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The Potential Cost-effectiveness of Quadrivalent versus Trivalent Inactivated Influenza Vaccine for the Portuguese Elderly Population

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ABSTRACT

Quadrivalent Inactivated Vaccines (QIV) are expected to replace Trivalent Inactivated Vaccines (TIV) over time. In Portugal, TIV is free of charge for risk groups, where the elderly are included. On its turn, QIV was recently launched in October 2018 and provides wider protection as it includes an additional lineage B strain. The main objectives of this project were to adapt the model developed by Universidad Francisco de Vitoria to the Portuguese elderly population in order to estimate the potential cost-effectiveness of switching from TIV to QIV from the National Health Service (NHS) perspective.

A decision tree model was created and data on Hospitalizations in the 2015/16 season were extracted from the National Database on Hospital Morbidity and used to inform the model. Both alternatives were compared. A one-way sensitivity analysis was performed to find the parameters with the biggest impact on ICER, and a probabilistic sensitivity analysis allowed to evaluate the robustness of the base case results.

By switching from TIV to QIV, the model estimated that about 37 confirmed influenza cases, five hospitalizations and one death could have been averted in the 2015/16 season in the elderly, resulting in a cost-saving of 20,695€. However, the higher cost of QIV would lead to a total increment of 2,848,924€ and the resulting ICER would be 14,242,844€/QALY, largely above the usual cost-effectiveness thresholds. PSA results reinforced the base case conclusions, with an 95% interval estimate of (7,047,221; 46,191,560) for ICER, also not including the usual acceptable values. One-Way Sensitivity Analysis (OWSA) allowed to find the disutility associated with ILI when no confirmed influenza and the cost of quadrivalent vaccine as the parameters most sensitive for ICER. From the NHS, this study concluded that QIV is not cost-effective for the elderly population.

KEYWORDS

Cost-effectiveness; Influenza; Trivalent Vaccine; Quadrivalent Vaccine; Elderly

RESUMO

A gripe sazonal é uma doença respiratória aguda que afeta as vias respiratórias e é provocada pelo vírus Influenza, sendo caracterizada por sintomas como febre, tosse, dores musculares e articulares e dores de cabeça. As epidemias ocorrem anualmente, principalmente no inverno e um dos grupos mais afetados são os indivíduos com idade igual ou superior a 65 anos. A vacinação é a forma mais eficaz de proteção contra a infeção pelo vírus.

Ao longo do tempo, é esperado que as vacinas inativadas tetravalentes venham a substituir as vacinas inativadas trivalentes. Em Portugal, as vacinas trivalentes são totalmente comparticipadas pelo Serviço Nacional de Saúde para grupos de risco, onde se incluem indivíduos com idade igual ou superior a 65 anos. Estas contêm duas estirpes de vírus influenza do tipo A e uma estirpe da linhagem B. Por sua vez, as vacinas tetravalentes foram recentemente lançadas no mercado, em outubro de 2018, e oferecem maior proteção, já que contêm uma estirpe adicional da linhagem B. O principal objetivo deste trabalho consistiu em adaptar o modelo desenvolvido pela Universidade Francisco de Vitoria ao contexto português, de forma a estimar a relação custo-efetividade associada à substituição das vacinas trivalentes pelas vacinas tetravalentes, na perspetiva do Serviço Nacional de Saúde (SNS). Para além disso, pretende-se também individualizar os custos por regiões NUTS II (Norte, Centro, Lisboa e Vale do Tejo, Alentejo e Algarve), considerando diferentes quotas de mercado.

Para avaliar a relação custo-efetividade da substituição das vacinas tetravalentes pelas trivalentes, foi utilizado um modelo de árvore de decisão onde o grupo alvo foi a população de Portugal Continental com idade igual ou superior a 65 anos. Foi considerado um horizonte temporal de 1 ano, uma vez que as epidemias de gripe se repetem anualmente. A medida de efeito considerada correspondeu ao *Quality Adjusted Life Year* (QALY), que mede os ganhos de saúde em quantidade e em qualidade, referindo-se à mortalidade e morbilidade, respetivamente.

