza-confirmed infection among the study patients relative to the number of patients potentially missed by the study. This was estimated based on all the patients admitted with a respiratory diagnosis in the participating hospitals during the study periods, according to the MED-ÉCHO database (ICD-10 codes used: J00–J990).

2) The proportion of respiratory diagnoses in the 4 participating hospitals, by age group, relative to the total respiratory diagnoses in Québec, according to the MED-ÉCHO administrative database (ICD-10 codes used: J00–J990).
3) The proportion of influenza viruses circulating during the study periods relative to the total influenza viruses reported throughout the year by the sentinel laboratories.

This exercise allowed us to estimate the total annual number of influenza-attributable hospitalizations in Québec. An example for the 2012–2013 season can be found in the French-language report published on the INSPQ website(45).

Note that the 5 years of the prospective study used to calculate averages for influenza-attributable hospitalizations include 2 severe influenza seasons with predominance of the A(H3N2) subtype: 2012–2013 and 2014–2015. The 2014–2015 season was additionally characterized by a vaccine effectiveness ranging from very low to null in Canada and Québec(85,86). Table 2 and Figure 3 present the number and rate of influenza-attributable hospitalizations in Québec that were used in the base-case scenario in the economic analysis.

Table 2 Number and average annual rate of influenza-attributable hospitalizations in Québec, extrapolated from the data derived from the Québec prospective study and from the IMPACT network, by age group and presence or not of a chronic condition, between 2011–2012 and 2015–2016

Estimate	0–5 months	6–23 months			24–59 months			5–17 years			18–59 years			60–64 years			65–74 years			≥ 75 years			Total
		With CC	Healthy	**Total**	With CC	Healthy	Total	With CC	Healthy	**Total**	With CC	Healthy	**Total**	With CC	Healthy	**Total**	With CC	Healthy	**Total**	With CC	Healthy	**Total**	
Annual average, prospective study(24–28)	**198**	36	**257**	293	69	**136**	205	48	**102**	150	667	196	863	282	46	328	867	97	964	2 666	347	3 012	6 013
Annual average, IMPACT	154	**99**	132	231	**112**	122	235	**122**	73	196	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Final retained	**198**	**99**	**257**	**356**	**112**	**136**	**248**	**122**	**102**	**225**	**667**	**196**	**863**	**282**	**46**	**328**	**867**	**97**	**964**	**2 666**	**347**	**3 012**	**6 194**
Rate/100 000	451	2 492	200	269	597	54	92	189	10	21	64	5	18	132	15	62	205	25	118	850	155	561	76

CC = chronic condition; NA = not applicable.

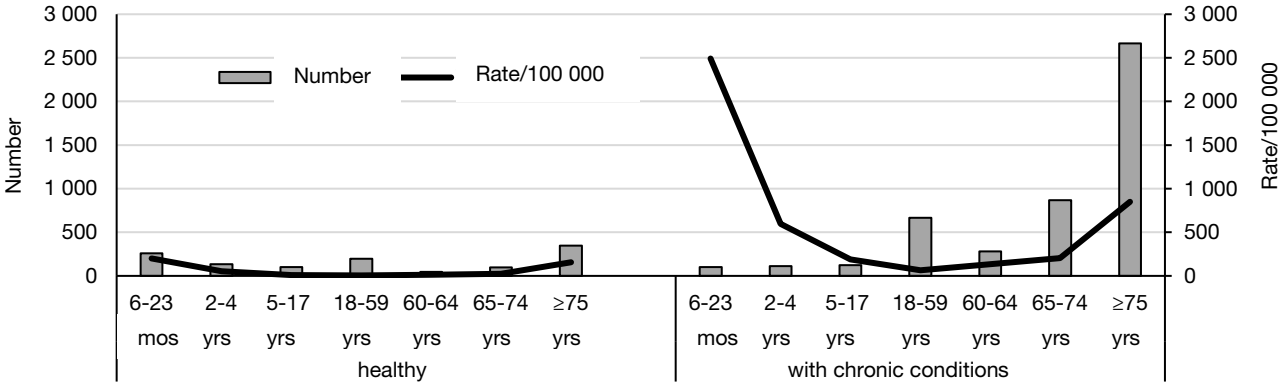
Estimates based on 4 years (2012–13 to 2015–16) (children) or 5 years (2011–12 to 2015–16) (adults).

Of the adults, 915 were admitted from LTCFs.

Figures in **bold** are those retained for the base-case scenario in the economic analysis.

Note: The total on the line "Final retained" may not correspond to the column total because of rounding. The number of hospitalizations presented in the table is estimated for a population having received the influenza vaccine (see vaccine uptake by age group in Section 3.2).

Figure 3 Annual influenza-attributable hospitalizations in Québec, by age group and presence or not of a chronic condition, number and rate/100 000, between 2011–2012 and 2015–2016



Annual influenza-attributable hospitalizations extrapolated from the prospective study with virological confirmation in 4 acute care hospitals in Québec during 5 influenza seasons (2011–2012 to 2015–2016), taking into account all the patients admitted with a respiratory diagnosis included in the MED-ÉCHO database; for children with a chronic condition, the data from the IMPACT network were extrapolated to the whole province of Québec.

Note: The number and rate of hospitalizations presented in the figure are estimated in a population having received the influenza vaccine (see vaccine uptake by age group in Section 3.2).

Estimates of influenza-attributable hospitalizations among children

Given that the 4 hospitals participating in the prospective study were not pediatric hospitals, the number of influenza-attributable hospitalizations, especially among children with a chronic condition, may have been underestimated. To resolve that issue, we used data from the IMPACT network for the past 5 years (data provided by Julie Bettinger). The average annual number of influenza-confirmed hospitalizations in the 3 pediatric hospitals in the IMPACT network in Québec (CHU Sainte-Justine, Montréal Children's Hospital and CHUL), by age group and by presence or not of a chronic condition, was extrapolated to the entire province. The extrapolation was performed by taking into account the proportion of hospitalizations for respiratory codes in the IMPACT network hospitals, by age group and presence or not of a chronic condition, relative to the other hospitals. The data are presented in Table 2.

The table shows that the highest figures for children with a chronic condition are those obtained from the IMPACT network, while for healthy children, the highest figures are those obtained from the prospective study. The final figures retained are the estimates for the children with a chronic condition from the IMPACT network, and the estimates for the healthy children from the prospective study (Table 2).

Additional details on the estimation of influenza-attributable hospitalizations in Québec are available in Appendix 3.

Role of the influenza virus in non-respiratory hospitalizations

Several research studies have focussed on demonstrating the relationship between the influenza virus and the onset of non-respiratory events, such as cardiac or vascular problems. In a self-controlled case series study with more than 22 000 patients identified from an administrative database, the risk of a myocardial infarction in the first 3 days following a medically attended acute respiratory infection (incidence rate ratio) was 4.19 (95% CI, 3.18–5.53)(87). In a case-control study including more than 11 000 patients presenting with myocardial infarction and more

than 9000 patients with stroke identified in a primary care database and with an influenza-confirmed respiratory infection detected in the 7 days preceding the infection, the adjusted odds ratio, compared with matched controls, was 2.10 (95% CI, 1.38–3.21) for myocardial infarction and 1.92 (CI 95%, 1.24–2.97) for stroke(88). A meta-analysis of case-control studies suggests that a respiratory infection (influenza-confirmed infection, influenza-like illness or unspecified respiratory infection) could double the risk of myocardial infarction(89). Given the use of non-specific outcomes in these studies, these results do not make it possible to differentiate the specific role of the influenza virus from the role of the other respiratory viruses. More recent studies examined the estimation of the role of the other viruses in cardiovascular events. The authors of an ecological study in England estimated the link between the circulation of different respiratory viruses and hospitalizations for myocardial infarction or stroke in individuals aged 45 years and older, using multivariable Poisson regression adjusted for environmental factors(90). Significant associations between different respiratory viruses (human metapneumovirus, respiratory syncytial virus [RSV], influenza, rhinovirus and adenovirus) and hospitalizations for myocardial infarction or hemorrhagic stroke were detected among individuals aged 65 years and older. The authors of a publication describing the results of a self-controlled case series design identified from administrative databases and carried out in Ontario found a significant association between a respiratory virus infection (influenza, RSV and other viruses) and myocardial infarction, in the 7 days following detection of the virus(91). Given that testing for the influenza virus is generally much more common than testing for the other respiratory viruses, it is easier to show the role of influenza relative to that of the other viruses. Additional studies with systematic specimen collections among patients at risk for cardiovascular events are necessary to be able to better quantify the specific role of influenza in triggering these events compared with that of the other respiratory viruses.

An indirect indication of the potential role of influenza in the etiology of cardiovascular events could be the demonstration of influenza vaccine effectiveness in preventing these events. Several systematic reviews and meta-analyses suggest that the influenza vaccine could protect patients against severe cardiovascular events such as hospitalization and death(89,92–94). The sometimes contradictory results of these reviews could be explained by the small sample sizes, the low number of events, the use of non-specific outcomes (respiratory infections or influenza-like illness), along with methodological differences. A Cochrane review published in 2015(95) concluded that there was not enough evidence to date to be able to establish whether influenza vaccine has a role to play in protecting against cardiovascular disease. A systematic review published in 2017(96) revealed the potential bias in the studies included in the systematic reviews that could also have contributed to the different conclusions observed. The authors concluded that the lack of good-quality data made it difficult to conclude whether the relationship between influenza and cardiovascular events is real. Good-quality randomized controlled trials (RCTs) with sufficient sample sizes are needed to estimate the effectiveness of influenza vaccine against cardiovascular events. To our knowledge, at least one clinical trial is in progress, with the preliminary results expected in 2020(97).

Even though the existing data are insufficient to date, it is plausible that the influenza vaccine may be an effective strategy for reducing cardiovascular events. Nevertheless, the number of these events is likely small relative to respiratory events, among influenza-associated events overall. In a Canadian study, the authors calculated the number of influenza-attributable hospitalizations among patients hospitalized with different diagnoses, by using indirect statistical methods applied to administrative databases(36). The number of influenza-associated hospitalizations for congestive heart failure (n = 273) was 37 times smaller than the number of influenza-associated respiratory hospitalizations (n = 9997, corresponding to < 3% of the total influenza-associated

hospitalizations among patients aged ≥ 65 years. Among the patients aged < 65 years, hospitalizations for congestive heart failure were not associated with influenza. Prospective studies that tested for influenza patients with medically attended cardiovascular symptoms during influenza virus circulation periods suggest that these patients account for around 10% of all patients with laboratory-confirmed influenza virus(98,99). Further details on these studies can be found in Appendix 3.

4.3.3 Comparison of the estimates of influenza-attributable hospitalizations in Québec with the estimates from the Public Health Agency of Canada and in the literature

Based on the average annual number of 12 200 influenza-attributable hospitalizations estimated using indirect statistical methods for Canada overall(83), we should observe approximately 3050 hospitalizations in Québec. Our estimate of 6194 influenza-attributable hospitalizations per year for the Québec population overall, based on the prospective study, is two times higher. Some of the assumptions used during the extrapolation of the data from the prospective study to all of Québec may have been exaggerated, or this higher number may reflect the severity of the 2012–2013 and 2014–2015 influenza seasons included in the calculation. It should also be noted that the influenza hospitalization rates estimated from the data in the prospective study are some of the highest reported in the literature.

4.3.4 Estimation of influenza hospitalizations in Québec for the sensitivity analyses in the economic analysis

To take into account the possibility of having missed patients not presenting with respiratory symptoms but who may have been hospitalized as a result of an influenza infection in the prospective study (such as patients hospitalized for cardiovascular events) and the uncertainty of some of the estimates, we multiplied the base-case value of the hospitalization rate by a factor of up to 3 in the sensitivity analyses. This multiplier corresponded to the highest estimate reported in the literature for influenza hospitalizations, irrespective of method and age group, as well as the difference between the estimates in the prospective study and those obtained by applying indirect statistical methods to the MED-ÉCHO administrative hospitalization database for some age groups(45).

4.4 Influenza-attributable deaths

4.4.1 Data from the literature and surveillance programs

Population-based rates

For children, the use of indirect statistical methods applied to administrative databases permitted estimation of influenza-attributable death rates from 0.3 to 0.6/100 000 among ages < 6 months(31); from 0.2 to 0.5/100 000 among ages 0–5 years (31,100), and from 0.1 to 0.2/100 000 among ages 5–17 years (100). To our knowledge, the only study with laboratory confirmation which presents population rates by age group among children is the one by Bhat et al.(101). The authors present data on a single severe influenza season (2003–2004) in the United States. In this study, the influenza-attributable rates are 0.88/100 000 among children aged < 6 months, 0.77/100 000 among those aged 6–23 months, 0.30/100 000 among those aged 2–4 years and 0.11/100 000 among those aged 5–17 years (101). The rates estimated from surveillance network data in the United States range from 0.07 to 1.1/100 000 for children aged < 18 years(39).

A recent study published in early 2018 presents the population-based death rates of influenza-confirmed infection among children aged < 18 years in the United States(102). Notification of influenza-associated pediatric deaths in the Influenza-Associated Pediatric Mortality Surveillance System has been compulsory in the United States since 2004. The number of deaths reported in this system between 2004–2005 and 2011–2012 (including the 2009–2010 pandemic influenza season) was reported in a publication in 2013(103), but it did not present population-based rates. The average annual rate of influenza-associated deaths during the 6 years included in the 2018 publication (from 2010–2011 to 2015–2016) is 0.15/100 000 for all children(102). The rate decreases with increasing age (from 0.66/100 000 for those aged < 6 months to 0.33/100 000 for ages 6–23 months and up to 0.1/100 000 for ages 13–17 years). The authors mention that half of the deceased children had a chronic condition, but they did not present population-based rates for children with a chronic condition or healthy children.

For adults, the rates presented in the literature range from 0.2/100 000 to 0.8/100 000 among ages < 65 years (31,36,37,79,100,104), from 5.9/100 000 to 98.3 /100 000 among ages 65 years and older (31,36,37,51,77,79,100,105,106), and from 47.5/100 000 to 119/100 000 among ages 75 years and older(100). The rates estimated from surveillance network data in the United States ranged from 0.6 to 1.7/100 000 among adults aged 18–64 years, from 8.6 to 54.6/100 000 among adults 65 years and older, and from 1.6 to 8.9/100 000 for the entire population(39).

