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Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

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To cite this article: Sophie Marbaix, Nicolas Dauby & Joaquin Mould-Quevedo (2023) Cost-effectiveness of the adjuvanted quadrivalent influenza vaccine in the elderly Belgian population, Expert Review of Vaccines, 22:1, 608-619, DOI: 10.1080/14760584.2023.2229917

To link to this article: https://doi.org/10.1080/14760584.2023.2229917

Published online: 04 Jul 2023.

EXPERT REVIEW OF VACCINES
2023, VOL. 22, NO. 1, 608–619
https://doi.org/10.1080/14760584.2023.2229917

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ORIGINAL RESEARCH

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Cost-effectiveness of the adjuvanted quadrivalent influenza vaccine in the elderly Belgian population

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ABSTRACT

Background: Between 2015 and 2019, when 62% of Belgian adults aged ≥65 years were vaccinated with standard quadrivalent influenza vaccines, influenza caused an average of 3,905 hospitalizations and 347 premature deaths per year in older adults. The objective of the present analysis was to estimate the cost-effectiveness of the adjuvanted quadrivalent influenza vaccine (aQIV) compared to the standard (SD-QIV) and high-dose (HD-QIV) vaccines in elderly Belgians.

Research Design and Methods: The analysis was based on a static cost-effectiveness model that captured the evolution of patients infected with influenza and was customized with available national data.

Results: Vaccinating adults aged ≥65 years with aQIV instead of SD-QIV would decrease the number of hospitalizations by 530 and the number of deaths by 66 in the 2023–2024 influenza season. aQIV was cost-effective compared to SD-QIV with an incremental cost of €15,227/quality-adjusted life year (QALY). aQIV is cost-saving when compared to HD-QIV in the subgroup of institutionalized elderly adults who were granted reimbursement for this vaccine.

Conclusion: In a health care system striving to improve the prevention of infectious diseases, a cost-effective vaccine such as aQIV is a key asset to reduce the number of influenza-related hospitalizations and premature deaths in older adults.

PLAIN LANGUAGE SUMMARY

Many older Belgians who get the flu are likely to go to hospital or even die. Some flu vaccines have been specially designed for adults 65 years old and older including one that contains a higher amount of flu particles and another that contains a unique additive called an adjuvant. Both vaccines improve the body's response to flu infection, but the adjuvanted vaccine is not yet available in Belgium. We used an economic model to compare hypothetical medical spending on Belgians who were vaccinated with the adjuvanted flu vaccine, the high dose flu vaccine, and a standard flu vaccine. We found that the adjuvanted vaccine would reduce flu hospitalizations and deaths in the elderly, which would in turn reduce medical spending on influenza in Belgium.

ARTICLE HISTORY
Received 30 April 2023
Accepted 22 June 2023

KEYWORDS
adjuvanted quadrivalent vaccine; cost-effectiveness; elderly; influenza; influenza disease burden

1. Introduction

Seasonal influenza is a contagious acute respiratory infection mainly caused by influenza virus of type A (A [H1N1] and A [H3N2]) and type B (B/Victoria lineage and B/Yamagata lineage). Diagnosis is mainly based on clinical symptoms, especially in the outpatient settings. Other acute respiratory viruses, such as respiratory syncytial virus (RSV), rhinovirus, adenovirus, and, more recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can also present as influenza-like illness (ILI), which makes it difficult to clinically differentiate between influenza and other pathogens. Laboratory testing, such as polymerase chain reaction (PCR), is required to confirm the influenza diagnosis [1,2].

The disease caused by influenza virus can be mild to severe and present a risk of death for the infected patient. In the general population, only half of infected patients will consult a physician to recover from influenza infection, but in the elderly group, more patients will need professional medical assistance [3]. Among frail patients, influenza infection can lead to severe complications (including pneumonia, myocarditis, myocardial infarction, stroke, encephalitis, and kidney failure) or worsening of the patient's underlying conditions [3,4].

Hospitalization as a consequence of influenza occurs mainly among adults 65 years and older as well as among patients with comorbidities, including frail elderly individuals [2]. During the 2018–2019 influenza season, Sciensano, the Belgian National Institute for Health, estimated 4,798 hospitalizations due to influenza virus in the elderly population (Sciensano, personal communication, 2022). A similar number of hospitalizations was reported by the national hospital database of the Ministry of Health (number of hospitalizations with International

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Classification of Diseases, 10th revision [ICD-10] codes J09 and J10) [5]. The ICD-10 is an internationally used list of diseases defined by the World Health Organization [6]. The number of hospitalizations due to influenza increases by a third should the J11 ICD-10 code (unspecified influenza viruses) be added to the codes J09 and J10 for the estimation of number of hospitalizations due to influenza. In the peak influenza season, demand for health care resources may be substantial, and hospitals may be overloaded. Prevention by vaccination consequently represents a key asset for the health care system.

Influenza is also a significant cause of mortality. Most deaths (90%) associated with influenza and its complications occur in patients aged 65 years and older [1,2,7]. Over the 2015–2019 period, the mortality risk in elderly patients hospitalized due to influenza was close to 10% [5,8].

Although antiviral drugs such as oseltamivir are available and reimbursed in the Belgian health care system and recommended for the management of severe influenza infection, their impact on mortality and complications remains controversial. As a consequence, vaccination remains the most effective way to prevent influenza infection and its complications [1,9].

In accordance with the WHO guidelines, the Belgian Superior Health Council recommends Belgian individuals belonging to risk groups be vaccinated with quadrivalent influenza vaccines (containing the two main influenza A virus subtypes and the two main influenza B virus lineages) [10,11]. Standard quadrivalent influenza vaccines (SD-QIV) have been available in Belgium since the 2015–2016 influenza season. In older adults, conventional influenza vaccine effectiveness is, however, often reduced due such factors as immunosenescence, frailty, and cumulative comorbidities [12,13]. Enhanced influenza vaccines have consequently been developed to improve the immune response in older adults, including the high-dose quadrivalent influenza vaccine (HD-QIV) containing four times the level of hemagglutinin (HA) antigen than in SD-QIV and the adjuvanted quadrivalent influenza vaccine (aQIV) containing the standard dose of HA antigen and MF59 (an oil-in-water emulsion of squalene oil) as an adjuvant that helps promote increased immunogenicity. Based on a systematic review of recently published literature using real-world data, vaccination of older adults with these 2 new alternative vaccines was associated with increased vaccine effectiveness in older adults [14]. Since the 2022–2023 influenza season, HD-QIV has been available on the Belgian market for adults aged 65 years and older, but reimbursement is limited to those living in residential institutions [15]. aQIV is expected to be soon accessible to the elderly population. The cost-effectiveness of this new influenza vaccine has already been demonstrated in other countries [16–19].