A árvore de decisão começa por ter em conta se os indivíduos foram vacinados, uma vez que a vacina contra o vírus influenza deve ser administrada no início de cada época gripal. De seguida, verifica se os indivíduos desenvolveram síndrome gripal, e posteriormente se têm gripe confirmada. Para os casos de gripe confirmada, é tido em conta se foi diagnosticada no contexto de consulta em Cuidados de Saúde Primários, hospitalização devido a pneumonia, doença respiratória ou doença cardíaca. Se a gripe foi diagnosticada em contexto de consulta, de seguida considera-se se evoluiu para hospitalização. Os pontos terminais dos caminhos da árvore de decisão dividem-se em: "Morte" ou "Saudável", sendo que o último inclui todos os indivíduos que não morreram, independentemente da sua condição. A árvore de decisão foi alimentada por probabilidades, custos e QALYs. Para cada caminho da árvore foram calculados os custos e QALYs esperados. O total destas duas medidas permite o cálculo do Rácio de Custo-efetividade Incremental (RCEI), o qual resulta da razão entre a diferença em custos entre as duas vacinas e a diferença em efeitos. Os dados de internamento foram extraídos da base de dados central de morbilidade hospital, sendo referentes à época gripal de 2015/16 e permitiram calcular as probabilidades de hospitalização e subsequente morte e custos associados. Os restantes dados foram extraídos de diversas fontes tais como: o Instituto Nacional de Estatística, relatórios divulgados pelo Instituto Nacional de Saúde Doutor Ricardo Jorge, entre outros.

Uma das principais fontes de incerteza no modelo é a incerteza paramétrica que resulta da estimação de parâmetros baseada em amostras. Desta forma, a análise de sensibilidade foi realizada de forma a, por um lado, encontrar os parâmetros com maior impacto na variação do RCEI, através da análise de sensibilidade univariada, e por outro, avaliar a robustez dos resultados do caso base, através da análise de sensibilidade probabilística. A primeira análise referida incluiu todos os parâmetros do modelo, e quando conhecido, foi considerado o intervalo de confiança, caso contrário foram considerados os limites ±20% do seu valor do caso base. Assim, os valores dos limites inferiores e superiores considerados, foram substituídos no modelo de forma a estimar o RCEI e os resultados foram

apresentados através de um diagrama de tornado, o qual ordena os parâmetros desde o de maior impacto até ao de menor impacto no RCEI.

A análise de sensibilidade probabilística avaliou a robustez dos parâmetros do caso base, nomeadamente dos parâmetros estimados com base em amostras, uma vez que os restantes se referem à população de 2015/16, não trazendo incerteza ao modelo para essa época gripal. Foi atribuída uma distribuição de probabilidade a cada um dos parâmetros em questão e foram realizadas 1000 simulações de Monte Carlo. Em cada iteração foi simulado um valor para os parâmetros com incerteza – valor probabilístico - com base na distribuição de probabilidade atribuída e os resultados do modelo foram guardados. Este processo teve como base o Teorema da Transformação Integral de Probabilidade. Para as probabilidades, foi atribuída a distribuição Beta, em que os parâmetros α e β foram estimados através do Método dos Momentos usando a média e o desvio-padrão da amostra. De forma semelhante, para as disutilidades foi atribuída a distribuição Gamma e Lognormal e os resultados foram comparados para perceber qual a distribuição que produzia menor variabilidade. Mais uma vez, recorreu-se ao método dos momentos para estimar os parâmetros das distribuições a partir da média e do desvio-padrão da amostra. Para a efetividade, tendo em conta que é calculada a partir de um Risco Relativo, foi aplicada a distribuição Lognormal. Os resultados da análise probabilística foram apresentados no plano Custo-efetividade e permitiram, ainda, traçar a curva de aceitabilidade de custo-efetividade (CACE) usando a medida *Net Benefit*. Esta medida permite a uniformização da escala entre custos e efeitos, podendo ser *Net Monetary Benefit* ou *Net Health Benefit*. Por fim, a CACE estabelece a probabilidade de uma vacina ser custo-efetiva para vários limites considerados.

De forma a individualizar os custos por regiões NUTS II, foram considerados vários cenários de quotas de mercado, nomeadamente, o cenário atual do SNS – 100% de quota de mercado para as vacinas trivalentes, um cenário de 50%-50% e ainda um cenário de 100% de quota para as vacinas tetravalentes.

De acordo com o modelo, a mudança para as vacinas tetravalentes levaria a que cerca de 37 casos de gripe confirmados, cinco hospitalizações e uma morte pudessem ter sido evitados na época de 2015/16 em pessoas com idade igual ou superior a 65 anos, resultando numa poupança de 20,695€ para o SNS. Contudo, o custo mais elevado da vacina tetravalente levaria a um incremento total de 2,848,924€ e um RCEI de 14,242,844€/QALY, bem acima dos limites usuais. A análise probabilística reforçou as conclusões do caso base, tendo o intervalo a 95% para o RCEI sido estimado a (7,047,221; 46,191,560). A análise univariada permitiu identificar a disutilidade associada a ter síndrome gripal sem confirmação de gripe e o custo da vacina tetravalente como os parâmetros mais sensíveis do modelo. A região Norte foi identificada como a região com os custos mais elevados, enquanto que a região Centro é a região com maior diferença em efeitos para todos os cenários.