In December 2017, a WHO working group published updated estimates of global influenza-associated mortality based on numerous influenza surveillance data, death registers and sophisticated statistical model results(106). The group estimated that each year between 291 243 and 645 832 influenza-associated deaths occur around the world, for a global rate of 4.0–8.8/100 000. The estimated average annual rate of influenza-associated deaths ranged from 0.1 to 6.4/100 000 for individuals < 65 years; from 2.9 to 44.4/100 000 for those aged between 65 and 74 years; and from 17.9 to 223.5/100 000 for those aged 75 years and older, with considerable variations across regions and countries. For Canada, this accounts for a median rate of 0.4/100 000 (95% credibility interval, 0.1–0.6) for individuals < 65 years; 6.1/100 000 (95% credibility interval, 1.7–10.5) for ages 65–74 years, and 44.5/100 000 (95% credibility interval, 19.0–70.3) for ages 75 years and older. The authors of that report mention the need to better understand the contribution of non-respiratory diagnoses to influenza-associated deaths.

Population-based rates are traditionally presented in the literature in aggregate form, without distinguishing between individuals with a chronic condition and healthy individuals. In some cases, if information on the proportion of chronic conditions among the influenza cases and in the population is available, stratified population-based rates can be calculated. Thus, in the study on influenza-associated deaths among children in the United States(102), assuming an annual cohort of approximately 4 million births in the United States, a proportion of 11% of chronic conditions in the pediatric population(107) and the presence of chronic condition in 50% of children who died from influenza, the death rate would be 0.75 per 100 000 among the children with a chronic condition and 0.9 per million among healthy children. The rates may have been underestimated by a factor of around 2 in this system(103), and the real rate would then be approximately 1.5/100 000 for children with a chronic condition and < 2 per million for healthy children.

Role of the influenza virus in the death of patients with non-respiratory diagnoses

Statistical models suggest that the death of patients with non-respiratory diagnoses may contribute from less than one third to more than half of all deaths attributable to influenza(34,37,108–114). Health problems, such as digestive, renal and neurological disorders, psychotic conditions, falls and accidental intoxication or other accidents are some of the diagnoses for which a statistically significant association with influenza has been found using these models. However, this does not seem very plausible. An exercise performed using Québec databases estimated as 31% the proportion of deaths from cardiovascular problems among the total number of influenza-associated deaths including respiratory and cardiovascular diagnoses (see Appendix 4 for further details). Interpretation of these results is difficult given the many uncertainties and limitations of these models. In particular, if the model does not take into account the other respiratory viruses circulating at the same time as the influenza virus or other environmental factors (such as temperature or humidity) that may also contribute to cardiovascular deaths, estimates attributable to influenza could be too high. Models that include, in addition to data on the circulating influenza virus, data on the circulation of other respiratory viruses or other environmental factors (such as the temperature or humidity) are able to attribute to the latter factors a certain number of deaths that would otherwise have been attributed to the influenza virus (47,104,115,116). A European network (European Monitoring of Excess Mortality for Public Health Action–Euro-MOMO)(117) monitors excess mortality in several European countries, using a standardized approach and producing weekly reports and periodic publications(110). In addition to influenza-attributable estimates, this network reports on the effects of temperature variations on mortality. For example, in an article published in 2011 on excess mortality attributable to influenza and to extreme temperatures in Denmark, Nielsen et al. estimated at 2.24/100 000 the median rate of deaths attributable to periods of extreme cold(109). When we take into account several factors that can potentially explain the events related to influenza infection, the number of outcomes attributed to influenza by statistical models may decrease relative to the models adjusted for a smaller number of explanatory factors. A preliminary analysis based on Québec data shows that the number of influenza-associated deaths by the statistical model decreases when the circulation of other respiratory viruses and ambient temperature are taken into account.

Proportion of deaths among patients hospitalized for influenza

According to several data sources, the proportion of deaths among patients hospitalized for influenza, all ages, is 1–4%; it is 1–8% for adults and 3–8% for persons aged 65 years and older(25–28,39,83,86,118–123). In a recent article comparing the effectiveness of two influenza vaccines in a population of approximately 3 million people aged 65 years and older in the United States, the data on influenza-confirmed hospitalizations and on deaths occurring in the 30 days following an influenza diagnosis (extractions from administrative databases) are presented for 2 influenza seasons (2012–2013 and 2013–2014)(124). During these 2 seasons, a total of 6040 influenza-confirmed hospitalizations occurred and 245 deaths occurred in the 30 days following an influenza diagnosis. By dividing the number of deaths (245) by the number of influenza-positive hospitalizations (6040) we arrive at a lethality of around 4% for the 2 seasons. The authors do not mention whether the influenza virus was the cause of death among the hospitalized patients.

According to Canadian surveillance data (IMPACT network), the proportion of deaths among children hospitalized for influenza between 2011–2012 and 2015–2016 ranged from 0% (0/692) to 0.9% (5/571)(125). As for adults hospitalized for influenza, according to data from the CIRN-SOS network for the period between 2012–2013 and 2015–2016, the proportion of deaths ranged from 4.8% (55/1153) to 6.5% (116/1798); for people aged 65 years and older, this proportion ranged from 5.9%

(34/575) to 8.1% (99/1225)(125). It is mentioned that most of these deaths were observed among the patients with a chronic condition, but details are not available regarding the number of deaths among patients with a chronic condition, compared with healthy patients.

4.4.2 INFLUENZA-ATTRIBUTABLE DEATHS ACCORDING TO THE QUÉBEC DATA USED FOR THE BASE-CASE SCENARIO IN THE ECONOMIC ANALYSIS

No death was reported among the children participating in the Québec prospective study during the 5 seasons. That is not surprising because the 4 hospitals participating in this study serve a population of about 150 000 children and the rate of influenza-attributable deaths among children reported in the literature is lower than 0.2/100 000. In total, 2 deaths were reported for the same period in the Québec hospitals participating in the IMPACT network (1 child aged 0–5 months without a chronic condition and 1 child aged 6–23 months with a chronic condition) (data provided by Julie Bettinger). Given that the number of deaths due to influenza is low among children, the rates cited in the literature were used for the economic analysis. The same rates were used for healthy children and those with a chronic condition, because data stratified by the presence or not of a chronic condition were not available at the time this analysis was being performed.

To estimate the number of deaths among hospitalized adults in the prospective study, we calculated the lethality among the enrolled patients with a confirmed influenza virus, by age group and presence of a chronic condition. Subsequently, this lethality was applied to the number of provincial influenza hospitalizations, as estimated in the corresponding chapter. In addition, to take into account the lack of sensitivity of the laboratory test among patients who consulted late, we applied the percentage of influenza detections to the patients who consulted late and who tested negative for the influenza virus and for the other respiratory viruses (Table 3).

Table 3 Illustration of the adjustment for the lack of sensitivity of the influenza test in the Québec prospective study

Age groups	Number of patients with ILI enrolled in the Québec prospective study* during the peak periods of 4 influenza seasons**	Influenza-positive patients			Patients who tested negative for all respiratory viruses among the visits > 8 days following symptom onset			Number of deaths among the visits > 8 days following symptom onset that could have been attributable to influenza	Total deaths, including those possibly due to influenza, among the visits > 8 days	
		Enrolled, n	Decd, n	Decd, n %	Enrolled, n	Decd, n	Decd, %			
18–64 years	483	275	1	0,4	75	2	2,7	1.1	2.1	(0,7%)
65–74 years	373	178	6	3,4	26	1	3,8	0.5	6.5	(3,6%)
≥ 75 years	953	473	29	6,1	76	10	13,2	5.0	34.0	(7,2%)
Total	1 953	926	36	3,9	177	13	7,3	6.9	42.9	(4,6%)

ILI: influenza-like illness; Decd: Deceased.

* Prospective study conducted in 4 hospitals in Québec.

** The 2013–2014 season is not included in the calculation because the other respiratory viruses were not tested during that season.

The number of influenza-attributable deaths that occurred among non-hospitalized patients in the acute-care hospitals was estimated using the data on influenza outbreaks in the LTCFs provided by the MSSS for 5 years (from 2011–2012 to 2015–2016). By adjusting for unreported data, we arrive at a total of 1093 deaths due to influenza infection, for an average of 219 per year among the residents of LTCFs, including 65 that occurred in acute-care hospitals and 154 deaths in LTCFs. For further details, see Appendix 4.

Table 4 presents the average annual number of influenza-attributable deaths in Québec based on the prospective study and on the data on the influenza outbreaks in LTCFs.

In the prospective study, more than one third of the deaths observed among the hospitalized influenza-positive patients were declared as not attributable to influenza. Two publications by the CNISP (Canadian Nosocomial Infection Surveillance Program), a network of 54 tertiary hospitals in the 10 provinces, present the surveillance results of cases aged 16 years and older hospitalized with laboratory-confirmed influenza(126,127). Outside the 2009 season, during which the H1N1 pandemic occurred, the proportion of influenza-attributable deaths (primary or contributing cause) among all the deceased patients with confirmed community-acquired or nosocomial influenza infections ranged from 47% (4.0% of attributable lethality/8.4% of total lethality during the 2006–2009 period) to 67% (4.5% of attributable lethality/6.7% of total lethality during the 2010–2011 period)(127). Influenza was declared to be the primary cause of death in only 19% of the cases of death due to laboratory-confirmed influenza (10 primary causes/53 total deaths during the 2006–2009 period and 14 primary causes/74 total deaths during the 2010–2011 period)(127). From 2006 to 2012, among all the cases of death with a community-acquired influenza infection, the lethality attributable to influenza was 67% (4.0% attributable/5.9% total); among the cases of death with a nosocomial infection, it was 70% (8.1%/11.6%)(126). Given that this network includes only tertiary hospitals, it is possible that the most gravely ill patients with the highest risk for complications and death were tested, resulting in the overestimation of the lethality attributable to influenza.

Based on the results from the Québec prospective study and from the CNISP network, it was decided that, for the economic analysis, two thirds of the deaths among the patients hospitalized for influenza would be attributed to influenza (Table 4) because these are the deaths in which the influenza infection may have played a role and they could consequently have been prevented by the administration of a vaccine.

Table 4 **Number and annual rate of deaths attributable to influenza in Québec extrapolated from the data in the Québec prospective study and from the notification on influenza outbreaks in the LTCFs, by age group and presence or not of a chronic condition, between 2011–2012 and 2015–2016***

	0–5 months	6–23 months		24–59 months		5–17 years		18–59 years		60–64 years		65–74 years		75 years +		in LTCFs	Total
		With a CC	Healthy	With a CC	Healthy	With a CC	Healthy	With a CC	Healthy	With a CC	Healthy	With a CC	Healthy	With a CC	Healthy		
No. of estimated deaths among the patients with influenza	0.39	0.03	0.99	0.06	0.75	0.07	1.11	5.0	1.5	2.1	0.3	31.6	3.5	191.4	24.9	153.6	417
Rate/100 000	0.88	0.77		0.30		0.11		0.14		0.47		4.3		40.3		384	5.2
No. of deaths attributable[1] to influenza	0.39	0.03	0.99	0.06	0.75	0.07	1.11	5.0	1.5	2.1	0.3	21.0	2.3	127.6	16.6	102[2]	282

CC: chronic condition

[1] Primary or contributing cause.

[2] Given that information on the proportion of deaths attributable to influenza among the patients who died in the LTCFs was not available, the proportion of 2/3 was applied, corresponding to that estimated in the acute-care hospitals.

Notes: The total deaths may not correspond to the line total because of rounding. The number of deaths presented in the table is estimated in the population having received the influenza vaccine (see vaccine uptake by age group in Section 3.2).

* The number of deaths among children is estimated based on the literature using the same rates for healthy children and children with a chronic condition (see text).

4.4.3 Comparison of the estimates of influenza-attributable hospitalizations in Québec with the estimates from the Public Health Agency of Canada and in the literature

Our global total for the entire population (5.2/100 000) is 2 times lower than the rate of 11.3/100 000 from Schanzer et al.(37) used by the PHAC. The rate of 11.3 was estimated using the outcome of all-cause mortality over the period from 1992 to 2009, in a population with vaccine uptake rates lower than those recently detected, and with a lower level of care compared with the progress made in recent years. It is also important to take into account the fact that the models using non-specific outcomes, such as all-cause mortality, are particularly sensitive to the lack of adjustment for other causes that may have played a role in the deaths. For example, it can be seen in the publication by Schanzer et al. that, in the model unadjusted for RSV, the number of deaths attributed to influenza is greater relative to the model taking into account RSV; the authors also mention that the model without inclusion of seasonality doubles the number of deaths attributed to influenza, relative to the model including seasonality. The authors took into account seasonality and circulating RSV, but they did not take into account the other respiratory viruses and environmental factors. In addition, they mention that changes in coding due to the conversion from ICD-9 to ICD-10 resulted in the doubling of the proportion of the deaths due to non-respiratory causes that were attributed to influenza by the model (from 23% to 49%). Thus, we could conclude in an overestimation of the number of deaths in that publication, primarily explained by (1) the historical period upon which this study was based; and (2) the uncertainties related to the modelling. It is difficult to quantify this overestimation.

The rates of influenza-associated deaths that we estimated in the different age groups correspond to the rates published in the literature and lie within the range of estimates for Canada published in the latest update by the WHO working group(106).

4.4.4 Estimation of influenza-attributable deaths in Québec for the sensitivity analyses in the economic analysis

To estimate the upper limit of the number of deaths among influenza patients in Québec, we applied an indirect statistical modelling method, based on the one used by the Public Health Agency of Canada (Schanzer et al.[36,37,79]), to data from the death record in Québec (using the diagnostic respiratory codes in all positions) and to the data on influenza circulation in Québec (from 2000–2001 to 2014–2015). The model took into account seasonality and the circulation of RSV. The other respiratory viruses were not included in the model, given that surveillance data for these other viruses were not available for the entire period examined.

For the 5 seasons used in estimating influenza burden in Québec, the statistical models associated influenza with an annual number of deaths in Québec, all ages, between 649 (2011–2012 season) and 2513 (2014–2015 season, upper limit of the 95% confidence interval [CI] = 2760). The estimate for the number of influenza-associated deaths for the whole province of Québec for 2014–2015, based on the prospective study, is 1000 deaths. As mentioned previously, these statistical models most likely overestimate influenza-attributable deaths. To take into account the possibility of a higher number of deaths and the uncertainty of the methods used, in the sensitivity analyses, we multiplied the parameters used in the base-case scenario by a factor of 2.8 (2760, upper limit of the 95% CI of the estimate from the statistical model for 2014–2015 divided by 1000, the estimate in the prospective study for 2014–2105). As mentioned previously (Section 4.4.1), excess influenza-attributable deaths, including those of patients hospitalized for a cardiovascular event, compared with the number of deaths estimated for patients hospitalized with a respiratory diagnosis was estimated in Québec as less than one third (see also Appendix 4); this excess is smaller than the multiplier of 2.8 (280%) described above. We nevertheless again broadened the possibility of an increase in the number of deaths by using a multiplying factor of 3 for the upper limit of the estimate of influenza-attributable deaths in the sensitivity analyses.