The objective of the present analysis is to evaluate cost-effectiveness of aQIV compared to SD-QIV in Belgian adults aged 65 years and older, from the national healthcare payer perspective. In the scenario analysis, a comparison to HD-QIV will be investigated. Access to this influenza vaccine is limited to a subgroup of the target population for aQIV.

1.1. Patients and methods

The cost-effectiveness analysis of aQIV was based on a decision tree structure that captured the evolution of patients infected with influenza. The target population of this analysis is adults aged 65 years and older.

1.2. Model structure

Both dynamic and static models have been applied in cost-effectiveness analyses of influenza vaccine in the elderly population [17–21]. A static approach was chosen for the health economic assessment of QIV options that are currently available and reimbursed in the Belgian marketplace [22,23]. A static model is supported by the WHO recommendations [24] for the limited epidemiologically influential target group. The customized model was originally developed to define the cost-effectiveness of adjuvanted influenza vaccine in Scandinavian countries [16].

The decision tree compares 4 vaccination alternatives in a cohort of adults aged 65 years and older (Figure 1): 1) aQIV, 2) HD-QIV, 3) SD-QIV, and 4) no vaccination. Each vaccination strategy or program considered the combination of an influenza vaccine with no vaccination as defined by vaccination coverage. The model population was subdivided into 2

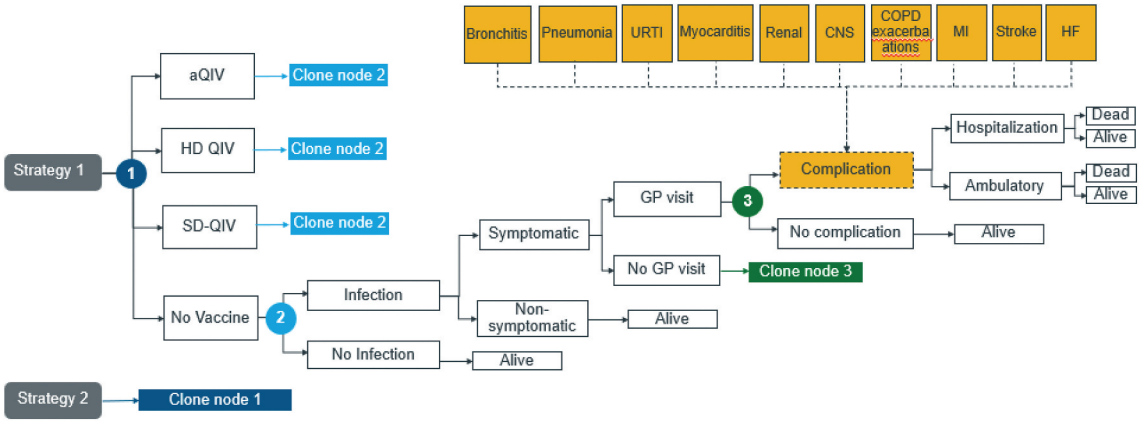

Figure 1. Cost-effectiveness model.

age subgroups: 65–74 years old and 75 years and older. The implementation of 2 age groups was justified by the variability in parameter values for vaccination coverage, propensity to seek professional medical assistance, mortality risk, and baseline quality of life.

The cost-effectiveness model estimated the probability of influenza infection for each vaccination alternative based on the influenza attack rate and the respective vaccine effectiveness against influenza strains A and B. The infected patients were symptomatic or asymptomatic. Asymptomatic patients (who are usually not registered in the epidemiological data) were assumed to have no further impact on this analysis. Symptomatic patients were self-limiting or sought medical assistance, which is mainly the case in the elderly population. Adults aged 65 years and older are also more at risk of developing complications consequent to influenza infection. The influenza-related complications considered in the present analysis overlap the complications included in other cost-effectiveness analyses of influenza vaccine [16,20–22] and included bronchitis, pneumonia or any unspecified upper respiratory tract infection (URTI), myocarditis, myocardial infarction (MI), renal or central nervous system (CNS) complications, stroke, and exacerbations of chronic obstructive pulmonary disease (COPD). Cardiac decompensation, defined as a worsening of patients with heart failure, has been reported but must be clearly differentiated from myocarditis. This complication was considered in the scenario analysis.

Patients infected with influenza who developed these complications may have been treated in ambulatory or hospital settings. It was expected that most hospitalized patients had previously consulted their general practitioner (GP). In the base case, it was conservatively assumed that fatal events only occurred among hospitalized patients. Inclusion of estimated mortality in nursing homes was considered in the scenario analysis.

The cost-effectiveness model provided detailed results on the influenza complications and hospitalizations avoided with the new vaccine as well as the associated health care savings. The final outcomes of this analysis are expressed as the incremental cost per life year (LY) gained and incremental cost per quality-adjusted life year (QALY).

The national health care payer perspective was primarily considered in this analysis, as the analysis aimed to ascertain information on reimbursement for the new vaccine. The health care perspective, including both national payer and patient costs, was included in the scenario analysis. Robust data were lacking to investigate the societal perspective and impact of elderly adults' infection on young caregivers' quality of life and absenteeism [25].

The time horizon of this analysis was the influenza season, namely, within one year. As influenza-related complications may result in premature death, the model accounted for potential years of life lost beyond the influenza season. These life years were estimated based on life expectancy data in the target population [8] and annually discounted at 1.5% as per Belgian pharmacoeconomic guidelines [26]. The QALYs lost were similarly estimated based on the evolution of utilities as people age. Such an approach was applied in previous cost-effectiveness analyses [16,23,27,28]. The scenario analysis considered 0% and 5% discount rates.