Da perspetiva do SNS, as vacinas tetravalentes não são custo-efetivas para indivíduos com idade igual ou superior a 65 anos. No entanto, mais investigação deve ser realizada no sentido de perceber o impacto das vacinas tetravalentes, não só para o SNS como a nível social.

PALAVRAS-CHAVE

Custo-efetividade; Gripe; Vacina Trivalente; Vacina Tetravalente; População Idosa

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ABBREVIATIONS

ACES/ULS - Agrupamentos de Centros de Saúde/ Unidades Locais de Saúde

ACSS - Administração Central do Sistema Saúde

AT - Antiviral Treatment

CBA - Cost-Benefit Analysis

CC – Cost Comparison

CCA – Cost Consequences Analysis

CDC - Center for Disease Control and Prevention

CE - Cost-Effectiveness

CEA - Cost-Effectiveness Analysis

CEAC - Cost-Effectiveness Acceptability Curve

CI - Confidence Interval

CNS - Central Nervous System

COPD - Chronic Obstructive Pulmonary Disease

CUA - Cost-Utility Analysis

DGS – Direção Geral de Saúde

DRG – Diagnosis-Related Group

DSA - Deterministic Sensitivity Analysis

EEA - European Economic Area

EU/EEA - European Union/ European Economic Area

GDP - Gross Domestic Product

GISRS - Global Influenza Surveillance and Response System

GNI - Gross National Income

GP - General Practitioner

HA – Hemagglutinin

HD - Heart Disease

HRQoL - Health-Related Quality of Life

ICD - International Classification of Diseases

ICER - Incremental Cost-Effectiveness Ratio

IIV- Inactivated Influenza Vaccines

ILI - Influenza-like Illness

INE - Instituto Nacional de Estatistica

INSA - Instituto Nacional de Saúde Doutor Ricardo Jorge

LAIV - Live Attenuated Influenza Vaccines

MC - Monte Carlo

ML – Maximum Likelihood

NA - Neuraminidase

NB - Net Benefits

NDHM – National Database on Hospital Morbidity

NHB - Net Health Benefit

NHS - National Health Service

NISP - National Influenza Surveillance Programme

NMB - Net Monetary Benefit

OWSA – One-Way Sensitivity Analysis

PSA - Probabilistic Sensitivity Analysis

QALY - Quality-Adjusted Life Year

QIV - Quadrivalent Influenza Vaccine

RCTs - Randomized Clinical Trials

RD - Respiratory Diseases

RIDTs- Rapid Influenza Diagnostic Tests

RNA - Ribonucleic Acid

RNG - Random Number Generator

RR - Risk Ration/Relative Risk

RSP - Retail selling Price

RT-PCR - Reverse Transcriptase-Polymerase Chain Reaction

TIV - Trivalent Inactivated Vaccine

WHO – World Health Organization

WTP - Willingness-to-pay

Chapter 1
INTRODUCTION

1 Introduction

Seasonal influenza is an acute respiratory illness caused by infection with influenza viruses. The infection may cause signs and symptoms like fever, cough, headache, muscle and joint pain and weakness (1). In Portugal, outbreaks occur every winter and are characterised by significant morbidity in the general population as well as increased mortality rates particularly in high risk groups, namely the elderly, patients with chronic or immunosuppressive conditions and pregnant women (2). About 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths are estimated to occur globally due to influenza outbreaks. In developed countries, the majority of influenza-associated deaths occurs in the elderly (1). In Portugal, a recent study estimated that $19.4/10^5$ extra hospitalizations occur each year due to influenza and pneumonia during influenza season. In the elderly, the number is about 3.5 times higher (3).

According to World Health Organization (WHO) vaccination is the most effective way to prevent seasonal influenza and subsequent severe outcomes. Inactivated influenza vaccines may protect against three or four influenza virus subtypes and therefore are named trivalent or quadrivalent vaccines, respectively. Quadrivalent Influenza Vaccines (QIV) contains the same viruses of Trivalent Inactivated Vaccines (TIV), which are two influenza A subtypes and one influenza B subtype, and an additional influenza B strain. Thus, quadrivalent vaccines provide wider protection against circulating influenza viruses (4).

In Europe, TIVs are available in all EU/EEA (European Union/ European Economic Area) countries, while quadrivalent are not available for use in all (5). In Portugal, QIV was launched in October 2018 (6).

Economic evaluations allow to compare different alternatives in terms of both their costs and consequences and include for example Cost-Effectiveness Analyses (CEA) (7). In Cost-effectiveness evaluations, costs are related to a single and common effect that may vary between the alternative healthcare programmes and consequences are measured in natural units or measures of Health-related quality of life (HRQoL). Results are usually presented as incremental cost per unit of effect. For the current work, results will be stated as €/QALY (Quality-Adjusted Life Year), (7).