5 Influenza vaccine effectiveness

5.1 Literature review

Lower influenza vaccine effectiveness (VE) values compared to previous data have been shown in recent years following improvement of the estimation methodology and the increasingly frequent use of laboratory confirmation of influenza with sensitive tests. The development of the test-negative design(128) has also contributed to its increasingly frequent application around the world. This brought to light the wide variability in VE, according to season, circulation of influenza-specific subtypes and strains, age, type of vaccine, frequency of vaccine administration, etc.

One of the first meta-analyses, including 31 studies (17 randomized trials and 14 observational studies) based on the detection of influenza by culture or by PCR, published in 2012, concluded that there was a pooled efficacy of 59% for trivalent inactivated vaccine among adults aged 18–64 years(129). No good-quality study was identified by the authors for children aged 2–17 years or for individuals aged 65 years and older for the trivalent inactivated vaccine. The live attenuated influenza vaccine was effective in 9 of the 12 seasons among children aged from 6 months to 7 years, for an overall efficacy of 75%; no good-quality study of children aged 8–17 years was identified. The live attenuated influenza vaccine was not effective against the A(H1N1)pdm09 strain among children aged 2–17 years in the United States in 2013–2014 and 2015–2016, and against influenza B in 2015–2016, whereas during the same periods and for the same strains, the inactivated vaccine demonstrated a VE of > 60%(130–132). In light of these data, the Advisory Committee on Immunization Practices (ACIP) in the United States did not recommend the use of the live attenuated influenza vaccine for the 2016–2017 season(133) or for the 2017–2018 season(134). The live attenuated influenza vaccine continues to be used in Finland and the United Kingdom, given the finding of a VE > 40% in the observational studies in these 2 countries (135,136). The reasons for these differences are not yet known.

In a more recent meta-analysis of 35 studies identified until July 2014 (5 countries, 9 influenza seasons) using a test-negative design, among individuals aged ≥ 60 years, VE against medically attended influenza infections (including all types and subtypes) during the seasonal influenza epidemics was calculated as 52% (95% CI, 41% to 61%) during the seasons with a good strain match and as 36% (95% CI, 22% to 48%) during the seasons with a poor match(137). These studies were conducted among individuals aged ≥ 60 years who were generally healthy and living in the community, who are not necessarily representative of all the population of older adults. In a recent re-analysis of individual data, again among individuals aged ≥ 60 years, based on approximately half the sources used in the initial meta-analysis, Darvishian et al.(138) calculated a VE of 44% (95% CI, 23% to 60%) during the seasons with a good strain match and a VE of 20% (95% CI, 3% to 34%) during seasons with a suboptimal match.

VE could be lower among older adults: in the meta-analysis by Darvishian et al.(138), it was 33% among those aged 60–74 years, but 16% among those aged 75 years and older. In a European multicentre study conducted during the 2016–2017 season and including 27 hospitals in 10 countries (the Integrated Monitoring of Vaccines in Europe-Plus [I-MOVE+] network), VE against the A(H3N2) strain was 25% among individuals aged 65–79 years and 13% among those aged 80 years and older(139).

Since 2004, the Canadian Sentinel Practitioner Surveillance Network (SPSN) has published annual estimates of vaccine effectiveness in preventing influenza outpatient visits. According to this network, the overall VE (all subtypes and ages) against influenza ranged from 37% to 68% from 2004–2005 to

2016–2017, excluding the influenza pandemic season (2009–2010) and the 2014–2015 season(140) (see also Appendix 5). Vaccine effectiveness was exceptionally low, 9% (95% CI, -14% to 27%) in 2014–2015([81] and Appendix 5). It is worth noting that even if patients of all ages are eligible in the SPSN, few elderly patients participate in it and, in general, these are patients in better health than those who are hospitalized. The VE estimates reported among hospitalized adult patients in the CIRN-SOS network were generally lower than those in the SPSN, but they are not available for all the seasons. For example, during the 2014–2015 season, the VE against hospitalizations with the influenza virus (any type/subtype) in the CIRN-SOS network was -17% (95% CI, -49% to 8%) among all adult patients and -25% (95% CI, -65% to 5%) among individuals ≥ 65 years.

The 2014–2015 season was marked by the predominance of the A(H3N2) strain, which was responsible for the majority of influenza-associated hospitalizations and deaths(31,32). In the SPSN, VE against the H3N2 strain was -17% (95% CI, -49% to 8%); in the CIRN-SOS network, it was -22% (95% CI, -67% to -11%) for all adults and -33% (95% CI, -104% to 13%) for individuals aged ≥ 65 years(85,141). In Québec, VE against the H3N2 strain among hospitalized patients ≥ 65 years was -33% (95% CI, -104% to 13%)(86).

The major antigenic drift (genetic mutations) of the large majority of the influenza A(H3N2) viruses circulating during the 2014–2015 season in Canada resulted in a decline in vaccine effectiveness(85,141). In the United States, where 68% of the isolated strains had undergone antigenic drift, VE against medically attended infections and hospitalizations due to influenza A(H3N2) was estimated as 23% overall; and as 14% among individuals aged ≥ 50 years(142). Even apart from special situations like that of the 2014–2015 season, vaccine effectiveness against the A(H3N2) strain was lower relative to the other strains. According to a recent meta-analysis of 56 studies published between 2004 and 2015 using the test-negative study design and influenza confirmation by PCR, the average VE was 33% against influenza A(H3N2), 61% against influenza A(H1N1), and 54% against influenza B(143). According to the age groups, VE against influenza A(H3N2), influenza A(H1N1) and influenza B among children (< 20 years) was 43%, 69% and 56% respectively; among adults aged 20–64 years it was 35%, 73% and 54% respectively, and among individuals aged 60 years and older it was 24%, 62% and 63% respectively.

A meta-analysis published in November 2017 presents a pooled VE for the period of 2010–2011 to 2014–2015 (including 4 of the 5 seasons used for the economic analysis) of 41% among individuals aged 18–64 years and 37% among those aged 65 years and older. Among individuals aged 65 years and older, VE against the A(H3N2) influenza virus was 43% during the seasons with a good strain match, while VE was 14% when genetic mutations were observed in the circulating strains(144).

An update of recent data on influenza vaccines among healthy children and adults published by the Cochrane group in February 2018 concluded that there was very limited good-quality data on VE against the most severe consequences of influenza, such as hospitalization or death, within these groups, as well as on VE among children younger than 2 years(145,146). In an update regarding individuals aged 65 years and older, the authors concluded that the data available to date on VE against complications due to influenza were of low quality, insufficient or old, and did not provide clear guidance concerning the safety, efficacy or effectiveness of influenza vaccines in this age group(147).

5.2 Vaccine effectiveness used for the economic analysis

Given that the base-case scenario in the economic analysis was based on Québec's situation (disease burden and VE) during the 2011–2012 to 2015–2016 seasons, a VE of 40% was retained bythe CIQ members. An alternative base-case scenario with a VE of 60% was examined during an intermediate stage. In the sensitivity analyses, variations in VE ranging from 10% to 90% were explored.

Indirect effectiveness of the influenza vaccine among children aged 0–5 months

Several publications present data on the fact that the influenza vaccine during pregnancy protects mothers and newborns(119,148,149). The maximum indirect impact of vaccination for pregnant women on protection against the influenza among children aged 0–5 months during Québec's influenza season was estimated to be less than 4–6% (see details in Appendix 5). It was decided not to take it into account in the economic analysis, because the impact of this indirect effectiveness is considered negligible. A sensitivity analysis incorporating this effect showed a minimal impact on the cost effectiveness of the program.

6 Economic evaluation

6.1 Method

The economic evaluation of the influenza immunization program was performed by comparing its costs and benefits against a scenario without an influenza immunization program.

A static model was applied to the following age groups: 6–23 months, 2–4 years, 5–17 years, 18–59 years, 60–64 years, 65–74 years and ≥ 75 years. For each age group, stratification by presence or absence of a chronic condition was also applied. The scenario including influenza-attributable hospitalizations and deaths corresponding to the objectives of the PIIQ was initially considered in the economic analysis. The CIQ members deemed it necessary to also evaluate office visits and emergency department visits to be able to make more-informed decisions. Thus, the health outcomes analyzed were deaths, acute-care hospitalizations and visits (office visits and emergency department visits) associated with influenza. To take into account the deaths occurring outside acute-care hospitals, we added influenza-associated deaths among the residents of LTCFs to the deaths of patients hospitalized for influenza.

To quantify not only the number of lives saved but also the changes to patients' quality of life brought about by applying this program, we estimated QALYs (quality-adjusted life years) for each of the scenarios. QALYs are measured by adjusting the length of life obtained by the health outcome using utility scores (preference or acceptability) for health conditions corresponding to a scale ranging from 0 (death) to 1 (perfect health). One year of life in perfect health counts for 1 and one year of life in less good health counts for a fraction of a year (< 1).

Thus, to evaluate the program by comparing costs and effects, results are presented in the form of a ratio, which is, in fact, a profitability index (or return on investment). This ratio is the product of multiple effects, brought back to a single dimension referred to as ICER (incremental cost-effectiveness ratio). In our analysis, the ratio is equal to the cost difference between strategies A (current immunization scenario) and B (absence of immunization), divided by the difference in the QALYs gained with these 2 strategies. Thus, the ICER is expressed as $/QALY gained (saved).

The analysis was performed from a healthcare system perspective. The temporal effect of the vaccine was assumed to be 1 year; a discount rate of 3% per year in the base-case scenario was applied to life expectancy at birth and the QALYs. Life expectancy and health-adjusted life expectancy (HALE) were calculated using actuarial mortality tables (see Appendix 6.1A). Given the many problems in estimating life expectancy by the period approach (or by the actuarial mortality table) in subpopulations/subgroups with a chronic condition, such as the impossibility of taking into account the fact that excess mortality associated with the chronic condition may vary as a function of age upon diagnosis and the time elapsed since diagnosis (150,151), the same life expectancy and HALE values were applied to the whole population, regardless of the presence of a chronic condition. Herd immunity was not taken into account. The costs of managing the vaccination program and the special influenza vaccination projects of the MSSS were not considered, but the costs for the administration of the vaccines were included. Inflation based on the consumer price index for health care and personal care in 2015 set by the government of Canada was used in cost estimation. All the costs are reported in 2015 Canadian currency.

To estimate the maximum theoretical effect that could be achieved with the vaccination program, we also compared the current strategy against a third scenario in which the entire population would be vaccinated (vaccine uptake = 100%).

Several base-case scenarios were explored. The parameters used with the corresponding sources and the discussion and approval dates by the CIQ members are presented in Appendix 6. Most of the parameters come from Québec sources. Vaccine uptake and disease burden by age group and presence or absence or a chronic condition, vaccine effectiveness and healthcare system costs are based on the data measured in Québec over the past 5 years (2011–2012 to 2015–2016). When local parameters were not available, estimates derived from the literature were retained. Details on the approaches used for estimating vaccine uptake, influenza disease burden (medically attended infections, hospitalizations and deaths) and VE are presented in chapters 3, 4 and 5.

Health outcomes and costs in the theoretical scenarios (1) absence of vaccination program and (2) vaccination for the entire population were derived from the current situation (2011–2012 to 2015–2016 seasons), taking into account the disease burden, vaccine uptake and VE observed in Québec.

Deterministic sensitivity analyses were performed to estimate the impact of the most significant parameters. The range of variation in these parameters is based on the extreme values observed during certain influenza seasons, and on the lower and upper limits of the confidence intervals for the estimates of the parameters in Québec or reported in the literature. A univariate analysis was performed to examine the effect of the variations of a single parameter on the ICER ($/QALY) of the program. A **probabilistic sensitivity analysis** was also performed to take into account the joint effects of multiple parameter variations. A triangular distribution was assigned to each parameter examined and the probabilistic sensitivity analysis was undertaken via 5000 iterations of the model.

To explore different options for the threshold value of the willingness to pay, we examined the economic evaluation guidelines issued by the Canadian Agency for Drugs and Technologies in Health (CADTH)(152,153), economic evaluation practices in Canada(154), WHO recommendations(155), and the recommendations used in other countries (the United Kingdom[156] and the United States[106,107]). The following thresholds were used: (1) $45,000 (corresponding to the per capita gross domestic product in Canada in 2015); (2) $100,000 (GDP multiplied by 2); and (3) $135,000 (GDP multiplied by 3). The threshold ultimately retained by the CIQ members was $45,000.

Detailed results concerning the parameters to be included in the economic analysis and in the different base-case scenarios examined, the sensitivity analyses and the probabilistic analyses were presented and discussed at CIQ meetings with attendance in June 2016, September 2016, December 2016, March 2017 and June 2017, as well as by conference call in October 2016, April 2017 and May 2017.

The final base-case scenario retained was the one including medically attended influenza infections and hospitalizations, vaccine effectiveness of 40% and a willingness to pay a threshold of $45,000. The parameters used in the base-case scenario can be found in Appendices 6.1A and 6.1B.

6.2 Results

6.2.1 BASE-CASE SCENARIO

Entire population

Table 5 presents the estimates for annual influenza-related health outcomes in Québec and costs associated with the vaccination program and the disease. The situations presented are the current situation, a scenario without vaccination (vaccine uptake of 0%) and a theoretical scenario in which the entire population would be vaccinated (vaccine uptake of 100%).

The annual influenza disease burden in Québec is currently estimated to be around 135 000 cases, including 6194 hospitalizations and 282 influenza-attributable deaths (Table 5). Compared with the absence of vaccination, the current program prevents more than 11 000 cases (including 1711 hospitalizations) and saves 116 lives. In the current situation, 2647 QALYs are lost due to influenza, with most being due to deaths (1414 due to deaths, 1016 due to medically attended infections and 216 due to hospitalizations). Compared with the absence of vaccination, 596 QALYs are gained (459 due to deaths, 73 due to medically attended infections and 63 due to hospitalizations). The annual average cost of the disease estimated for Québec's healthcare system for the total Québec population is ≈ $54 million, with most of it (≈ $42 million) being associated with hospitalizations, and around 1/5 (≈ $11 million) associated with visits (office and emergency department visits, including the cost of medications covered by the public health insurance plan). The costs associated with hospitalizations are higher than those associated with medically attended infections, and even if we observe many more medically attended infections than hospitalizations, hospitalizations have a greater impact on the cost effectiveness of the program.

The annual average cost estimated for the vaccination program is ≈ $39 million, of which one third (≈ $12 million) is allocated to the purchase of vaccines and two thirds (≈ $27 million) to administration.

The total annual cost of the program and the disease for the healthcare system is estimated to be ≈ $93 million. Compared with the absence of a program, the total cost is ≈ $26 million higher (≈ $39 million more for the program and ≈ $13 million less for the disease, see Table 5).

In the base-case scenario compared with the absence of a vaccination program, the ICER is $42,938 per QALY, which is below the threshold of $45,000. At this threshold, we can therefore conclude that the program is cost effective overall.