1.3. Inputs

Inputs considered in the present cost-effectiveness analysis were derived from publicly available case-control trials, national databases, the health technology assessment (HTA) body's reports, and the literature. Belgian medical and epidemiological experts were also contacted to validate inputs or assumptions made in the absence of data. Where permission was required to use these sources, it was obtained. No patient-specific, identifying data were used in the analyses; therefore, no approval from an ethics review board was necessary.

1.3.1. Epidemiological and clinical burden

1.3.1.1. Influenza attack rate among unvaccinated elderly adults. Influenza incidence varied yearly. The WHO estimates the annual global influenza attack rate among unvaccinated adults to be between 5% and 15% [29]. Based on a systematic literature review, Somes et al. [30] estimated an annual pooled influenza attack rate of 7.2% (95% confidence interval [CI], 4.3%-12%) among unvaccinated elderly adults (regardless of the need for medical assistance). In the absence of Belgian-specific data for this attack rate, we applied the lower range estimated by the WHO, namely, 5% [29]. This parameter was subject to scenario analysis.

1.3.1.2. Influenza attack rate among vaccinated elderly adults. The attack rate in vaccinated adults was derived from the influenza attack rate in unvaccinated older adults and the respective vaccine effectiveness [29,31–33]. Among elderly adults vaccinated with the standard-dose quadrivalent vaccine, an influenza attack rate of 3% was estimated.

1.3.1.3. Vaccination coverage. From the national health survey conducted in 2018, it was estimated that 61.9% (95% CI, 58.1%-65.6%) of Belgian adults aged 65 years and older are vaccinated against influenza infection [34]. This vaccination coverage was confirmed by another source considering the number of reimbursed influenza vaccines in the Belgian elderly population of 1.38 million in 2021 (INAMI-Pharmanet, personal communication, 2022).

1.3.1.4. Elderly population seeking medical assistance. Sciensano set up a GP and laboratory network to closely monitor the number of patients (vaccinated and unvaccinated) seeking GP assistance for ILI and PCR-confirmed influenza symptoms. Over the first 4 influenza seasons with quadrivalent vaccines (the 2015–2016, 2016–2017, 2017–2018, and 2018–2019 seasons, and pre-SARS-CoV-2 period of the 2019–2020 season), the mean incidence of ILI was estimated at 2.0% and that of PCR-confirmed influenza at 1.1% in the elderly population [2]. The incidence rate reported by Sciensano was expected to underestimate the actual number of influenza-infected elderly adults seeking medical assistance. Various reasons may be put forward: 1) the data reported by Sciensano excluded patients infected with influenza who consulted for a diagnosis other than ILI; and 2) the data reported by Sciensano excluded infected patients who consulted

a specialist directly, called the GP for ILI symptoms, visited the emergency room, or were hospitalized without previous GP consultation [35]. A recent publication reported a higher 5.7% influenza incidence rate over 2 influenza seasons (2017–2018 and 2017–2019) in a community-dwelling elderly population [36]. For these reasons, the present analysis considered that the number of infected cases as reported by Sciensano was underestimated, and 58% of the infected elderly adults were considered to be seeking medical assistance. This percentage of patients seeking medical assistance has been reported in previous studies [3,35,37].

1.3.1.5. Complications. Respiratory diagnoses other than influenza are the most frequent complications and include bronchitis, pneumonia or any URTI, and acute exacerbation of COPD. Myocarditis, MI, renal or CNS complications, and stroke are the nonrespiratory complications associated with influenza infection. Renal complications refer to acute renal failure, glomerulonephritis, and nephrotic syndrome. CNS complications include meningitis, psychosis, epilepsy and Guillain-Barré syndrome. The probabilities of developing these complications were mainly derived from an observational study conducted in the United Kingdom [4] and adapted for a previous cost-effectiveness analysis [20]. The nature of the complications and the risk of hospitalization due to complications were validated by Belgian experts. All nonrespiratory complications were assumed to require hospitalization. Bronchitis and URTIs were mainly managed in outpatient settings. The risk of hospitalization due to pneumonia was derived from a previous Belgian cost-effectiveness analysis [38]. A similar risk of hospitalization was assumed in the case of COPD exacerbations based on the number of hospitalizations due to influenza in combination with pneumonia and COPD diagnoses [3].

In the present analysis, influenza-related mortality was estimated conditional upon hospitalization. The in-hospital mortality risk was mainly sourced from a previous cost-effectiveness analysis [20] adapted to take into account the Belgian age distribution or a more adequate reference [38,39].

Table 1 summarizes the epidemiological, clinical, and utilities inputs used in the present cost-effectiveness analysis.

1.3.2. Vaccine effectiveness

1.3.2.1. Effectiveness of SD-QIV. The effectiveness of the standard quadrivalent influenza vaccine was estimated based on the respective efficacy against the circulating A and B strains as obtained from a meta-analysis [31] and the influenza strain distribution in the elderly Belgian population [41]. Among older adults (aged >60 years), Belongia et al. reported

Table 1. Epidemiological, clinical and utilities inputs.