In 2017, a cost-effectiveness analysis of Spanish influenza vaccination has been developed by *Universidad Francisco de Vitoria* (INFLUFV model) and was aimed at comparing all influenza vaccination programmes available for use in the elderly and individualize costs by regions (8,9).

As no cost-effectiveness analysis of Portuguese influenza vaccination has been reported in literature, the adaptation of the Spanish model to the Portuguese scenario could allow better knowledge about Portuguese reality and help health authorities developing more accurate policies about influenza vaccination. Moreover, it will be an important step towards developing an Iberian model. Thus, the main aims of this project are the following:

- Adapt and validate the INFLUFV model, developed by *Universidad Francisco de Vitoria* for Spain, to Portugal;
- Estimate the potential cost-effectiveness of switching from TIV to QIV in the Portuguese elderly;
- Develop a model which allows to individualize the expected costs of influenza vaccination in the elderly by NUTS II, according to population characteristics.

Chapter 2

LITERATURE REVIEW

2 Literature Review

2.1 Influenza Viruses Types

Seasonal influenza is an acute respiratory infection caused by influenza virus which circulate in all parts of the world and it spreads easily from person to person (1). There are 4 types of seasonal influenza viruses, types A, B, C and D. According to the convention published in February 1980 in the Bulletin of the World Health Organization, the strain designation for influenza virus may contain the following information in the following order: the antigenic type (e.g. A, B, C), the host of origin (e.g. swine), geographical origin, strain number, year of isolation, for influenza A viruses, the hemagglutinin and neuraminidase antigen description in parentheses (e.g. (H1N1)) (1).

Only influenza A and B viruses circulate and cause seasonal epidemics of disease. Influenza C viruses are less frequent in humans and when they appear cause mild infections. Type C virus is usually associated with common cold–like symptoms and sporadically with lower respiratory tract illness. Commonly, infection by type C virus is asymptomatic. On the other hand, influenza D viruses are not reported to cause illness in humans (1,10).

Influenza A viruses are classified into subtypes according to the combinations of the Hemagglutinin (HA) and the Neuraminidase (NA). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes (11). Currently circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses. Influenza B viruses are not classified into subtypes but can be broken down into lineages. Currently circulating influenza type B viruses belong to either B/Yamagata or B/Victoria lineage (12).

2.2 Epidemiology

Influenza outbreaks are recorded every year. In the temperate zones of the northern and southern hemispheres (like Portugal and Spain), influenza outbreaks occur during the winter, while in the tropics, influenza outbreaks occur throughout the year (13,14). An influenza pandemic can occur when a new and different type of influenza A virus emerge and it is able to infect humans who were not immunized yet (11,12). The most recent pandemic was in 2009, caused by A(H1N1)2009 virus after which it became a seasonal influenza serotype (12). In Portugal, 1,189 persons were hospitalized, around 10% in intensive care units. The most people affected were younger than 30 years old (0-9 years (25%), 10-19 years (35%) and 20-29 years (17%)). This pandemic caused 124 deaths, 87% of them occurred in people younger than 65 years old, and the main cause of death was primary viral pneumonia (15).

In the 20th century, three global influenza pandemics were also recorded. The most severe pandemic was “Spanish Flu” which swept the continents in 1918–1919, affected 500 million people, and caused about 30-40 million deaths worldwide, mostly among people aged 15-35 years. In 1957, H2N2 influenza pandemic (Asian flu) caused an estimated 1-2 million fatalities worldwide. The 1968 H3N2 influenza pandemic (Hong Kong flu) caused an estimated 700,000 to 1 million fatalities worldwide (16).

2.3 Genetic Changes

Pandemics are associated with influenza A viruses, as their hemagglutinin and neuraminidase antigens have propensity to undergo antigenic variation periodically. These major variations are named *antigenic shifts*. In contrast, minor variations are designated *antigenic drifts* (14). While type A viruses undergo major and minor changes, type B viruses change only by *antigenic drifts* – that is why pandemics are caused by type A viruses. *Antigenic shifts* may involve the hemagglutinin alone or both,

hemagglutinin and neuraminidase, and consist of a reassortment of genes among different influenza A viruses infecting the same host cell (either human cells or animal cells). The result is a new influenza A subtype, to which people have not developed immunity yet (17,18). On average, *antigenic shifts* occur every 10 years (11). *Antigenic drifts* happen continually over time as the virus spreads within population and replicates. As *antigenic drifts* are small changes, the new virus produced is closely related to the previous one, remaining with similar antigenic properties, so the immune system can recognize it and respond. However, the accumulation of hemagglutinin and neuraminidase genes mutations within a single strain of virus may result in an antigenically different virus, which is no more recognized by the immune system. For this reason, the composition of influenza vaccines is reviewed every year (17,18). Influenza B virus undergo less frequent and less extensive variation than those of influenza A viruses, which may explain the lesser extent of the disease.