In the theoretical situation of vaccination for the entire population (vaccine uptake = 100%), we would prevent a total of 45 974 cases, with the vast majority representing medically attended infections (44 603 medically attended infections, 1372 hospitalizations and 74 deaths); the gain in QALY would be 706 more than that in the current situation (Table 5). In that situation, the program would cost ≈ $171 million (4 times more than the current situation), while the disease would cost ≈ $13 million less (25% less) than the current situation. Assuming a threshold of $45,000, the program would no longer be cost effective in these conditions: the ICER for the total population vaccination scenario, compared with the current situation, is $168,368 per QALY.

Table 5 Annual health outcomes related to influenza in Québec and costs associated with the vaccination program and the disease, current situation (2011–2012 to 2015–2016), scenario with the absence of vaccination (vaccine uptake = 0%), and scenario with vaccination of the entire population (vaccine uptake = 100%)

Outcomes and costs	Current situation[1]	Scenario with vaccine uptake = 0[2]	Difference with current situation	Scenario with vaccine uptake = 100%[2]	Difference with current situation
Health outcomes					
Total no. of cases (visits + hospitalizations)	134 736	146 126	11 389	88 762	-45 974
Visits	128 542	138 220	9 678	83 939	-44 603
Hospitalizations	6 194	7 905	1 711	4 822	-1 372
Deaths[3]	282	398	116	209	-74
Total QALYs lost	**2 647**	**3 243**	**596**	**1 941**	**-706**
QALY deaths	1 414	1 873	459	1 109	-305
QALY hospitalizations	216	280	63	170	-46
QALY visits	1 016	1 090	73	662	-355
Costs					
Total costs (program + disease)	**$92,622,772**	**$67,031,754**	**-$25,591,019**	**$211,499,973**	**$118,877,201**
Program cost[4]	$39,024,392	$0	-$39,024,392	$170,887,567	$131,863,175
Vaccine purchases	$11,686,880	$0	-$11,686,880	$54,316,729	$42,629,849
Administration	$27,337,512	$0	-$27,337,512	$116,570,838	$89,233,326
Disease cost[5]	$53,598,381	$67,031,754	$13,433,373	$40,612,406	-$12,985,974
Hospitalizations	$42,314,986	$54,786,656	$12,471,670	$33,168,119	-$9,146,867
Visits[6]	$11,283,395	$12,245,098	$961,703	$7,444,287	-$3,839,108
ICER (-$/QALY)			**$42,938**		**$168,368**

1 The parameters used in this scenario correspond to the average of the last 5 influenza seasons in Québec (2011–2012 to 2015–2016) for vaccine uptake, disease burden by age group, presence or absence of chronic condition, vaccine effectiveness and healthcare system costs.

2 Health outcomes and costs in this scenario are derived from the current situation, taking into account current vaccine uptake.

3 Deaths attributable to influenza (all the deaths among patients with influenza aged < 65 years; 2/3 of the deaths among patients with influenza aged ≥ 65 years). The deaths observed outside acute-care hospitals (in LTCFs) are included.

4 Only healthcare system costs are considered; whereas administrative costs (promotion of the vaccination campaign, management of the vaccines [storage, transportation, losses], etc.). and the costs related to adverse events following immunization are not included.

5 Only healthcare system costs are considered.

6 Including the costs of prescription drugs covered by the public health insurance plan.

IC: intensive care.

QALY: quality-adjusted life year.

ICER: incremental cost-effectiveness ratio.

Age groups

Although the current program is cost effective overall with a threshold of $45,000, the situation varies according to age group. This section presents the summary of the analyses by age group; further details by age group can be found in Appendix 6.2.

Contrary to the analysis for the entire population where the majority of QALY lost was attributable to deaths, in the healthy population aged 6 months to 64 years and among young individuals aged from 6 months to 17 years with a chronic condition, the majority of QALY lost are attributable to medically attended infections (Figure 4).

The costs of the disease are dominated by those associated with medically attended infections in the healthy population aged 6 months to 59 years; in the other groups, hospitalizations cost more than medically attended infections (Figure 5).

The number needed to vaccinate (NNV) to prevent an influenza-associated visit (office and emergency department) ranges from 24 (healthy children aged 6–23 months) to 14 (6–23 months with a chronic condition) to 575 (healthy adults aged 65–74 years) to 360 (adults aged 65–74 years with a chronic condition) (Figure 6, see also Appendix 6.3). The NNV to prevent an influenza-associated hospitalization among children aged 6–23 months is 1157 individuals if they are healthy and 79 if they have a chronic condition. For adults aged 18–59 years, it is 44 446 for healthy individuals and 3526 for those with a chronic condition. To prevent one death among healthy individuals, we need to vaccinate 300 130 children aged 6–23 months, or 5.9 million individuals aged 18–59 years. The NNV to prevent one death among individuals with a chronic condition ranges from 254 416 among children aged 6–23 months to 2.1 million among children aged 5–17 years (Figure 6). Given that the same influenza-associated death rates were used for healthy children and children with a chronic condition (see Section 4.4.2), the NNV to prevent a death should be similar in both groups. However, vaccine uptake is different among healthy children and those with a chronic condition. Thus, the NNVs to prevent a death, calculated from the unvaccinated population, are slightly different (Figure 6).

Among the groups with a chronic condition (all included in the current program), the program is cost effective in the extreme age groups (6 months to 4 years and 65 years and older); it is not cost effective for individuals aged 5–64 years (Figure 7). The program is not cost effective for any of the groups in good health, even the groups currently included in the program (6–23 months and 60 years and older) (Figure 7). However, it approaches the threshold of $45,000 for healthy individuals aged 75 years and over.

Figure 4 **QALYs lost in the current situation (2011–2012 to 2015–2016), by age group and presence or absence of a chronic condition**

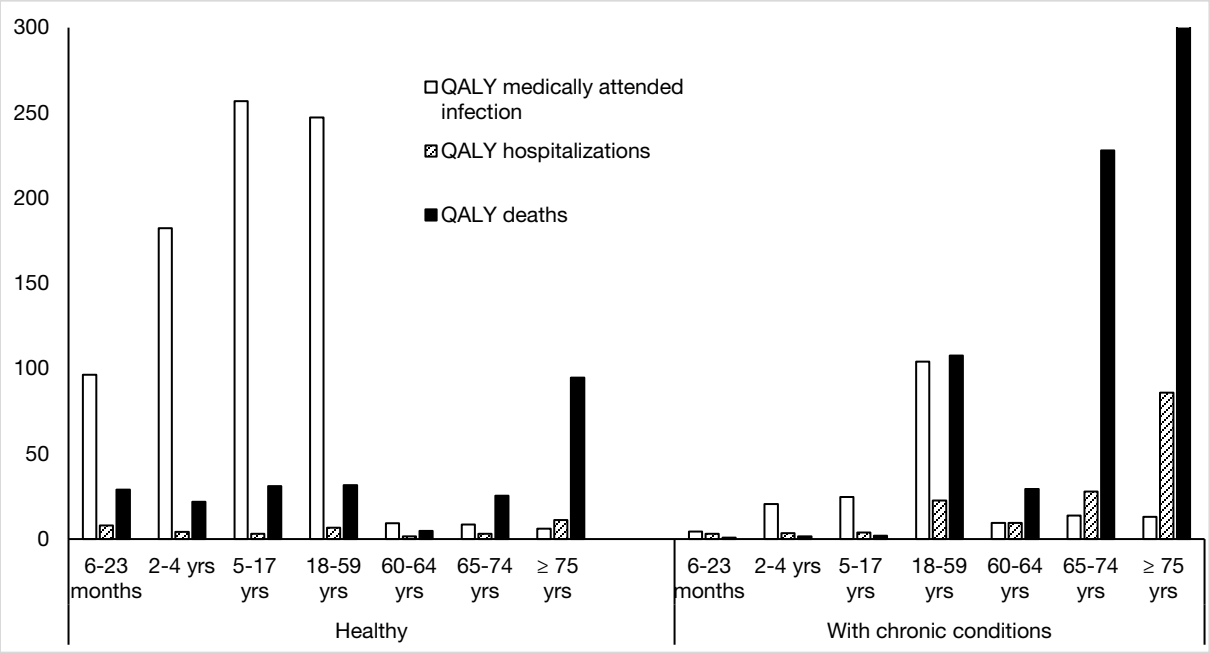


Figure 5 **Cost of the program and the disease (hospitalizations and visits) in the current situation (2011–2012 to 2015–2016) in Québec, by age group and presence or absence of a chronic condition**

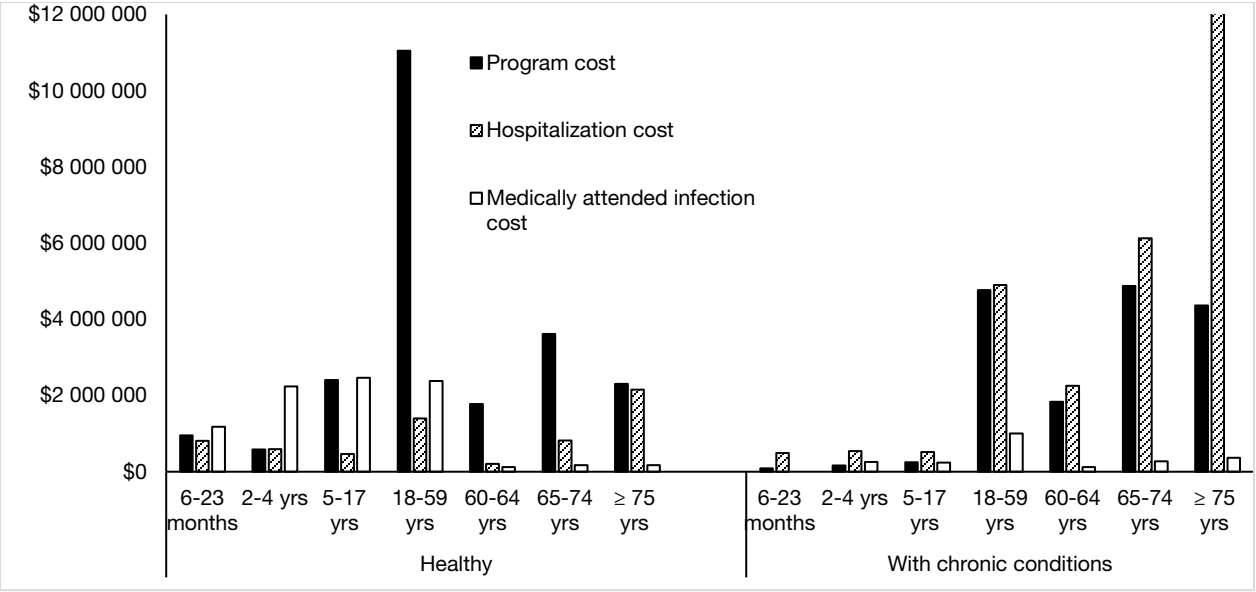
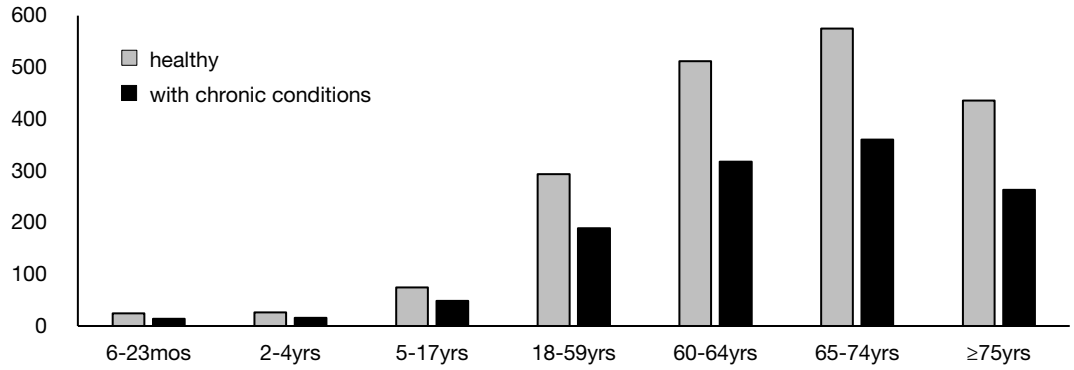
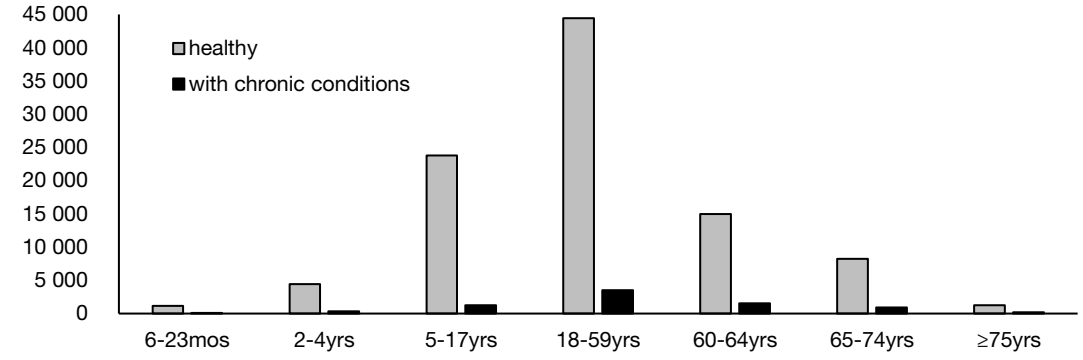


Figure 6 Number needed to vaccinate against influenza to prevent a visit (office and emergency department), a hospitalization and a death among healthy individuals and individuals with a chronic condition, by age group in Québec

Number needed to vaccinate to prevent an influenza-associated visit (office and emergency department)