	65–74 years	75 +years	Source
Population (in 2023)	1,239,022	1,124,603	[40]
Epidemiological data			
Influenza attack rate among unvaccinated elderly adults	5%	5%	[29]
Influenza incidence rate among patients vaccinated with the standard-dose quadrivalent vaccine (estimation)	3%	3%	[29,31,41], Sciensano data
Vaccination coverage	53.2%	70.8%	[34]
Patients seeking ambulatory professional care	40.6%	75.4%	[3,35,37]
Probabilities of developing influenza-related complications (% hospitalization rate; % mortality rate)			
Bronchitis	3.85% (1.0%; 0.03%)	3.85% (1.0%; 0.03%)	[4,20]
Pneumonia	1.46% (59.0%; 5.23%	1.46% (61.0%; 8.71%)	[4,20,38]
URTI	6.05% (1.0%; 0.03%)	6.05% (1.0%; 0.03%)	[4,20]
Myocarditis	0.89% (100%; 7.10%)	0.89% (100%; 7.10%)	[4,20,39], expert advice
Renal complications	0.18% (100%; 13.8%)	0.18% (100%; 29.83%)	[4,20], expert advice
CNS complications	0.35% (100%; 2.9%)	0.35% (100%; 2.9%)	[4,20], expert advice
COPD exacerbations	0.99% (59.0%; 0.03%)	1.42% (61%; 0.03%)	Derived from [3], expert advice
Myocardial infarction	0.13% (100%; 11.9%)	0.13% (100%; 22.33%)	[42], expert advice, adapted from [20]
Stroke	0.75% (100%; 28.20%)	1.79% (100%; 28.20%)	[43], expert advice, adapted from [20]
Vaccine effectiveness			
aQIV (adjuvanted)	56.1%		[33,41], Sciensano
HD-QIV (high dose)	54.7%		[32,41], Sciensano
SD-QIV (standard dose)	40.2%		[31,41], Sciensano
Utilities and disutilities			
Baseline	0.82	0.69	[44]
Symptomatic influenza	−0.15 for 5 weeks		[35]
Hospitalization due to complications other than MI or stroke	−0.38 for 9 to 12 days		[20]
Hospitalization due to MI/stroke	−0.2102 (MI)/-0.2554 (stroke)		[20,45]
Ambulatory care for complications	−0.13 for URTI −0.25 for bronchitis/pneumonia/ COPD		[20] assumption

URTI, upper respiratory tract infection; MI; myocardial infarction; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; aQIV, adjuvant quadrivalent influenza vaccine; HD-QIV: high dose quadrivalent influenza vaccine; SD-QIV: standard dose quadrivalent influenza vaccine.

a pooled vaccine efficacy of 24% (95% CI, −6% to 45%) for A (H3N2), 62% (95% CI, 36%-78%) for H1N1pdm09, and 63% (95% CI, 33%-79%) for type B [31]. Over the years, the distribution of influenza strains circulating in the Belgian population has substantially changed. Based on expert advice, we considered the mean distribution over the last 5 influenza seasons (the pre-SARS-CoV-2 pandemic period of 2019–2020 and the 2014–2015, 2015–2016, 2016–2017, 2017–2018, and 2018–2019 seasons). A(H3N2) was the most prevalent strain, representing 58% of influenza cases; A(H1N1) represented 18.9%, and the influenza B strains represented 23.1% of cases (Sciensano, personal communication, 2022).

1.3.2.2. Effectiveness of HD-QIV. The efficacy of HD-QIV was sourced from the FIM12 clinical trial, which compared a high-dose trivalent influenza vaccine (HD-TIV) with a standard-dose trivalent influenza vaccine (SD-TIV) among elderly adults, demonstrating vaccine efficacy of the high dose relative to the standard dose of 24.24% (95% CI, 9.29%-36.52%) [32]. It was assumed that the relative effectiveness of HD-QIV was equivalent to that of the HD-TIV compared to SD-TIV, which was applied in a recently published cost-effectiveness analysis [23]. Therefore, setting the relative efficacy of HD-QIV vs. at 24.2% (based on Diaz-Granados 2014 [32]) and the efficacy of SD-QIV of 40.2% (based on Belongia 2016 [31] and strains distribution), the estimated vaccine effectiveness for HD-QIV was calculated as follows: $1 - [(1-24.2\%) \times (1-40.2\%)] = 54.7\%$.

1.3.2.3. Effectiveness of aQIV. The efficacy of aQIV was sourced from a recent meta-analysis [33] that reported the relative vaccine effectiveness of the adjuvanted trivalent influenza vaccine (aTIV) compared to HD-TIV. The pooled estimate of the relative efficacy of aTIV compared with HD-TIV indicated a comparable effect, with a slight nonsignificant superiority of 3.2% (95% CI, −2.5% to 8.9%) [33]. It was assumed that the relative vaccine effectiveness of the 2 quadrivalent vaccines would be equivalent to the relative vaccine effectiveness of the 2 trivalent vaccines. Thus, the effectiveness of aQIV vs. no vaccination was derived from the estimated efficacy of HD-QIV vs. no vaccination and the relative efficacy of the aQIV vs. HD-QIV. Considering that the estimated vaccine efficacy for HD-QIV is 54.7%, and the relative efficacy aQIV vs. HD-QIV is 3.2% [33], the estimated vaccine effectiveness for aQIV was calculated as follows: $1 - [(1-3.2\%) \times (1-54.7\%)] = 56.1\%$.

The vaccine effectiveness applied in the present cost-effectiveness analysis, as derived from the distribution of the main influenza strains and the vaccines' respective efficacies against these strains, is reported in Table 1.

1.3.3. Utility inputs

1.3.3.1. Baseline utilities. The Belgian utility values in the target population were sourced from Van Wilder et al. [44].

1.3.3.2. Disutility value due to influenza and its complications. The mean disutility value due to symptomatic influenza was derived from the utility decrements over 5 weeks in the study by Mao et al. [35]. The publication by Cai et al. provided disutility values for influenza-related complications [20]. The duration of disutility was adapted to account for the longer impact (3 additional days) of complications requiring hospitalization compared with those treated in ambulatory settings [37]. The disutility inputs for myocardial infarction and stroke were considered over a 1-year time horizon and were derived from a Belgian cost-effectiveness analysis in cardiology [45]. Utility and disutility values are summarized in Table 1.

1.3.4. Economic burden

1.3.4.1. Vaccine administration. A full GP consultation was considered for the administration cost of the influenza vaccine, as the vaccine was expected to be administered during a vaccination-specific consultation.

1.3.4.2. Ambulatory care cost of influenza symptoms. The cost for ambulatory care of influenza infection was sourced from an observational study conducted among adults aged older than 60 years [35]. The results of this study were aligned with the outcomes of a previous study conducted in the general Belgian population [37]. The costs were inflated to 2023 costs based on the health index as reported by Statbel [46].