2.4 Transmission and Incubation

Influenza virus spreads easily, particularly in crowded areas - for example, schools and nursing homes. Virus transmission occurs mainly through droplets generated by coughs and sneezes, but also through hand-to-hand contact and fomite transmission. The droplets released when someone coughs, sneezes or talks can spread up to one meter, and consequently, infect people in a close proximity. Incubation period ranges from one to four days (usually two days) (12,14,19).

2.5 Pathogenesis

Influenza viruses are enveloped, they belong to the Orthomyxoviridae family and their genome consists of single-stranded RNA (Ribonucleic Acid) viruses of negative polarity (16,20). The core nucleoproteins allow to distinguish the four types of influenza viruses. The single-strain of RNA is divided into eight segments and each segment may comprise one or two genes. For instance, segment four contains hemagglutinin gene and segment six includes neuraminidase gene (15,21).

When an immunologically susceptible person inhales the aerosol from respiratory secretions of infected individuals and the virus is not neutralized by secretory antibodies (acquired from vaccination or previous virus contact), the respiratory epithelium is infected. The cells affected are essentially ciliated epithelial cells, but also alveolar cells, mucous gland cells, and macrophages (14,22).

Hemagglutinin and neuraminidase have an important role in influenza virus infections. Hemagglutinin binds to respiratory epithelial cells and allows cellular infection, where the virus replication occurs within 4 to 6 hours. Neuraminidase spikes provide the virus access to cell surfaces by hydrolyzing mucus in the lungs (18) and cleaves the bond between newly replicated virions and cell surface, leading to the spread of infection (14,23,24).

2.6 Symptoms and Complications

According to the World Health Organization, seasonal influenza is characterized by a sudden onset of fever, dry cough, headache, muscle and joint pain, severe malaise, sore throat and a runny nose. The cough can be severe and can last two or more weeks. Influenza infection can cause either mild illness with afebrile respiratory symptoms like the common cold or can lead to severe prostration and even death (12). In uncomplicated influenza, the acute illness lasts between two and five days, and most patients have largely recovered in 1 week, although cough may persist for 1 to 2 weeks longer. However, high risk groups may experience severe influenza illness. Such groups include young children, adults aged 65 years and older, pregnant women and people with certain chronic medical conditions, including

cardiac or respiratory diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression (14,25).

Pneumonia is the most significant complication of influenza (14). Primary influenza viral pneumonia is characterized by persistent fever, progressive cough, dyspnea, and cyanosis following the initial presentation. It is the least common but most severe of the pneumonic complications. The groups at highest risk for this complication are people ≥ 65 years, particularly those with cardiovascular disease and nursing home patients. People < 65 years with chronic pulmonary disorders may be at risk as well (14,22). Secondary bacterial pneumonia occurs after acute influenza. It is characterized by a reappearance of fever and other bacterial pneumonia symptoms after 2 or 3 days of acute influenza. The most common pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* (14). These organisms colonize the nasopharynx and, consequently, cause infection. Elderly people with chronic pulmonary and cardiac disease are the most susceptible to secondary bacterial pneumonia (14,22). Mixed viral and bacterial pneumonia is the most common pneumonic complication. Patients who develop this condition, show a gradual progression of the acute illness or transient improvement followed by clinical exacerbation. This kind of pneumonic complications occurs essentially in patients with chronic cardiovascular and pulmonary diseases (14).

Other respiratory complications may include worsening of Chronic Obstructive Pulmonary Disease (COPD) and exacerbation of chronic bronchitis and asthma. Extrapulmonary complications comprises myositis, rhabdomyolysis, and myoglobinuria. Myocarditis and pericarditis have been associated with influenza infections as well. Regarding the Central Nervous System (CNS), encephalitis, transverse myelitis, and Guillain-Barré syndrome, have been reported during influenza (14,22). Finally, influenza infection usually contributes to worsening of underlying cardiovascular, pulmonary, or renal function, which sometimes means irreversible changes, leading to death (14).

2.7 Diagnostic

During periods of high influenza activity and inside epidemics situations, influenza infections are usually clinically diagnosed. When influenza occurs outside of a typical season, the infection of other respiratory viruses, e.g. rhinovirus, respiratory syncytial virus, parainfluenza and adenovirus, may mimic acute influenza - Influenza-Like Illness (ILI) - which makes the clinical differentiation of influenza from other pathogens difficult. When differential diagnostic is needed, the diagnostic methods used are Rapid Influenza Diagnostic Tests (RIDTs) and tests requiring a swab collected from patient's nose or throat, in order to perform direct antigen detection, virus isolation, or detection of influenza-specific RNA by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR). Although RIDTs provide results in only 10-15 minutes, they are less accurate and sensitive than other tests (12,26).