Number needed to vaccinate to prevent an influenza-associated hospitalization



Number needed to vaccinate to prevent an influenza-associated death

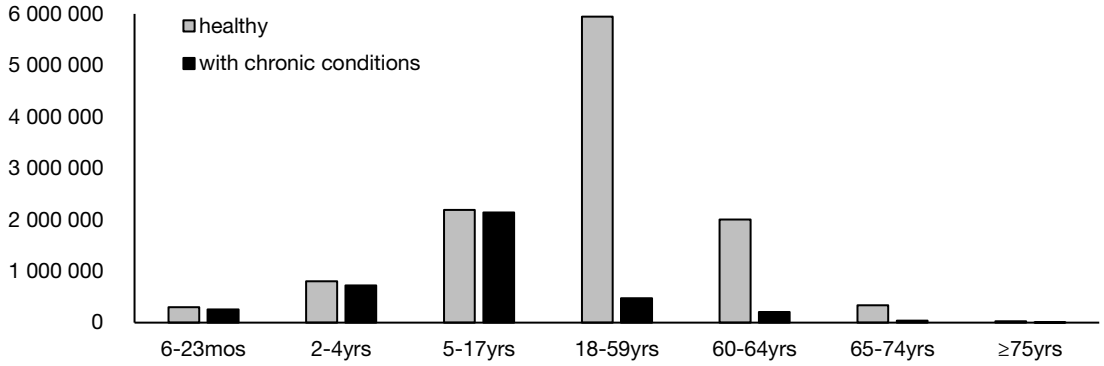
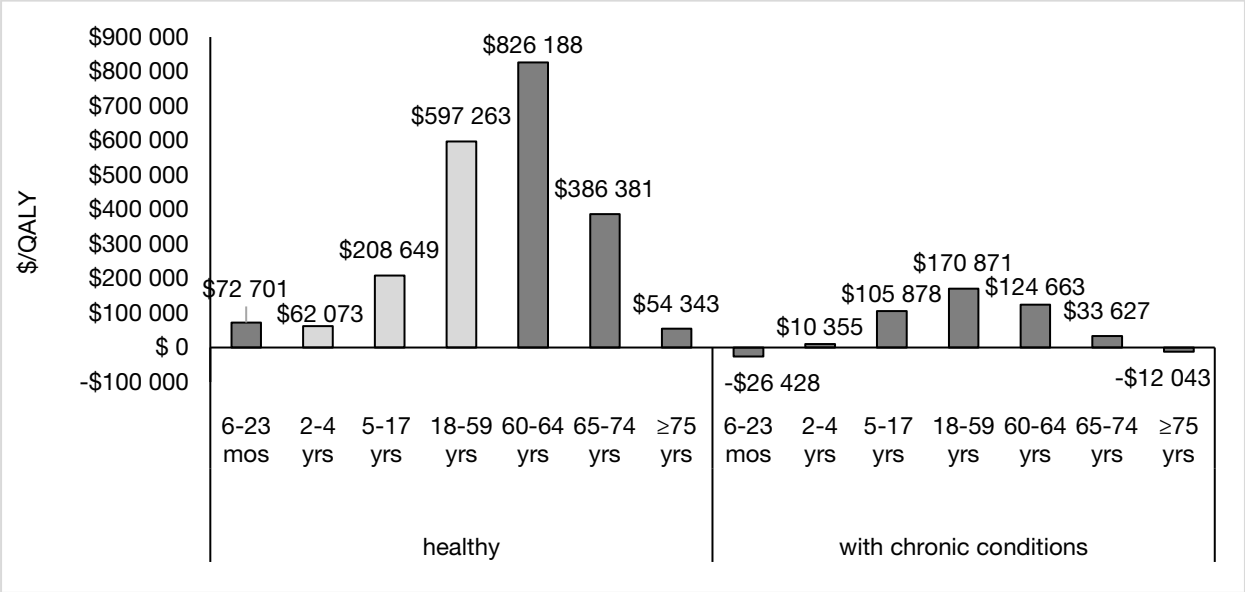


Figure 7 ICER ($/QALY) of the current program in Québec, compared with the absence of a program, by age group and presence or absence of a chronic condition



Note: Dark grey represents the groups included in the current program.

6.2.2 SENSITIVITY ANALYSES

Table 6 summarizes the results of the deterministic sensitivity analyses. This table presents the ICER obtained in the base-case scenario for each group examined, along with the impact of the most significant variables. Further details can be found in Appendix 6.4. It also presents the probability of achieving the threshold of $45,000 in the probabilistic analysis combining all the variations of the parameters examined. For example, in the group of healthy children aged 6–23 months, none of the variations in the hospitalization rate or mortality rate lead to an ICER < $45,000 per QALY, but multiplying the visit rate by 1.75 or a VE ≥ 60% would produce an ICER < $45,000 per QALY. A detailed presentation of the results of the probabilistic analysis for the different groups and different outcomes can be found in Appendices 6.5A and 6.5B.

Among some groups for whom the program was not cost effective in the base-case scenario, different parameter variations could lead to a program ICER below the threshold of $45,000 (Table 6). These groups are: healthy children aged 6–23 months and 2–4 years (for increases in the visit rates > 1.5 times the rate in the base-case scenario and a VE > 60%, youth aged 5–17 years with a chronic condition (for increases in the visit rates > 2.5 times the rate in the base-case scenario and VE > 80%), and individuals aged 60–64 years with a chronic condition (for increases in the hospitalization rates > 2.0 times the rate in the base-case scenario and VE > 70%). None of the parameter variations used made the program cost effective at the threshold of $45,000 in the groups of healthy individuals aged 5–74 years and of those aged 18–59 with a chronic condition.

Table 6 Summary of the results of the sensitivity analyses in the economic analysis

Age groups		Baseline scenario, ICER ($/QALY)	Deterministic sensitivity analysis				
			Impact of **univariate** variation of parameters				**Probabilistic analysis**, probability for the threshold of $45,000[2]
			Visit rate (variations[1] from 0.2 to 3)	Hospital. rate (variations[1] from 0.25 to 3)	VE (variations from 10% to 90%)	Mortality rate (variations[1] from 0.5 to 3.0)	
6–23 months	Healthy	$72,701	**> x1.75**	Not CE[3]	≥ **60%**	Not CE[3]	**58%**
	With a CC	**-$26,428**	**CE**[4]	< x0.25	**CE**[4]	**CE**[4]	**100%**
2–4 years	Healthy	$62,073	**> x1.5**	Not CE[3]	≥ **60%**	Not CE[3]	**65%**
	With a CC	**$10,355**	≤ x0.25	**CE**[4]	< 30%	**CE**[4]	**100%**
5–17 years	Healthy	$208,649	Not CE[3]	Not CE[3]	Not CE[3]	Not CE[3]	0%
	With a CC	$105,878	**> x2.5**	Not CE[3]	≥ **80%**	Not CE[3]	32%
18–59 years	Healthy	$597,263	Not CE[3]	Not CE[3]	Not CE[3]	Not CE[3]	0%
	With a CC	$170,871	Not CE[3]	Not CE[3]	Not CE[3]	Not CE[3]	13%
60–64 years	Healthy	$826,188	Not CE[3]	Not CE[3]	Not CE[3]	Not CE[3]	0%
	With a CC	$124,663	Not CE[3]	**> x2.0**	≥ **70%**	Not CE[3]	47%
65–74 years	Healthy	$386,381	Not CE[3]	Not CE[3]	Not CE[3]	Not CE[3]	0%
	With a CC	**$33,627**	**CE**[4]	≤ x0.75	≥ **40%**	≥ **x0.7**	**93%**
75+ years	Healthy	$54,343	Not CE[3]	**> x1.25**	≥ **50%**	≥ **x1.3**	**83%**
	With a CC	**-$12,043**	**CE**[4]	< x0.25	**CE**[4]	**CE**[4]	**100 %**

ICER: incremental cost-effectiveness ratio.

QALY: quality-adjusted life year.

CC: chronic condition.

Note: The cells not in bold reflect scenarios that are not cost effective; the cells in bold reflect scenarios that are cost effective (ICER ≤ $45,000 per QALY). Further details on the sensitivity analyses can be found in Appendices 6.4 and 6.5.

1 Variations x times the rate in the base-case scenario.

2 Probability of achieving an ICER ≤ $45,000 per QALY for the combined variations in the visit rate from 0.2 to 3 times the rate in the base-case scenario; hospitalization rate from 0.25 to 3 times the rate in the base-case scenario; mortality rate from 0.5 to 2.8 times the rate in the base-case scenario, and VE from 30% to 70%.

3 Not CE: not cost effective (ICER > $45,000 per QALY) for all the variations appearing in the column headings.

4 CE: cost effective (ICER ≤ $45,000 per QALY).

6.3 Discussion

The economic analysis revealed the fact that, from a healthcare system perspective, the current influenza immunization program is cost effective overall, compared with the absence of a program, at the $45,000 threshold (ICER = $42,938 per QALY). Vaccination for the total population (vaccine uptake = 100%), compared with the current situation, would not be cost effective (ICER = $168,368 per QALY).

There are significant differences, depending on the age group. The program is cost effective for children aged 6 months to 4 years and for adults aged 65 years and older with a chronic condition in the base-case scenario. It is not cost effective for individuals aged 5 to 64 years with a chronic condition in the base-case scenario, but could become cost effective in the case of an increase in the visit rate of at least 2.5 times or a VE ≥ 80% for those aged 5–17 years, and in the case of an increase in the hospitalization rate of at least 2.0 times and a VE ≥ 70% for individuals aged 60–64 years.

None of the parameter variations examined led to a considerable improvement in the program's cost effectiveness for adults aged 18–59 with a chronic condition. It was not possible to perform more refined analyses by chronic condition subtype, owing to the lack of data on this topic. Given that chronic conditions are very heterogeneous with a spectrum of severity ranging, for example, from well-controlled mild diabetes to severe immunosuppression, we cannot exclude the fact that, among the most vulnerable patients aged 18–59 years, the program could be cost effective.

The program is not cost effective at the $45,000 threshold for healthy children aged 6 months to 4 years, the ICER slightly exceeding this threshold among ages 6–23 months ($72,701) and among ages 2–4 years ($62,073). For ages 6–23 months, it becomes cost effective in the case of a multiplication of the visit rate by at least 1.75 or a VE ≥ 60%. For ages 2–4 years, it becomes cost effective in the case of a multiplication of the visit rate by at least 1.5 or a VE ≥ 60%. No reasonable increase in the hospitalization rates or mortality rates in these 2 groups has a significant impact on cost effectiveness. The program is not cost effective for healthy individuals aged 5–74 years, neither in the univariate analyses nor in the probabilistic analyses, considering the joint effect of the variation of several parameters.

The parameters used come mostly from Québec sources; they were discussed in detail and approved by the CIQ members. We believe that the assumed values are reasonable and reflect the best knowledge to date. The burden of influenza-attributable hospitalizations and deaths is based on the values observed in Québec during the past 5 influenza seasons, including 2 severe seasons, and takes into account vaccine uptake in Québec during the same seasons. These estimates were calculated from the prospective study conducted in acute-care hospitals in Québec and were adjusted to take into account a potential underestimation of the hospitalizations and deaths among patients with respiratory disorders, due to the fact that some patients may have been missed by the methodology used, or due to the laboratory test's lack of sensitivity in the case of a late visit. Statistical models based on Québec administrative databases were also used, to measure the uncertainty of the parameters obtained and to assess the range of possible values for the sensitivity analyses. Hospitalizations also included nosocomial infections due to influenza.

The average VE value used in the base-case scenario takes into account the values observed in Québec and Canada during the same seasons. The costs used reflect the real situation during these 5 seasons and take into account recent changes in the healthcare system, including the recent changes in physician compensation. In fact, the decrease in the fees for vaccination visits had an impact on the decrease in program costs and the increase in its cost effectiveness. Some of the

variations of the parameters considered in the sensitivity analyses may have been exaggerated, but they are based on different estimation methods and are plausible because they could occur during some particular seasons.

In general, we believe that the parameters used in the base-case scenario benefited the cost effectiveness of the PIIQ. For example, the values of influenza disease burden probably lie within the maximum possible values, given that two severe influenza seasons were used to measure this burden, including one extreme season with a vaccination effectiveness ranging from very low to null. We should consider the fact that influenza co-infections with other respiratory viruses were not taken into account: all the influenza-confirmed infections were considered to be associated with influenza, even if, for a significant proportion of the hospitalizations, especially among children, more than one respiratory virus was detected(24–27). The severity of the mixed infections could be due to influenza or to other respiratory viruses.

Furthermore, the cost of the program was underestimated because promotional and management costs were not included. The adverse events of the influenza vaccine were not considered in the economic analysis, but they may have a certain impact on the costs incurred by the healthcare system and by the public. Annual changes to the vaccine lead to a certain level of unpredictability regarding the vaccine's safety profile. Further details on short-term and long-term adverse events can be found in the section on vaccine characteristics and safety (Section 9.2).

Comparison with other economic analyses

Most of the economic evaluations of the impact of influenza immunization are predictive, that is, they are performed at a pre-implementation stage, in order to inform decision makers about the added value of the changes to make to the existing programs. Post-implementation or retrospective analyses are less common, but they offer the possibility of using real data to assess the existing programs and to generate more precise estimates of program impact, compared with predictive evaluations(158).

To our knowledge, our economic analysis is to date the only prospective economic evaluation designed to examine the cost effectiveness of an existing influenza immunization program, compared with the absence of such a program, based on real data observed during several influenza seasons from a healthcare system perspective. Given the long existence of the program and the major changes that have occurred in the healthcare system, it is not realistic to obtain pre-implementation data. To establish a basis for comparison (absence of a program), we applied the vaccine uptake and the VE measured in the Québec population to the current situation (disease burden). This procedure is contrary to predictive models where one starts from the current situation to evaluate a future change to the program.

Several economic evaluations of influenza immunization have been performed in recent years(159–175). A brief summary of these publications can be found in Appendix 6.6.

Limitations of the economic evaluation presented in this report

The limitations of this economic analysis are the following:

1) The uncertainty of specific parameters, such as the estimation of the proportion of individuals with a chronic condition by subgroup, and the lack of precision regarding the severity of the chronic conditions and their association with influenza complications. Sensitivity analyses by varying the proportion of chronic conditions in the Québec population did not show that this parameter had a significant impact on the results. More refined analyses targeting the most vulnerable populations

would be relevant; we were not able to perform them owing to the lack of data necessary for this evaluation.

2) The use of a single VE value in all the subgroups examined in the base-case scenario. One could expect a better VE in the younger and healthier population, and a lower VE among older patients or patients with certain chronic conditions. To compensate for this limitation, variations of VE from 10% to 90% were applied in the sensitivity analyses (see Appendices 6.4 and 6.5).

3) The lack of consideration of herd immunity. Given that children are known to be major and effective influenza transmitters in the community, vaccinating them with an effective vaccine could, theoretically, reduce the transmission of influenza among them, in their families, in schools and in the community. For this indirect effect (herd immunity) to take place, significant vaccine uptake must be achieved. A minimum uptake of 50% was necessary to observe an indirect effect among unvaccinated individuals in the context of a school-based vaccination campaign(176). An uptake of 83% among children aged 36 months to 15 years was achieved in a study where the protection of unvaccinated individuals in the community was reported(177). It is worth mentioning that the former study was conducted in a relatively young Hutterite community with few seniors and with little contact outside the community. Another challenge in extrapolating these results is their dependence on (1) the structure of contacts by age group; and (2) the behaviour of infected persons, which can change in the presence of respiratory symptoms and therefore modify the probability of transmission(166); the two can vary, depending on the country or period under study. In Québec, in the context of the low vaccine uptake observed (20% among ages 6–23 months, 10% among ages 2–17 years), herd immunity is unlikely to play a significant role in the population's overall protection against influenza.

4) The lack of analysis by influenza type and subtype and by type of influenza vaccine. Given that the analysis is based on parameters observed in Québec, the use of aggregate data should be valid because it takes into account the real distribution of influenza strains in the population and of VE, as well as the real costs of the vaccines used in Québec.