1.3.4.3. Cost of complications. The hospitalization costs related to influenza complications were derived from the KCE report 204 [3]. The authors of this report investigated the cost of combined diagnoses (including influenza) in different age groups [3]. It was assumed that healthy patients hospitalized due to influenza complications presented similar costs to patients with underlying conditions who were hospitalized due to influenza infection. For missing data, the hospitalization cost as reported in the financial hospital database of the National Institute for Health and Disability Insurance (NIHDI) was applied [47]. Two publications with Belgian data were used for the cost estimation of complications treated in ambulatory settings [35,38].

Table 2 summarizes the economic inputs used in the present cost-effectiveness analysis. Patient costs were reported for the scenario analysis. The estimates took 10 days of hospitalization into consideration.

2. Results

2.1. Base case

In 2023, the Federal Planning Bureau estimated that 2,363,625 Belgian adults were aged 65 years and older [40]. If 62% of these elderly adults are vaccinated with SD-QIV, we estimate that during the influenza season, 50102 of them will be infected with influenza and seek professional medical care. This number is in line with the estimate reported in a previous Belgian study [23]. Based on our cost-effectiveness model, we also estimate that 3,949 of these elderly adults will be hospitalized and 477 will die due to

Table 2. Economic burden inputs.

Resource use	NIHDI reimbursed *Unit cost (EUR)	Patient** cost (EUR)	Source
Vaccines			
aQIV	€24.73	€8.71	Seqirus
SD-QIV	€12.94	€4.08	[15]
HD-QIV	€32.62	€11.14	[15]
Vaccine administration	€24	€6	[48]
Ambulatory professional care	€52.71	€27.74	[35,46]
Complications: hospitalization costs (mean)			
Bronchitis/URTI	€14,055	€198.63	[4,45,49]
Pneumonia	€14,786	€198.63	[4,45,49]
Myocarditis/Myocardial infarction	€9,338	€198.63	[4,45,49]
Renal complications	€6,402	€198.63	[45,49,50]
CNS complications	€5,666	€198.63	[45,49,50]
COPD exacerbations	€12,729	€198.63	[4,45,49]
Stroke	€12,538	€198.63	[4,45,49]
Complications: ambulatory costs (mean)			
Bronchitis/URTI	€52.44	€35.10	[35,46] assumptions
Pneumonia/COPD exacerbations	€1,060.33	€452.09	[38,46,50] assumptions

NIHDI, National Institute for Health and Disability Insurance.
*Public price reduced by the patient's co-payment or cost reported at charge of NIHDI.
**Co-payment at charge of ordinary beneficiaries.

Table 3. Outcomes in number of events, LYs, QALYs, and costs during the influenza season.

Results in Belgian population aged 65+ years	Considering 62% vaccine coverage with aQIV	Considering 62% vaccine coverage with SD-QIV	Incremental
Outcomes in number of events, LYs and QALYs			
Estimated number of infected patients seeking medical care	43,183	50,102	−6,920
Estimated number of infected patients being hospitalized	3,419	3,949	−530
Estimated number of patients who will die from influenza	410	477	−66
LYs	27,617,751	27,617,095	656
QALYs	18,927,513	18,927,062	451
Health care costs and savings			
Cost for vaccination (vaccine + administration)	€70,920,601	€53,761,687	€17,158,914
Cost for ambulatory care	€3,544,711	€4,101,589	-€556,878
Cost of hospitalizations	€39,387,613	€45,511,298	-€6,123,684
Total health care costs	€113,852,925	€103,374,574	€10,478,351

aQIV, adjuvanted quadrivalent influenza vaccine; LYs, life years; QALYs, quality-adjusted life years; SD-QIV, standard quadrivalent influenza vaccine.

Table 4. ICER and effectiveness expressed in LYs and QALYs.

Outcomes	aQIV compared to SD-QIV
Incremental LYs	656
Incremental QALYs	451
Incremental health care costs	€10,478,351
ICER (in LYs)	€ 15967
ICER (in QALYs)	€ 15227

aQIV, adjuvanted quadrivalent influenza vaccine; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SD-QIV, standard quadrivalent influenza vaccine.

complications related to influenza. These numbers are in line with the hospitalizations and deaths reported by Sciensano over the last years in the pre-COVID era.

A switch to aQIV will result in a decrease in the number of hospitalizations by 530 and premature deaths by 66 over one influenza season. Considering general life expectancy data and age-based utilities, aQIV will save 656 LYs and 451 QALYs over time (Table 3).

To avoid these 66 premature deaths over one influenza season and save 656 LYs over the long term (Table 3), the national health care system will need to invest €10.5 million (Table 4) for the adoption of aQIV in 1.46 million elderly adults. The initial additional €17.2 million required for vaccination with aQIV will be partially compensated by €0.6 million medical outpatient savings and €6.1 million hospitalization savings (Table 3).

Vaccination of elderly Belgian adults with aQIV instead of SD-QIV will require an additional health care budget of €10.5 million but will save 656 LYs. aQIV can be considered a cost-effective alternative to SD-QIV with an incremental cost-effectiveness ratio (ICER) of €15,967 per LY and €15,227 per QALY (Table 4).

Due to uncertainty regarding some parameters and in accordance with Belgian pharmacoeconomic guidelines, these cost-effectiveness results were submitted to sensitivity and scenario analyses [26]. The scenario analysis investigated the cost-effectiveness results of aQIV compared to HD-QIV, which was recently granted reimbursement in the institutionalized elderly population in Belgium.