2.8 Treatment

Patients who do not belong to a high-risk group should be managed with symptomatic treatment, which is aimed at relieving symptoms of influenza, such as fever or joint pain. Additionally, patients should be advised to stay home in order to minimize the risk of infecting people around them (12).

Otherwise, antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications. According to *Orientação 007/2015 (Portuguese guidelines)* from Directorate-General of Health and Centers for Disease Control and Prevention (CDC), it is recommended antiviral treatment for the following high-risk complications groups:

- adults aged 65 years and older;

- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), and metabolic disorders (including diabetes mellitus), neurologic and neuromuscular or oncologic conditions;
- persons with immunosuppression, including that caused by medications or by HIV infection;
- persons who are extremely obese (i.e., body mass index is equal to or greater than 40 in adults);
- persons aged younger than 19 years who are receiving long-term aspirin therapy;
- women who are pregnant or postpartum (within 2 weeks after delivery) or in case of termination of pregnancy (at any gestational age and within 2 weeks);

Antiviral treatment is also recommended for healthcare professionals with influenza in contact with patients (26–28).

In Portugal, oseltamivir phosphate is the antiviral treatment available (marketed under the trade name Tamiflu®). Oseltamivir belongs to neuraminidase inhibitors class (glycoproteins found on the virion surface – see sections 2.1 and 2.5). The recommended dosage and duration of Oseltamivir treatment for adults is 75mg twice a day for 5 days. However, dosage and duration should be adjusted according to patient illness (26,27,29).

2.9 Prevention

According to WHO, "the most effective way to prevent the disease is vaccination" (12). Vaccination should be administered annually in order to provide optimal protection. Influenza Surveillance System in Portugal is usually activated on week 40 (October) of a given year (*n)* and lasts up week 20 (April) of the following year (*n+1)* (fig. 2.1) (30,31). So it is recommended the administration of the vaccine during all autumn and winter, preferably until the end of the year *n* (6). The development of immunity against influenza viruses takes about two weeks after vaccination (19).

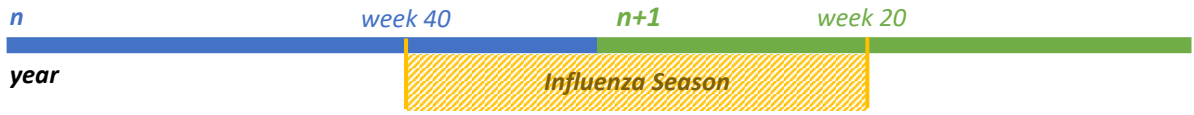


Figure 2.1 *Duration of a typical influenza season (prepared by the author)*

In 2003, the World Health Assembly recommended the Member States and the European Economic Area (EEA) countries to improve seasonal influenza vaccination coverage with the aim of reaching 75% of vaccination coverage rate in the elderly and among persons with chronic illnesses by 2010 (32). In 2005, it was reaffirmed by a European Parliament declaration and in 2009, the European Council extended the deadline until 2015 (32,33). However, several European countries reported declining vaccination coverage among older people from 2008/09 to 2014/15 seasons. Portugal reported an increase in vaccination uptake throughout these seasons (34). In 2015/16 season, influenza vaccination coverage was 50.1% in Portugal (35).

A Cochrane study reviewed eight Randomized Clinical Trials (RCTs) assessing efficacy against influenza or effectiveness against ILI or safety in the elderly and concluded that risk of influenza decreases from 6% to 2.5%, and risk of ILI decreases from 6% to 3.5% between unvaccinated and vaccinated groups (≥ 65 years of age) during a single season. Furthermore, results indicate that 30 persons need to be vaccinated to prevent one person having influenza as well as 42 need to be vaccinated to prevent one person having an ILI (36).

For the 2015/16 season, the CDC estimated that 5.1 million influenza illnesses, 2.5 million influenza-associated medical visits and 71,000 influenza-associated hospitalizations have been averted by influenza vaccination in the United States. Furthermore, CDC estimated that influenza vaccination prevented 3,000 pneumonia and influenza deaths and between two and four times more the number of deaths associated with respiratory and circulatory diseases, (37). In the European Union it is estimated that influenza vaccination prevents up to 37,000 deaths each year (38).

2.9.1 Types of seasonal influenza vaccines

The role of vaccines is to simulate an infection to allow the body to produce antibodies and activate other defense mechanisms against the threat. Antibodies destroy the threat and stay in the body, providing immunity (36).