5) The use of the same HALE value in the healthy population and in the population with a chronic condition. The HALE among individuals with chronic conditions could be expected to have been overestimated, while it was underestimated among healthy individuals. The impact on the economic evaluation would be the underestimation of the ICER among individuals with a chronic condition and its overestimation among healthy individuals.

6) The societal perspective was not considered. On the one hand, the addition of non-medically attended diseases and their impact on quality of life, the use of over-the-counter medications, or the impact of the disease on work absenteeism and loss of productivity would increase cost effectiveness. On the other hand, the addition of the decrease in quality of life or the costs associated with adverse effects following vaccination would reduce the ICER. Note that, in several countries, it is recommended to include solely direct healthcare system costs in their health-technology assessment guidelines(178).

7 Program objective and immunization strategy

Influenza can cause a spectrum of effects ranging from mild symptomatic infection to hospitalization and death.

Although the economic evaluation took into account medically attended influenza infections, the CIQ recommends that the **primary objective of the PIIQ should be to reduce influenza-associated hospitalizations and deaths.**

To attain this objective, the CIQ recommends **a targeted vaccination strategy for specific groups based on age and presence of a health condition at high risk for influenza-associated hospitalizations and death.** However, the PIIQ will not have the expected impact unless the targeted individuals are reached and vaccinated. The decline in vaccine uptake observed in recent years in the groups of individuals at highest risk for complications suggests that maintaining the current strategy will not make it possible to reach a large proportion of the targeted individuals. This report identifies the groups that should be prioritized instead of dispersing the efforts to reach individuals at lower risk. **A vaccine uptake of at least 80% should be achieved in the groups at high risk** for influenza-associated hospitalization and death and targeted by the PIIQ**,** owing to the presence of a chronic condition or their age.

8 Approach used for the decision making regarding the inclusion or not of each group in the PIIQ

Following the different CIQ meetings held during the work of revising the PIIQ, there was no consensus on the addition or withdrawal of specific target groups considered in the program. Consequently a strategy by questionnaire based on the Delphi method(179–181) was selected to make the decision-making process more transparent and to reach a majority recommendation for each of the groups considered in the program. A questionnaire was developed according to age group and the presence of a chronic condition and was designed to determine the level of agreement of the CIQ members on whether or not to include each group in the PIIQ, as well as the criteria playing a role in their decisions. Criteria based on the analytical framework by Erickson and De Wals(182), such as economic considerations, vaccine safety, compliance, and program acceptability and feasibility were used.

A detailed description of this approach can be found in Appendix 7.

The considerations by group used in the decision-making process are described in the following section.

8.1 Summary of the considerations by group

8.1.1 Groups considered in the economic analysis

- **Unchanged groups**

Maintenance of inclusion

Groups with chronic conditions

For the groups with chronic conditions for which the program was proven to be cost effective (6–23 months, 2–4 years, 65–74 years, and 75 years and older), the CIQ members unanimously decided to keep them in the program.

For the groups with chronic conditions for whom the program is not cost effective based on established criteria (5–17 years, 18–59 years and 60–64 years), other criteria played a role in the decision to recommend their maintenance in the program. It was mentioned that although the program is not cost effective for these groups considering the $45,000 threshold, the results are much more favourable than those for the healthy groups (see Figure 7). Disease burden is more significant among patients with a chronic condition, compared with healthy individuals. Consequently, the number needed to vaccinate to prevent one case in the groups with chronic conditions, compared with the healthy groups, is approximately 1.5 times lower for medically attended infections, up to 19 times lower to prevent a hospitalization, and up to 13 times lower to prevent a death.

One of the elements that generated considerable discussion among the CIQ members was the fact that chronic conditions are very heterogeneous and that the risk of influenza-associated complications is not necessarily comparable across the full continuum of severity of chronic conditions. The authors of a systematic review and meta-analysis including 234 articles (239 studies) and 610 782 participants analyzed the quality of the evidence supporting the fact that certain groups are considered to be at high risk for influenza-related complications(183,184). The authors performed a systematic review of studies presenting

associations between at least one potential risk factor (age, chronic condition, pregnancy, ethnicity) and different severe outcomes or complications of influenza (pneumonia, hospitalization, admission to an intensive care unit, ventilator support or death) among patients with pandemic influenza (183 studies) or seasonal influenza (56 studies), along with a meta-analysis, in order to calculate measures of global effect and to appraise the heterogeneity of the studies. A large majority of the studies (92%) used laboratory tests to confirm influenza virus infection. The quality of the evidence was evaluated using GRADE (Grading of Recommendations Assessment, Development and Evaluation)(185). In the studies including seasonal influenza, the presence of at least one risk factor was associated with pneumonia, admission to hospital or to an intensive care unit, and death. Significant differences were noted according to the risk factor included in the analysis. For all the combinations examined, the quality of the evidence was deemed to be low or very low. The authors recommended that public health organizations and policy makers should acknowledge the low quality of the evidence supporting recommendations for influenza vaccination for individuals deemed at high risk for influenza, and the need for rigorous studies with good interpretation of the associations between influenza-related risk factors and complications revealed by the different studies.

Some more severe chronic conditions are likely to be more significant risk factors for influenza-related complications, compared with less severe or well-controlled conditions, but the lack of evidence to date does not permit clear identification of the most vulnerable individuals. The inclusion of all chronic conditions regardless of the severity of the condition could be a strategy to ensure that very vulnerable individuals in each of the groups with chronic conditions examined might benefit more from vaccination.

Further reasons that led the CIQ members to lean favourably toward maintaining all the groups with chronic conditions are: acceptability by health professionals and by the public, coherence with other provinces and other countries, consistency with the overall program, and the importance of individual protection. Vaccination uptake is better among individuals with chronic conditions compared with healthy groups, but it is far from optimal. It is not known if the most vulnerable patients are better reached because the vaccine uptake obtained in the surveys is probably diluted across the chronic conditions. Specific data by type or severity of chronic condition are not available for the moment. Implementing specialized immunization structures in tertiary-care centres where patients with chronic conditions have frequent contact with the healthcare system could improve access to vaccination by these patients and their family contacts(186) and therefore increase vaccine uptake in these groups.

Healthy group

The only healthy group which the CIQ recommends maintaining in the program is the one of individuals aged 75 years and older. In this group, the cost-effectiveness threshold of $45,000 is only slightly exceeded ($54,343). The program nevertheless becomes cost effective in this group with the multiplication of the hospitalization rate by 1.25, the multiplication of the mortality rate by 1.3, or a VE $\geq$ 50%. The probabilistic analysis shows that the probability of being cost effective at the $45,000 threshold in this group is 83%.

The CIQ recommends that the PIIQ should include all individuals with a chronic condition at risk for influenza-related complications, and healthy individuals aged 75 years and older.

Maintenance of exclusion

Healthy children aged 2–4 years

Following the 2012 evaluation of the relevance of including this group in the PIIQ, which included an economic analysis(187), the CIQ did not recommend its addition. Compared with the 2012 analysis, several elements were updated in line with current knowledge and recent cost changes, which led to a decrease in the ICER estimated for this age group. The parameters included in this economic evaluation that had a significant impact on this decrease are: (1) the fee for a vaccination visit (2 times lower) relative to the fee considered in 2012; (2) the inclusion of an influenza-attributable death rate two times higher in 2017 than in 2012; (3) the inclusion of QALYs associated with medically attended infections and hospitalizations (only the QALYs associated with death were included in 2012). For example, the cost effectiveness ($/QALY) in the current economic analysis without the QALYs lost due to medically attended infections and hospitalizations (including only the QALYs lost due to death) would be $497,013, compared with the estimate of $574,092 in 2012.

Although the cost-effectiveness estimate in the current evaluation is better than in 2012, it does not reach the $45,000 threshold. Medically attended infections are the main component that contributed to this result: the ICER would have been $583,056 if medically attended infections had not been included in the economic analysis.

The other elements supporting the decision to maintain the exclusion of the group of healthy children aged 2–4 years from the PIIQ following the 2012 report(187) have remained unchanged. In addition to the argument that the disease burden in this group is composed especially of medically attended infections (outcomes not targeted by the objectives of the PIIQ, see Chapter 7), the other elements are: (1) the program's difficulty in reaching children at high risk for hospitalization and death, and the need to concentrate vaccination efforts on these individuals rather than dilute them on individuals at lower risk; (2) the challenges regarding program acceptability and feasibility; and (3) the uncertainties about repeated influenza vaccination and its long-term safety.

Healthy children aged 5–17 years

The disease burden in this group is very low; it is by far dominated by outpatient visits. Very few hospitalizations are observed (32 676 visits and 102 hospitalizations per year in Québec) and deaths are rare. The ICER in this group ($208,649 per QALY) is very far from the set threshold of $45,000. In addition, none of the parameter variations considered reasonable, even during severe influenza seasons, led to a significant change; in the probabilistic analysis, the probability of being cost effective at the $45,000 threshold is 0%. The other elements mentioned in the preceding paragraph regarding the healthy group aged 2–4 years also apply to the healthy group aged 5–17 years.

Healthy individuals aged 18–59 years

As in the previous group, the disease burden in this group is very low; it is once again dominated by outpatient visits (29 644 per year in Québec); few hospitalizations (n = 196) are observed and deaths are exceptional. The ICER in this group ($597,263 per QALY) is even more further from the set threshold than in the healthy groups of children aged 2–4 years and 5–17 years. If only hospitalizations are considered, the ICER is $4.5 million per QALY. None of the variations of the parameters led to a significant change with regard to the set threshold. In the probabilistic analysis, the probability of being cost effective at the $45,000 threshold is 0%. Long-term safety considerations are also not negligible in this group, as well as the potential issues related to repeated vaccination.

The CIQ recommends that healthy individuals aged 2–59 years should not be included in the PIIQ.

- **Groups for which a change is recommended in the PIIQ**

Healthy children aged 6–23 months

In 2004, the Advisory Committee for Immunization Practices (ACIP) in the United States and the National Advisory Committee on Immunization (NACI) in Canada recommended, for the first time, influenza vaccination for healthy children aged 6–23 months(188,189). This decision was based on a hospitalization rate in this group that was comparable to that observed in the other groups considered to be at high risk for influenza. A large number of pediatric deaths observed during the 2003–2004 season following the emergence of a new strain of A(H3N2) influenza(101) contributed to this decision. Following the recommendations by the NACI, this group was added to the influenza immunization program of most of the Canadian provinces, including Québec. It should be mentioned that, at the time this group was added to the influenza immunization programs, the overall group of children aged 6–23 months, regardless of the presence of chronic conditions, was considered. More recent data show that, during most influenza seasons, the disease burden among children aged 6–23 months is less significant compared with initial estimates, and that it is instead concentrated among children with a chronic condition.

In the base-case economic scenario, the inclusion of healthy children aged 6–23 months is not cost effective, according to the set threshold of $45,000 (ICER = $72,701 per QALY). Their inclusion could be cost effective under certain conditions that may be observed during the most severe seasons, in which we could observe an increase in the medically attended infections rate of 1.75 times that in the base-case scenario, or if vaccination effectiveness were greater than 60%. No reasonable variation in the hospitalization rate or mortality rate yielded an ICER < $45,000 per QALY (the multiplication by 3 of the current hospitalization rate yields an ICER of $54,050; a multiplication by 3 of the mortality rate yields an ICER of $50,674). In the probabilistic analysis, the probability of being cost effective at the $45,000 threshold is 58%. In our analysis, the administration of 2 doses was considered, while, in reality, some 50% of children in this group receive only a single dose, which overestimates the cost of the program. At the same time, vaccine effectiveness is also overestimated because a single dose would have less vaccine effectiveness, compared with 2 doses.

As in all the other groups of children and young adults, the main component of the disease burden in this group is that of outpatient visits (12 269 visits and 257 hospitalizations per year); deaths are quite rare. If only hospitalizations had been included in the economic analysis, the ICER would have been $294,305 per QALY. Note that the death rate used is the one reported for the group combining healthy children and children with a chronic condition; one could think that among healthy children, this rate would be lower and that consequently the cost effectiveness of the program is overestimated. For example, the death rate of 0.77/100 000 used in the economic analysis among healthy children aged 6–23 months is > 2 times higher than the aggregate rate in this same group, including children with a chronic condition, in the United States (0.33/100 000)(102).

As mentioned in Chapter 2, in most European countries, influenza vaccination is not recommended for children. In the 9 out of 30 countries where vaccination for children aged 6–23 months is recommended, there is no distinction between healthy children and those with a chronic condition.

Public acceptance of vaccination for this group is low, as illustrated by the gradual drop of VE (≥ 1 dose) from over 30% in the early 2000s to 19% in 2015–2016 (about half of those vaccinated received 2 doses).

Finally, this group is probably the most affected by the uncertainties related to the potential long-term impacts of influenza vaccination and of repeated vaccination.

Healthy individuals aged 60–64 years

Individuals aged 60 years and older were added to the PIIQ in 2000 in view of a potential increase in influenza vaccination indications in preparation for the pandemic(190). To our knowledge, a higher risk for influenza complications was not demonstrated in this group. Evaluation of the influenza disease burden shows that the influenza-attributable hospitalizations and deaths among healthy individuals aged 60–64 years are few in number. The ICER in this group ($826,188 per QALY including medically attended infections, $2,059,796 per QALY without such visits) is far from achieving the set threshold. None of the parameter variations examined lead to a reasonable improvement in the ICER; the probability of being cost effective at the $45,000 threshold, taking into account all the parameter variations examined, is equal to 0%. To prevent one influenza-attributable hospitalization or death, it is necessary to vaccinate about 15 000 and more than 2 million individuals respectively, at a cost of nearly $300,000 and more than $38 million, to prevent one influenza-associated hospitalization or death respectively. Less than one third of the individuals in this group get vaccinated each year.