2.2. Sensitivity analyses

A one-way deterministic sensitivity analysis (DSA) was applied to the key parameters of this cost-effectiveness analysis

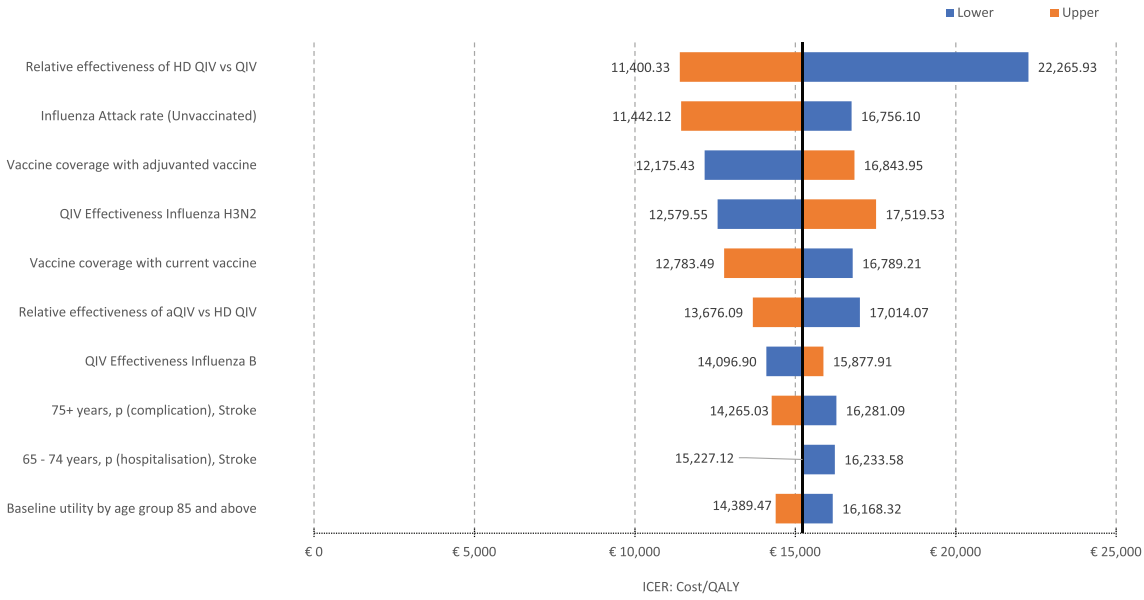

Figure 2. Deterministic sensitivity analysis (DSA) of the top 10 drivers apart from vaccine cost.

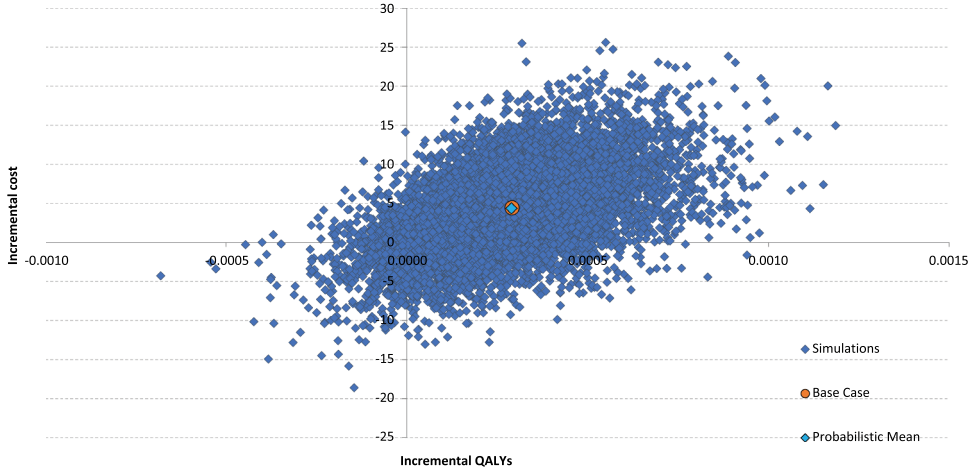

Figure 3. Cost-effectiveness plane.

(Figure 2). The mean effectiveness data varied along their 95% CIs, while the other parameter values varied by ±20%. Apart from vaccine cost, the key drivers of this analysis were the relative effectiveness of aQIV, the attack rate of influenza, the vaccination coverage, and the effectiveness of the current vaccine on the most prevalent influenza strains (Figure 2). Notably, across the wide range of aQIV rVE, results remained robust.

The outcomes reported in the one-way deterministic sensitivity analysis were confirmed in the probabilistic sensitivity analysis where all parameters were simultaneously varied according to a defined probabilistic distribution (beta for effectiveness and utilities values; gamma for the cost data) for 10,000 iterations. In the present cost-effectiveness analysis, based on the current available data, the probability of aQIV being cost-effective was estimated to be 82% at a willingness-to-pay threshold of €35,000. In 17% of the iterations, aQIV was a dominant alternative. The spread in QALYs was explained by the 95% CIs of the efficacy parameter as reported for the quadrivalent influenza vaccine (Figure 3) [31]. The cost-effectiveness acceptability curve in Figure 4 shows the probability that an intervention is cost-effective compared to another at a certain willingness to pay. At a threshold below €16,000, SD-QIV is more frequently cost-effective than aQIV. Beyond a willingness to pay of €16,000, aQIV is a preferred option as it provides a higher effectiveness at an acceptable cost.

2.3. Scenario analysis

To further investigate the uncertainty of some values and assumptions, a scenario analysis was conducted. This analysis confirmed the key impact of the influenza attack rate. Increasing the influenza rate to 7.2% [30] increased the

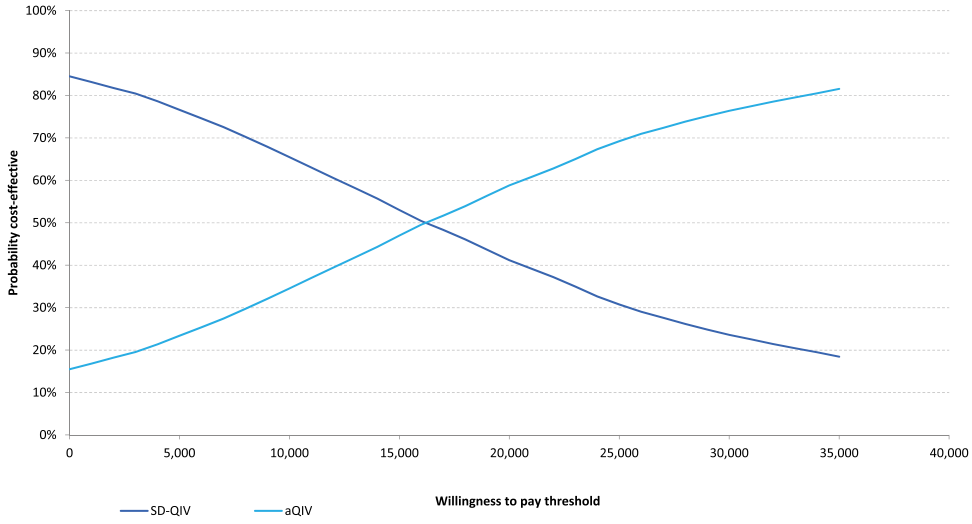

Figure 4. Cost-effectiveness acceptability curve.

numbers of estimated hospitalizations and deaths. Based on the current situation of vaccination with SD-QIV, the number of hospitalizations would increase to 5,686, and the number of deaths increase to 686 if this 7.2% influenza rate is applied. These higher estimates might be explained by the inclusion of hospitalizations and deaths with influenza as the secondary diagnosis, with the primary diagnosis being influenza complications instead of influenza infection. In this scenario, the ICER decreased to €7,608/QALY.