There are two main types of seasonal influenza vaccines, namely Inactivated Influenza Vaccines (IIV) and Live Attenuated Influenza Vaccines (LAIV) (5). The inactivated vaccines available in EU/EEA may contain either split virion influenza virus products (viral structure is broken up by a disrupting agent) or subunit influenza products (only contain surface antigens – H and N) (5,36). The different inactivated influenza vaccines developed are trivalent, trivalent adjuvanted and quadrivalent. Trivalent vaccines are the most common inactivated influenza vaccines and protect against three different influenza viruses, specifically two influenza A strains and one influenza B lineage, as described in the following section. In some EU/EEA countries, adjuvanted trivalent vaccines are available for older people to empower immune response (5,39). Quadrivalent inactivated influenza vaccines are available since 2014/2015 season in some EU/EEA countries and contain one more influenza B strain in addition to those included in trivalent vaccines. QIVs are expected to replace TIVs over time (5). LAIV are approved in some EU/EEA countries since 2011. They are indicated for children or adolescents aged 2-17 years old for intranasal use and are available as quadrivalent vaccines (5).

2.9.2 Vaccine Composition

Seasonal vaccines against influenza viruses contain three or four strains, which are selected every year based on which influenza viruses are causing illness in humans, the extent of the virus spread and the effectiveness of vaccination in the previous season. This selection is carried out by WHO and supported by information gathered from the Global Influenza Surveillance and Response System (GISRS) (39,40).

As mentioned above, trivalent vaccines contain only one influenza B lineage (Victoria or Yamagata lineage). The irregular circulation of influenza B lineages makes the decision on which lineage to include in TIV difficult. When the chosen B lineage is not the same as the lineage responsible for most of cases in a season with significant circulation of influenza B, it is named an influenza B vaccine mismatch. From 2000 to 2013, the proportion of influenza type B over all influenza seasons was 22.6% worldwide and 21.4% in northern hemisphere. Influenza B vaccine mismatch was observed in roughly 25% of the seasons (41). Quadrivalent vaccines have been developed to avoid mismatch cases. However, in many countries, only trivalent vaccines are recommended, what may be associated with unavailability of quadrivalent vaccines, higher cost of QIV, potential positive impact not recognized or vaccine authorization in process (5). In Portugal, QIV was first marketed in October 2018 (42).

Table 2.1 summarizes the recommendations of the WHO and DGS on the composition of trivalent and quadrivalent influenza vaccines for 2015/16 season (this work relies on data from this

season) and 2018/19 season (6,43–45). In 2015/2016 season in Europe (including Portugal), influenza A(H1N1)pdm09 was predominantly detected, followed by influenza B (mainly Victoria lineage), but to a lesser extent (46,47).

Table 2.1 *Recommendations on the composition of influenza virus trivalent and quadrivalent vaccines for 2015/16 and 2018/19 seasons (6, 44-46)*

Season	Vaccine	Composition
2015/16	TIV	- A/California/7/2009 (H1N1)pdm09-like virus; - A/Switzerland/9715293/2013 (H3N2)-like virus; - B/Phuket/3073/2013-like virus.
	QIV	The above and - B/Brisbane/60/2008-like virus
2018/19	TIV	- A/Michigan/45/2015 (H1N1)pdm09-like virus; - A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; - B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage).
	QIV	The above and - B/Phuket/3073/2013-like virus (B/Yamagata lineage)

2.9.3 Scenario in Portugal

According to *Orientação 018/2018* from DGS, seasonal influenza vaccination is highly recommended for the following groups:

- Individuals aged 65 years or older;
- Chronic or immunosuppressed patients aged 6 months or older;
- Pregnant women;
- Health professionals and other healthcare givers.

For most of them (including ≥ 65 years), trivalent vaccines are administered free of charge in the primary healthcare units. Quadrivalent vaccines are not yet reimbursed by the National Health Service (NHS).

Table 2.2 summarizes the authorized vaccines in Portugal by influenza strain. According to *Infomed* platform, there are 9 seasonal TIV and four QIV authorized in Portugal, in a total of 13 seasonal influenza vaccines. However, only one trivalent vaccine and one quadrivalent vaccine are marketed, namely Influvac® and VaxigripTetra®, respectively (48). In 2015, two additional trivalent vaccines were available, namely Fluarix® and Istivac® (30) and no quadrivalent vaccine was marketed.