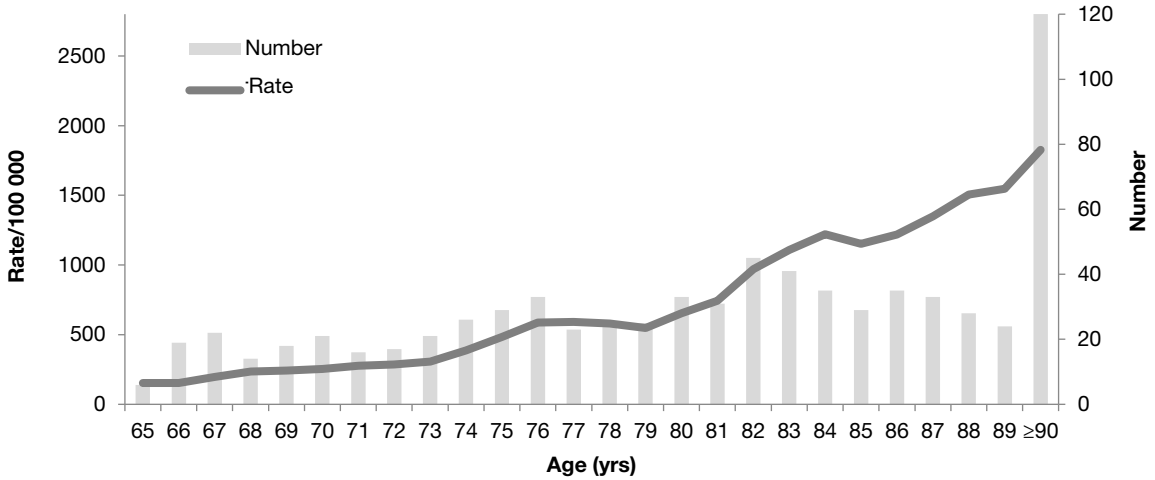
Healthy individuals aged 65–74 years

According to the data from the Institut de la statistique du Québec, life expectancy at birth has gradually increased in Québec from 74.9 years in 1980–1982; to 79.1 years in 2000–2002; to 82.2 years in 2013–2016(191). Health-adjusted life expectancy has risen from 71.1 years in 2003 to 72.8 years in 2007–2008 (data from the Infocentre, INSPQ). More recent data are not available for the moment, but one could think that healthy life expectancy has increased over the past few years. Individuals live longer and in better health now than at the period of time when the PIIQ was introduced.

The literature often presents aggregate data among individuals aged 65 years and older, but this does not necessarily reflect the risks that gradually increase with age. We examined influenza-confirmed hospitalizations in the prospective study conducted in 4 hospitals in Québec during the peaks of the last 6 influenza seasons, by year of age (Rachid Amini, personal communication). The influenza disease burden among healthy individuals aged 65–74 years is greater than that among individuals aged 60–64 years. However, the increase in risk is gradual within the group aged 65–74 years, while a larger change is observed starting from 75–76 years; an acceleration is observed after 80 years (Figure 8). The rate stratified by the presence of a chronic condition cannot be calculated because we do not have population-based denominators for the presence of a chronic condition by year of age. Nevertheless, we can see in Figure 8B that the increase in the total number of hospitalizations in the group aged 65–74 years is mostly due to patients with a chronic condition. The risk among healthy individuals aged 65–74 years can therefore be presumed to be quite stable.

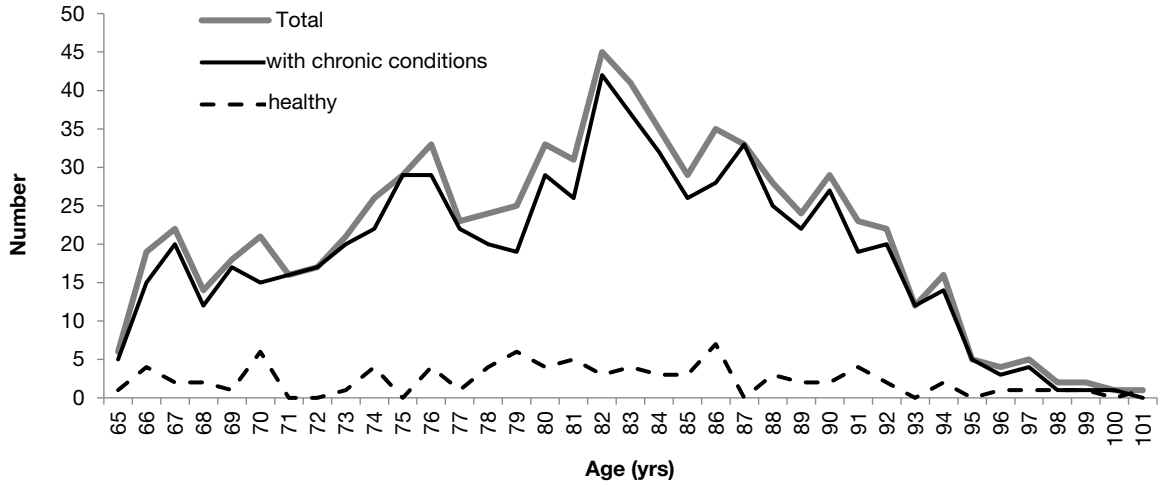
Figure 8 Hospitalizations with influenza-confirmed infection during the peaks of 6 influenza seasons (2011–2012 to 2016–2017) in the 4 hospitals participating in the prospective study, patients aged 65 years and older, by year of age

A) Number and rate of hospitalizations



Note: A third-order moving average was applied to the rate, in order to reveal trends.

B) Number of hospitalizations among patients with a chronic condition vs healthy individuals



The ICER in this group ($386,381/QALY, including medically attended infections, $507,645/QALY without such visits) is much higher than the $45,000 threshold. None of the parameter variations examined leads to a decrease in the ICER to this threshold; the probability of being cost effective at the $45,000 threshold, taking into account all the parameter variations examined, is equal to 0%. To prevent one influenza-attributable hospitalization or death, it is necessary to vaccinate more than 8000 and more than 300 000 individuals respectively, at a cost of around $150,000 to prevent one hospitalization and more than $6.5 million to prevent one death. Slightly fewer than half (48%) of the individuals in this group get vaccinated each year.

From an operational viewpoint, this group presents advantages, knowing that several vaccines may be given at this age (vaccine against pneumococcus and against shingles). On the other hand, the CIQ members expressed concerns about the possible effects of repeated vaccination in this group.

This group was the subject of discussion during all 3 stages of the Delphi approach. During the third stage (attendance at a CIQ meeting), the discussions converged toward the finding that, in this group, the benefits of influenza vaccination could not outweigh the risks. In most cases, influenza does not present a risk of complications in this group, but vaccination could theoretically have negative repercussions later on (potential implications of repeated vaccination). Consensus was reached by the members against the inclusion of this group. The members mentioned the issues surrounding the communication of the decisions regarding the proposed changes and the need to properly formulate messages to the general public.

The CIQ recommends that healthy children aged 6 to 23 months and healthy adults aged 60 to 74 years be withdrawn from the PIIQ.

8.1.2 GROUPS NOT CONSIDERED IN THE ECONOMIC ANALYSIS

Vaccination of individuals susceptible to transmitting influenza to individuals at high risk for influenza-associated hospitalization and death

Vaccination of healthcare workers

Healthcare workers (HCWs) are exposed to seasonal influenza, as any other person in the community, and are susceptible to acquiring the disease at work or outside work(192). When HCWs are infected and present with respiratory infection symptoms caused by influenza or other respiratory pathogens, a large proportion of them continue to work(193,194). Care settings are subject to numerous nosocomial outbreaks caused by respiratory pathogens, including influenza. Although their contribution to these outbreaks has not been quantified, HCWs could sometimes be the source or involved in the transmission of influenza in healthcare settings. Such outbreaks are not inconsequential. In addition to the impacts on the health of HCWs and patients, the presence of outbreaks may require more complex admissions management, delay planned leave and lead to difficult human resource management owing to absenteeism and may necessitate the temporary closure of a care unit in some cases. In addition, in closed settings or in care units with patients at risk for complications, prophylactic antivirals are often prescribed leading to additional costs for the healthcare system.

The influenza vaccine provides direct protection to HCWs, similar to that of other persons of the same age. Despite the low quality of the scientific evidence on the indirect impact of the vaccination of HCWs on the reduction of the disease and mortality among patients, it remains likely that this vaccination prevents cases among patients and facilitates the management of influenza outbreaks by reducing the number of cases. **The CIQ recommends that all healthcare workers receive the vaccine.**

Furthermore, in the presence of outbreaks in healthcare settings, the exclusion of HCWs until the end of the contagion period is important to prevent the propagation of respiratory infections, including influenza. This exclusion would have the advantage of preventing the transmission not only of influenza but also of other pathogens that could be the cause of respiratory symptoms.

At the CIQ meeting of December 2017, the following definition of HCWs was retained:

"Any person who provides health care to, or who comes **in close contact** with, individuals at high risk, as defined by the PIIQ, whether in a hospital, LTCF, medical or dental clinic, CLSC, or in another

residential or care setting (e.g., physician, nurse, paramedic, pharmacist, dental professional, nursing or medical student, laboratory technician, volunteer worker [non-exhaustive list]). The term includes healthcare trainees and their professors. In addition to the workers mentioned above, this term also includes the first responders who provide care."

Since the HCWs most susceptible to transmitting influenza to patients are those who are symptomatic and who have close contact with patients, **the vaccination offer should give priority to the HCWs who provide direct care to patients in hospitals and LTCFs**. Furthermore, HCWs presenting with respiratory infection symptoms should take the necessary steps to prevent transmission to patients, whether this infection is due to influenza or to another respiratory virus.

Vaccination of the contacts of individuals at high risk for influenza-associated hospitalization and death, other than HCWs

There are limited data indicating that individuals who are vaccinated against influenza indirectly protect their community contacts. A recent systematic review on the indirect effectiveness conferred by vaccination in a community setting was unable to conclude on the existence of such protection and on the necessary conditions to be able to observe it(195). To date, the only good-quality study that has demonstrated indirect protection was conducted in a Hutterite community in which the contact network was limited to members of the community and in which the vaccine uptake achieved was very high(177). Moreover, the majority of studies on the indirect effects of influenza immunization have involved vaccination of children. There are limited data on the indirect effects of adult immunization(195).

It remains biologically plausible that we can protect individuals at high risk for influenza complications by vaccinating their close contacts. When a member of a household presents with a respiratory infectious disease, there is a high risk of transmission to the other household contacts. These contacts represent the main, if not the single, source of contamination for individuals at high risk for complications who have few or no contacts outside the home. For vulnerable individuals who have frequent contacts outside the home, immunizing their household contacts could also contribute to reducing the risk of influenza, but would have no impact on all the other sources of infection. For patients who have frequent contacts outside the home, the relative risk reduction for influenza could be low, even if the absolute risk reduction remains the same. In other words, by vaccinating the close contacts of individuals at high risk for influenza complications, we would prevent the same number of influenza virus infections among vulnerable individuals with few or no outside contacts as among individuals with frequent outside contacts.

In line with the objective of reducing mortality and morbidity among individuals at high risk for complications, **the CIQ recommends that persons residing in the same household as, and caregivers for, individuals at high risk for influenza-associated hospitalization and death (including children younger than 6 months) receive the vaccine**.

Vaccination of pregnant women

The PIIQ currently recommends vaccination for all pregnant women with medical conditions associated with a high risk for influenza complications. For healthy pregnant women, vaccination is recommended for the 2nd and 3rd trimesters. A literature review published in 2009 described the existing data on influenza disease burden among pregnant women with comorbidities and healthy pregnant women, the risk to the fetus, immunological data and vaccine effectiveness, protection of infants following immunization of pregnant women, and vaccine safety(196). An increased risk of seasonal influenza during the first trimester of pregnancy relative to non-pregnant women was not demonstrated among healthy women, while evidence exists on an increase risk as of the 2nd

trimester. The authors concluded that annual seasonal influenza vaccination could be warranted during the entire pregnancy of women with comorbidities, but it was not justified in pregnant women beginning in early pregnancy.

A recent article found an association between vaccination in the 1st trimester and the risk of spontaneous abortion(197). This study has several serious methodological limitations that make its conclusions very debatable. However, it illustrates the importance of being cautious in the context where there is no evidence of increased risk for influenza or its complications during the 1st trimester. The CIQ's position therefore remains unchanged relative to its ruling in response to the questions raised by the Groupe sur l'acte vaccinal in March 2014: "For healthy pregnant women, owing to the paucity of data on the safety of vaccination in the 1st trimester and on influenza burden, which is not higher than that among non-pregnant women, it is recommended to wait until the 2nd trimester before getting vaccinated. Nevertheless, a pregnant women without health problems may decide to get vaccinated in the 1st trimester for her own protection, because this is not a contraindication."

The CIQ maintains its recommendation to vaccinate all pregnant women with a chronic condition, irrespective of the term of pregnancy, as well as healthy pregnant women in the 2nd or 3rd trimester of pregnancy.

Residents of nursing homes, long-term care facilities and intermediate resources

For the purposes of this exercise, the individuals living in nursing homes, long-term care facilities or intermediate resources are considered indistinguishably, given the type of setting in which they reside.

It was not possible at this stage to perform a complete economic analysis of influenza vaccination among the residents of these settings, given the lack of robust data on the prevalence of specific chronic conditions and on these residents' life expectancy, on specific components of disease burden, and on vaccine effectiveness in this population. Nonetheless, it is possible to assert that influenza-associated morbidity and mortality remain higher in this population than in the other groups. Vaccine effectiveness could be lower here than in the other populations, but it is nevertheless expected that the vaccine confers upon this vulnerable population some degree of protection during most seasons. Program acceptability and feasibility in this group currently poses no problem, given the fact that vaccine uptake among the residents of LTCFs in Québec exceeds 80%.

The CIQ recommends maintaining vaccination for the residents of nursing homes, long-term care facilities or intermediate resources.

Vaccination for the other groups included in the PIIQ

The other groups included in the PIIQ, such as individuals living in remote or isolated communities, and children and adolescents (below the age of 18 years) receiving long-term acetylsalicylic acid therapy (see Table 7 in Section 8.1.3), were not re-evaluated in this current advisory, given the lack of evidence for these groups, and limited time.

The CIQ recommends maintaining vaccination for these other groups included in the PIIQ.

8.1.3 SUMMARY OF THE CHANGES RECOMMENDED BY THE CIQ

Table 7 summarizes the recommended changes to the PIIQ.

Table 7 Groups currently included in the PIIQ and new recommendations by the Comité sur l'immunisation du Québec

Currently included	New recommendations
Individuals at high risk for influenza-associated hospitalization and death, due to their age or health	
Children aged from 6 to 23 months	Withdraw healthy children; no change for children with a chronic condition
Individuals aged 60 years and older	Withdraw healthy individuals aged 60–74 years; no change for individuals aged 60–74 years with a chronic condition and for those aged ≥ 75 years
Individuals aged 6 months and older with a chronic disease or condition, according to the indications in the *Protocole d'immunisation du Québec* (PIQ)	Maintenance of the recommendation to vaccinate
Children and adolescents (below 18 years) receiving long-term acetylsalicylic acid therapy	Maintenance of the recommendation to vaccinate
Residents of nursing homes, long-term care facilities and intermediate resources*	Maintenance of the recommendation to vaccinate
Pregnant women with a chronic disease or condition (the vaccine may be administered regardless of the term of pregnancy)	Maintenance of the recommendation to vaccinate
Healthy pregnant women in their 2nd or 3rd trimester (13 and more weeks)	Maintenance of the recommendation to vaccinate
Individuals living in remote or isolated communities	Maintenance of the recommendation to vaccinate
Travellers with a chronic disease or condition and who will go to a region with circulating influenza virus (tropical regions: year-round; Southern Hemisphere: April to September)	Maintenance of the recommendation to vaccinate
Vaccination of individuals susceptible to transmitting influenza to individuals at high risk for influenza-associated hospitalization and death	
Household contacts of individuals at high risk for complications (including children aged 0–6 months) and caregivers of individuals at high risk for complications (e.g., daycare staff)	The CIQ recommends that persons residing in the same household as, and caregivers for, individuals at high risk for influenza-associated hospitalization and death (including children younger than 6 months) receive the vaccine
Individuals, particularly healthcare workers, who, through their work or activities, have frequent contact with individuals at high risk for complications	The CIQ recommends that all HCWs[1] receive the vaccine. The vaccination offer should be given in priority to the HCWs who provide direct care to patients in hospitals and LTCFs.