Compared to HD-QIV, aQIV can be considered a dominant alternative, because aQIV is expected to be less expensive and slightly more effective or at least as effective.

A more conservative effectiveness of aQIV was also analyzed, considering effectiveness similar to that of HD-QIV. In this scenario, the ICER increased to €17,721.

If the patients' direct health care costs are included in the analysis, the ICER increases due to the higher patient copayment for aQIV that is only partly covered by health care savings in ambulatory and hospitalization care. Adjuvanted quadrivalent vaccines remain a cost-effective alternative to standard vaccines. We lacked robust data to investigate a broader perspective that would include the impact on the young relatives who would take care of their sick elderly parent [25]. In that case we might expect an improvement of the ICER.

Table 5 summarizes the different scenarios that have been studied.

3. Discussion

The objective of the present analysis was to estimate the cost-effectiveness of aQIV compared to SD-QIV, which has been reimbursed for risk groups, including adults 65 years and older, since the 2015–2016 influenza season in Belgium. The vaccination coverage in this age group is estimated to be

Table 5. Scenario analyses.

Parameters	Base case inputs	Scenario analysis inputs	ICER (base case: €15,227)
Comparator	SD-QIV	HD-QIV	Dominant
Influenza attack	5%	7.2% [23,30]	€7,608
Corresponding number of hospitalizations in SD-QIV strategy	3,949	5,686	
Corresponding number of deaths in SD-QIV strategy	477	686	
Price of adjuvanted influenza vaccine (NIHDI)	€24.73	€22.11	€9,686
Complications: cardiac decompensation due to worsening of heart failure	Not included	Included (frequency equal to that of myocarditis, based on expert opinion [16])	€11,904
Complications: mortality rate in nursing home (outpatient)	Not included	Included [20,38]	€14,617
Disutility and duration due to symptomatic influenza	−0.15 for 35 days [35]	−0.32 for 9 days [20]	€17,160
Discount rate on long-term effects	1.5%	0% 5%	€14,239 €17,314
Effectiveness of aQIV (vs. comparator SD-QIV)	3.2% relative superiority vs. HD-QIV	equal to HD-QIV	€17,721
Cost perspective	National payer (NIHDI); direct health care costs	National payer + patient perspective	€24,447

aQIV, adjuvanted quadrivalent influenza vaccine; HD-QIV, high dose quadrivalent influenza vaccine; NIHDI, National Institute for Health and Disability Insurance; SD-QIV, standard dose quadrivalent influenza vaccine.

constant at approximately 62%, which is below the 75% recommended by the WHO [3,10]. Vaccination coverage slightly increased during the SARS-CoV-2 pandemic period, but trends indicate a return to prepandemic levels. Performant vaccines are of crucial importance. The switch from the previous trivalent vaccine to the quadrivalent vaccine has improved protection against influenza infection. Elderly populations vaccinated with SD-QIV lack optimal protection due to immunosenescence, frailty, and cumulative comorbidities. HD-QIV has been proven to enhance the immune response in this population [32], but its reimbursement has been limited to elderly adults living in nursing homes or other residential institutions [15]. aQIV is expected to be a less expensive alternative to HD-QIV and presents at least similar immunogenicity against influenza in the elderly population [33]. As such, vaccine recommendation agencies such as the US Advisory Committee on Immunization Practices (ACIP) or the UK Joint Committee on Vaccination and Immunization (JCVI) recommend enhanced vaccines for adults aged ≥ 65 in preference to standard-dose influenza vaccines, but do not state a preference on the grounds of differences in effectiveness [51,52].

The Belgian cost-effectiveness results of aQIV were consistent with results reported in other countries [17–19]. Similar to these studies, the present cost-effectiveness analysis was based on a static model that might have underestimated the benefits of vaccination, as it did not take into account the possible herd immunity effect within the elderly group and with other age groups. The customized static model was initially built to evaluate the cost-effectiveness of aQIV in Scandinavian countries [16].

Other limitations of the present cost-effectiveness analysis exist regarding input data. As described in this paper, there was still uncertainty and heterogeneity in the influenza attack rates. We considered a conservative approach in the base case analysis, with an estimated 5% influenza attack rate in the unvaccinated population, which resulted in a 3% attack rate in the population vaccinated with SD-QIV. As a key driver of cost-effectiveness outcomes, this parameter was further subjected to scenario analysis. An influenza attack rate of 7.2%, as reported in a recent systematic literature review [30], was applied. This scenario improved the ICER at €7,608/QALY.