* Formerly called "Residents of any age in residential centres or long-term care facilities."

[1] Recommended definition for "healthcare worker" (HCW): "Any person who provides health care to, or who comes in close contact with, individuals at high risk, as defined by the PIIQ, whether in a hospital, LTCF, medical or dental clinic, CLSC, or in another residential or care setting (e.g., physician, nurse, paramedic, pharmacist, dental professional, nursing or medical student, laboratory technician, volunteer worker [non-exhaustive list]). The term includes healthcare trainees and their professors. In addition to the workers mentioned above, this term also includes the first responders who provide care."

The population at high risk for complications and targeted by the new recommendations in 2018 totals approximately 2.5 million individuals; for a vaccine uptake of 80%, approximately 2 million individuals would need to be vaccinated (Table 8).

Table 8 Estimated population in the groups targeted by influenza immunization, according to the new recommendations by the CIQ, and number of individuals to vaccinate if a vaccine uptake of 80% is to be achieved

Main groups targeted by the PIIQ	Estimated population in 2017[1]	Number of individuals to vaccinate to achieve vaccine uptake of 80%
Individuals at high risk for influenza-associated hospitalization and death, due to their age or health		
Individuals aged 6 months to 74 years with a chronic condition[2]	1 815 851	1 452 681
Individuals aged 75 years and older[3]	664 463	531 570
Total	2 480 314	1 984 251

[1] Estimation of the Québec population by age on July 1, 2017, Institut de la statistique du Québec.

[2] To calculate the population with a chronic condition, we used the proportion of children with a chronic condition estimated from the case-control studies conducted in 2010, as reported in telephone interviews with the parents of children randomly selected from the Québec population(29,30). Among the adults, the proportion of chronic conditions in the different subgroups was calculated from the data on the presence of chronic conditions reported in the *Enquête québécoise sur la vaccination contre la grippe saisonnière et le pneumocoque de 2015–2016* (Manale Ouakki, personal communication). See also Section 3.2. The detailed proportions of chronic condition by age group which served to calculate the number of individuals to vaccinate can be found in Appendix 6.1A.

[3] This number includes the 37 365 residents of any age in nursing homes, long-term care facilities and intermediate resources. Source: MSSS, *Rapport statistique annuel des centres hospitaliers et des centres d'hébergement et de soins de longue durée et d'activités en CLSC* (*Formulaire AS-478).* MSSS, production DGASA février 2017.

9 Other considerations

An in-depth revision of the different aspects of the PIIQ (immunization strategies, feasibility, acceptability, equity, and ethical, legal and political considerations) was performed in 2007(1). That revision was performed from the perspective of a gradual expansion of the PIIQ. In the present revision of the PIIQ, efforts focussed on the recent elements that led to questions regarding the expected impact of the PIIQ in its current format. Some of these elements were discussed in the previous sections, where relevant. This section adds certain considerations not mentioned so far in this document.

9.1 Weight assigned to the economic analysis in the decision making

The economic analysis performed presents a measure of performance (measured by cost effectiveness) of the PIIQ in the different age groups. Economic profitability is one element among many to consider. Several recent reflections put into question the important weight given to the results of economic analyses among the other elements having an impact on the decisions whether or not to accept changes to an immunization program and point out the need to take into account several elements(155,198,199). For example, influenza disease burden is significant, but we could question the weight given to prevention in medically attended infections relative to the weight given to prevention of hospitalizations and death. In fact, Steven Black(198) puts into question the fact that the more cost-effective programs may be favoured over programs that reduce severe morbidity and mortality, but do not necessarily provide economic benefit deemed acceptable, and also mentions the risk of making vaccines a tool for achieving cost savings instead of rightly considering them a public health intervention targeting human suffering, death and disability.

In a recent document by the WHO on the different pros and cons of using cost-effectiveness thresholds, the authors draw attention to the possibility of making poor decisions if countries' decision-making processes do not take into account each country's specific characteristics and the uncertainty in the models used(200). They point out that the results of economic evaluations should be taken into account, alongside other considerations, such as their impact on the budget and feasibility, by using a transparent, consistent and fair decision-making process framework.

9.2 Vaccine characteristics and safety

Research studies are underway to improve influenza vaccine production technologies, but it will be many years before we see the fruits of this labour. It is unlikely that vaccine costs will decline; new vaccines are more expensive without necessarily offering a greater benefit relative to the older vaccines. At the same time, certain adverse events following immunization have recently come to light and are the subject of in-depth research. In a recent review of the safety of influenza vaccines, a total of 108 vaccines with unique product names have been identified over the past decade(201). Some of the adverse effects are specific to certain vaccine formulations, while others could be more general phenomena.

Short-term side effects of the influenza vaccine are generally minor, and these vaccines are considered safe(108,109). However, given that these vaccines are reformulated every year, unexpected adverse events may arise for some vaccine formulations, such as oculorespiratory syndrome reported in Europe(202) and in Canada(203), Guillain-Barré syndrome reported for the vaccines produced in 1976 (risk of 1/100 000) and for the pandemic vaccines of 2009 (risk of 1/1–3 million)(201,204), narcolepsy reported following administration of a pandemic vaccine formulation in

2009(205), or severe reactogenicity reported in Australia during the 2015–2016 season(206). Most of these effects are rare. Several recent publications have found a negative impact of repeated vaccination on VE(207–209). This phenomenon was first reported 40 years ago(210). Repeated vaccination has sometimes been observed to provide lower protection than the first vaccination, but better than the absence of vaccination(207,211). In 2014–2015, an increase in disease risk following repeated vaccination(212) was observed in Canada, Italy and Japan. In other circumstances, repeated vaccination could improve VE. A recent review of the literature since the 1970s, along with a meta-analysis of the studies presenting VE between 2010–2011 and 2014–2015, shows substantial heterogeneity in repeated vaccination effects for different seasons and different influenza virus subtypes(213). The lack of consistency in the findings on the impact of repeated vaccination does not mean that this is simply a random variation. Certain hypotheses have been proposed to explain the variability in the results, such as "original antigenic sin"(214) or antigenic distance between the vaccine strains and the epidemic strains(215), but this remains speculative for the time being.

Lastly, another effect recently shown is the possibility of inducing mutations in vaccine strain egg adaptation during vaccine production. These mutations may modify the antigenicity of the vaccine strain relative to the selected strain for production and may consequently result in lower VE, as reported for the 2012–2013 season(216) and the 2016–2017 season(217).

9.3 Acceptability

The new recommendations by the CIQ run counter to the North American recommendations. In this context, the advisory on the revision of the PIIQ was sent to different professional associations representing key stakeholders within the Québec population to obtain their comments, that is: Société québécoise de gériatrie (SQG); Association des médecins gériatres du Québec (AMGQ); Fédération des médecins omnipraticiens du Québec (FMOQ); Association des pédiatres du Québec (APQ); Ordre des infirmières et des infirmiers du Québec (OIIQ); Association des spécialistes en médecine préventive du Québec (ASMPQ); and Association des médecins microbiologistes-infectiologues du Québec (AMMIQ). All the associations that responded (SGQ, FMOQ, APQ, OIIQ, ASMPQ and AMMIQ) expressed agreement with the CIQ's recommendations. The comments and suggestions received were incorporated into the final version of the advisory.

9.4 Program evaluability

The economic analysis of the PIIQ encountered several challenges, that is, the lack of data on several of the components required for such analysis, among others. For influenza-attributable hospitalizations, the existence of a prospective study in 4 acute-care hospitals in Québec for several years allowed extrapolation of some data to the entire province. However, this study has a limited sample size, and it is often faced with a lack of power for stratified analyses.

The impact on outpatient morbidity was difficult to evaluate, given that the existing Québec data are not specific. Currently, the number of individuals with medically attended ILI for which a specimen is collected as part of the surveillance performed by the Réseau des groupes de médecine de famille (GMF) au Québec [network of family medicine groups (FMG) in Québec] remains minimal and does not permit calculation of population-based rates.

The data on outbreaks in LTCFs were very useful, but the reports on this topic were often incomplete or completed differently, according to region. In addition, we do not know the extent to which the

deaths reported during the outbreaks were all due to influenza, given that during some outbreaks only the first cases are subject to diagnostic confirmation and that many of the other respiratory viruses may circulate during the influenza season and may also cause deaths.

The existing surveys allowed us to obtain data on chronic conditions and vaccine uptake, but data were not available for all the subgroups.

The revision of the PIIQ in 2007 mentioned the need for a permanent infrastructure making it possible to monitor the program in all its aspects and to revise it systematically in light of new knowledge. In 2017, this need is even more warranted owing to the rapid advance of new vaccine production technologies, improvement of the methods for diagnosing respiratory infections and for estimating influenza disease burden, as well as changes in the methods for estimating VE.

During the writing of this report, several elements that need to be better explained or implemented came to light:

- The role of influenza relative to that of the other respiratory viruses in the morbidity and mortality among the residents of LTCFs;
- Estimation of vaccine uptake among patients with a severe chronic condition;
- Estimation of the proportion of different chronic conditions in narrower age strata, at least in the age groups examined in this advisory report;
- Identification of better strategies for reaching the various target groups, including the possibility of vaccinating at-risk individuals in the healthcare settings where they are followed;
- Estimation of the cost of administering the influenza vaccine, according to the different target groups and different healthcare settings;
- A more precise estimation of influenza vaccine effectiveness to prevent hospitalizations during each influenza season;
- Strengthening of surveillance of the annual influenza epidemics and their health impact;
- Access to data on the influenza vaccine doses administered by age group and presence of a chronic condition; a vaccination register containing complete and detailed information could improve the quality of the information on vaccine uptake and on the types of vaccines received, which is currently collected during population-based surveys;
- Clarification of the role of influenza in non-respiratory hospitalizations and deaths.

Some of these questions could be answered by using the data generated by the prospective study in the Québec hospitals, but additional resources would be needed, to be able to increase the sample size of this study. Influenza-attributable morbidity could be evaluated using the data from the prospective study jointly with the Québec administrative databases (MED-ÉCHO and *Fichier des décès*) and the provincial surveillance data on respiratory viruses. Working groups could be created to study other questions, such as quantifying the role of influenza in LTCFs, or identifying better strategies for reaching the groups targeted by the PIIQ.

In parallel, monitoring advances in knowledge concerning the effectiveness of different influenza vaccine formulations and also short-term and long-term vaccine safety in different population groups should continue, to be able to take this into account in future economic evaluations.

10 Recommendations by the CIQ

In light of the evaluation of the scientific data available in early 2018 on influenza disease burden, vaccine effectiveness and vaccine uptake, along with the results of the economic evaluation and the evaluation of the other elements considered, the CIQ has formulated the following recommendations:

1) Confirm that the primary objective of the PIIQ is to reduce influenza-associated hospitalizations and deaths.

2) Maintain a targeted vaccination strategy for individuals at high risk for hospitalization and death, and place priority on achieving vaccine uptake of at least 80% within these groups.

3) Withdraw healthy children aged 6–23 months and healthy adults aged 60–74 years from the list of groups at high risk for influenza-associated hospitalization and death, but maintain the other groups currently included in the PIIQ. These withdrawals are definitely not intended to generate savings by cutting the cost of the program, because it will be necessary to administer the same number of vaccines annually to increase vaccine uptake to at least 80% in the risk groups.

4) Concentrate efforts on promoting and improving vaccination services for individuals at highest risk for influenza-associated hospitalization and death.

5) The CIQ recommends that all healthcare workers receive the vaccine. The vaccination offer should give priority to healthcare workers who provide direct care to patients in hospitals and LTCFs.

6) The CIQ recommends that persons residing in the same household as, and caregivers for, individuals at high risk for influenza-associated hospitalization and death (including children younger than 6 months) receive the vaccine.

7) Put in place a permanent infrastructure to continually evaluate the important aspects of the PIIQ (disease burden, vaccine effectiveness, vaccine uptake and program impact) in order to be able to quickly make any necessary adjustments to the planning and implementation of the PIIQ. (Recommendation also formulated in 2007).

11 Conclusion

Scientific knowledge concerning influenza disease burden and influenza vaccination effectiveness has greatly evolved over the past 10 years. Quantification of the disease burden in the different groups has improved, VE has been shown to be lower than previously thought, and questions have been raised about the impact of repeated vaccination. The current report proposes to maintain a targeted vaccination program for individuals at high risk for influenza-associated hospitalization and death, and to give priority to achieving optimal vaccine uptake among them.

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Summary of the conflict of interest disclosures by the members of the Comité sur l'immunisation du Québec (CIQ)

NOVEMBER 2017

The Institut national de santé publique du Québec (INSPQ) asked the members of the Comité sur l'immunisation du Québec (CIQ) to produce a disclosure in order to identify their situations liable to lead to a conflict of interest over the past three years in relation to the advisory on the revision of the *Programme d'immunisation contre l'influenza au Québec.*

1 No conflict of interest to declare:

Julie Bestman-Smith, Dominique Biron, François Boucher, Marjolaine Brideau, Nicholas Brousseau, Ngoc Yen Giang Bui, Hélène Gagné, Vladimir Gilca, Maryse Guay, Catherine Guimond, Patricia Hudson, Monique Landry, Richard Marchand, Caroline Quach, Céline Rousseau, Chantal Sauvageau, Evelyne Toth, Bruno Turmel.

2 Reseach funds obtained as the principal investigator or co-investigator from private corporations whose products or activities fall within the field of influenza immunization:

Alex Carignan: Sanofi Pasteur;

Gaston De Serres: (GSK);

Philippe De Wals: GSK, Sanofi Pasteur;

Rodica Gilca: Sanofi Pasteur;

Bruce Tapiéro: GSK.

3 Consulting or presentation fees or travel expenses (TE) received from private corporations whose products or activities fall within the field of influenza immunization

Gaston De Serres: Consulting fees: GSK, Ontario Nurses Association;

Philippe De Wals: Presentation TE: Novartis, Consortium de Pharmaceutiques, Consulting TE: GSK;

Marc Lebel: Consulting fees: GSK. Consulting TE: GSK.

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