The risk of complications associated with influenza infection was derived from a UK observational study published in 2000 [4] and updated based on expert opinion. Detailed national data on the interaction between influenza infection and patients' underlying conditions or the emergence of complications among healthy patients would have been supportive to accurately capture the burden of influenza infection in the current Belgian context. Because influenza infection can cause health complications or worsen an underlying condition, we expect that currently available data focusing on the primary diagnosis of influenza underestimate the full burden of influenza [53,54]. The national hospital database represents an alternative source of information to the Sciensano database. This database registers the primary and secondary diagnoses consequent to hospital admission. Influenza can be reported as a secondary diagnosis for patients initially admitted to the hospital for a complication or worsening of an underlying condition consequent to influenza infection. From 2017–2019, the national hospital database registered 48% of hospitalizations with secondary diagnoses of influenza in the total number of hospitalizations involving an influenza diagnosis (ICD-10 codes J09-J11) [5]. A similar rationale might be applied to the mortality parameter, but we lacked data. The burden of influenza largely influenced the cost-effectiveness outcomes. Accurate epidemiological data are of crucial importance. Based on the demographic perspectives in 2023, our cost-effectiveness analysis estimates 3,949 hospitalizations due to influenza among elderly adults if they are vaccinated with SD-QIV. This number of hospitalizations is in line with the average of 3,905 hospitalizations reported by Sciensano over the first 4 influenza seasons since reimbursement of the quadrivalent vaccine began (Sciensano, personal communication 2022). The epidemiological data adopted in the present cost-effectiveness analysis were in line with available Belgian data. The number of hospitalizations reflected the primary diagnosis of influenza and disregarded hospitalizations with a secondary diagnosis of influenza that started during hospitalization or influenza complication that caused the primary admitting diagnosis. We opted for a conservative approach in the base case. A recent cost-effectiveness analysis of HD-QIV considered a far higher number of hospitalizations than that in our analysis for a similar number of infected adults seeking medical assistance among adults vaccinated with SD-QIV [23].

The effectiveness of the vaccine is highly dependent on the strains circulating during the influenza season. Variation in circulating strains, especially in mismatched seasons, may contribute to significant differences in effectiveness between the season in which the vaccine was first studied and authorized and subsequent seasons. Due to high heterogeneity over the years, we considered the mean distribution of the strains over the last 5 influenza seasons, as per expert advice. In the future, the actual effectiveness of the vaccine will be highly dependent on the distribution of circulating strains and may vary widely from one influenza season to another. We also assumed the same effectiveness among all elderly adults, regardless of their age or underlying condition.

Regarding the direct cost estimations, we considered one full GP consultation for the administration of the vaccine. The vaccination cost might be reduced should the health authorities implement an elderly vaccination program with simultaneous administration of vaccines (i.e. the influenza vaccine together with the COVID-19 vaccine) or the administration of the vaccine during a routine visit for patients with underlying conditions.

The cost-effectiveness model assumed hospitalizations to be conditional upon influenza-related complications, which had an impact on the cost of hospitalization. The mean hospitalization cost was estimated at € 11.526 in this elderly population (excluding an estimated €199 charged to the

patient) based on a previous study [3]. This cost was lower than the cost applied in a cost-effectiveness analysis of HD-QIV [23]. Some hospitalized patients will end up in the intensive care unit. Post-intensive care hospitalization has been subject to investigation by KCE [55]. The authors of the KCE study emphasized the long-term effects of hospitalization in the intensive care unit [55]. These long-term effects can be a source of additional health care costs. In the present cost-effectiveness analysis, the costs after hospitalization discharge were not taken into consideration, which might represent an underestimation of the actual value of vaccination [25].

Influenza infection is associated with high rate of antibiotic consumption, and limited evidence suggests an impact of vaccination on antibiotic prescriptions [56]. Our model did not take into account the possible side effects of antibiotics. Moreover, we also did not account for broader effects such as the long-term impact on trends in antimicrobial resistance [25]. Due to a lack of robust data, this analysis has also disregarded the potential impact on caregivers' quality of life and absenteeism. This broader perspective should be part of future evaluations [25].

Finally, our analysis considered a period before the COVID-19 pandemic. Currently data on the impact of endemic COVID-19 on influenza incidence are lacking. This analysis should be updated when sufficient data are available to appropriately anticipate the evolution of COVID-19 infection and its impact on influenza incidence.

4. Conclusions

To improve response immunity among elderly adults, high-dose and adjuvanted influenza quadrivalent vaccines have been developed. Based on currently available knowledge, the present analysis suggested that aQIV is cost-effective compared to SD-QIV, with an ICER of €15,227/QALY from a public payer perspective. The results were subject to sensitivity and scenario analyses. Key drivers included the influenza attack rate as well as the effectiveness and price of vaccines. Increasing the influenza attack rate from 5% to 7.2% decreased the ICER to €7,608/QALY. This scenario assumed that the current number of hospitalizations and deaths reported by Sciensano disregards the hospitalizations registered with a secondary diagnosis of influenza, the primary diagnosis being complications due to influenza infection. When compared to HD-QIV, aQIV is cost-saving, with an at least similar effectiveness. This analysis suggests that vaccination with aQIV is a cost-effective alternative to current influenza vaccines to reduce the number of hospitalizations and deaths at an acceptable cost for the public payer. It may be that a gradual adoption of aQIV may be the best way to proceed while preventing an important number of hospitalizations and deaths.

Acknowledgments

The authors acknowledge the support given by Professor Dr. Willy Peetermans, infectiologist at University Hospital UZ Leuven, Belgium, and Professor Dr. Bert Vaes, general practitioner, Belgium, for the review of the model components, inputs and draft paper. The authors also acknowledge the support given by Germaine Hanquet, independent epidemiologist, Belgium, for the review of the model components and inputs. Medical consultant C. Gordon Beck provided editorial support for the final manuscript which was funded by CSL Seqirus.

Funding

This paper was funded by Seqirus CSL.

Declaration of interest

S Marbaix was contracted by CSL Seqirus U.S.A Inc. to conduct this study and organize panel discussion with epidemiological and clinical experts. JF Mould-Quevedo is employed by CSL Seqirus and a shareholder of CSL Limited. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

One reviewer was previously an employee of Seqirus. The remaining reviewers have no other relevant financial relationships or otherwise to disclose.

Author contribution statement

Conception and design: JF Mould-Quevedo and S Marbaix; analysis and interpretation of the data: S Marbaix and JF Mould-Quevedo; Drafting of the paper or revising it critically for intellectual content: S Marbaix, N Dauby, JF Mould-Quevedo; Final approval of the version to be published: S Marbaix, N Dauby, JF Mould-Quevedo. All authors agreed to be accountable for all aspects of the work.

Data availability statement

All data used (except price of aQIV) in this analysis are publicly available from the sources cited in Table 1.

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