Table 2.2 *Authorized vaccines in Portugal by influenza strain. Data taken from INFARMED I.P. Pesquisa de Medicamentos. http://app7.infarmed.pt/infomed/pesquisa.php. Accessed December 18, 2018.*

	TIV	QIV	Total
Authorized	9	4	**13**
A/Michigan/45/2015(H1N1)	5	3	**13**
Other A(H1N1) strain	4	1	
A/Singapore/INFIMH-16-0019/2016 (H3N2)	4	3	**13**
Other A(H3N2) strains	5	1	
B/Colorado/06/2017 (B/Victoria lineage)	4	3	**13**
Other B/Victoria lineage strain	5	1	
B/Yamagata lineage	0	4	**4**

2.10 Economic Evaluation of Seasonal Influenza Vaccination

As an worldwide public problem, influenza viruses circulate and cause illness all over the world and can diminish human health and increase high budget impact in all countries (12). Many economic evaluations assessing the influenza vaccination programmes have been carried out worldwide, particularly in industrialised countries.

As mentioned in the introduction, economic evaluations are performed to identify, measure, value and compare the costs and consequences of different therapeutic alternatives in what respects to the different types of influenza vaccination. When comparing more than one programme, the difference in costs is compared with the difference in consequences (what can be measure in terms of health status or another outcome of interest), in an incremental analysis, where the Incremental Cost-Effectiveness Ratio (ICER) usually is the main outcome (7).

With the aim of finding studies on the economic evaluation in the area of influenza vaccination, it has been performed a literature search on MEDLINE (PubMed) and Google Scholar databases to find recent systematic review papers which include economic evaluations about seasonal influenza vaccination. Two systematic review papers are highlighted here:

- Pieter T. de Boer, Britt M. van Maanen, Oliver Damm, Bernhard Ultsch, Franklin C.K. Dolk, Pascal Crépey, Richard Pitman, Jan C. Wilschut & Maarten J. Postma (2017) A systematic review of the health economic consequences of quadrivalent influenza vaccination, Expert Review of Pharmacoeconomics & Outcomes Research, 17:3, 249-265; (49)

- Shields GE, Elvidge J, Davies LM. A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union. BMJ Open 2017;7:e014847.(50)

Both systematic reviews papers analysed a total of 23 studies (some studies were common to both papers). Each study was verified whether it met the inclusion criteria, namely, the comparison of inactivated trivalent vaccines with quadrivalent vaccines and the inclusion of people aged 65 years or older. Seven studies were excluded. Out of 16 studies included (51–66), 2 studies were performed only in the elderly (52,54).

Table 2.3 summarises the characteristics of main interest from the most relevant studies, specifically, country, type of health care evaluation, type of model, populations, type of vaccine, perspective and, payer's and societal perspective results. Thirteen studies were funded by pharmaceutical companies.

Country

The countries included in the review were US, Canada, UK, Germany, Spain, Finland, Australia, and Hong Kong, which are all industrialised countries and belong either to America, Europe, Oceania or Asia continents. One of the studies estimated the economic impact of QIV in 5 EU countries (EU-5) (France, Germany, Italy, Spain and UK) from 2002 to 2013 (10 seasons) and therefore extrapolated to all 27 EU countries (EU-27).

Type of Health Care Evaluation

Health care evaluations may include either only description of a single intervention in terms of costs or consequences, or comparison of different therapeutic alternatives. Cost-comparison analysis (CC) compares only the costs between two or more alternatives (7), while cost-consequences analysis (CCA) compares the costs and consequences and report the results separately – the costs are not

combined with the consequences. The results are presented as "total savings". A full economic evaluation includes the comparison of two or more courses of action and involves costs and consequences in an incremental analysis. Cost-effectiveness evaluations, cost-utility and cost-benefit analyses are examples of that. In Cost-effectiveness evaluations, costs are related to a single and common effect that may vary between the alternative healthcare programmes and consequences are measured in natural units or measures of Health-related quality of life (HRQoL). Cost-utility and cost-benefit analyses may include more than one effect which does not need to be common to both alternatives and consequences are measured in healthy years (quality adjusted lived years) and monetary units, respectively (7). In literature, cost-utility analysis can be referred to as cost-effectiveness analysis.

In what regards to the type of health care evaluation, 13 studies conducted a cost-effectiveness analysis and the results were expressed as costs per QALY gained. The other three conducted a cost-comparisons analysis, two of them were considered a cost-consequence analysis (see table 2.3).

Modelling Approach

Two modelling approaches can be distinguished - static and dynamic models. Static models do not consider the impact of the health status of one individual on the health of one or more persons. Dynamic approach considers direct and indirect effects of vaccination, being of special interest for infectious diseases. Indirect effects include effects on the unvaccinated population, that is, herd protection, as well as different patterns between different age groups (age shifts) (7,49,50). From 16 studies, 11 used static modelling approach, while 5 carried out dynamic models (see table 2.3).

Perspective

The perspective consists of the point of view from which the analysis is conducted. Some studies considered more than one perspective, namely, societal and payer's perspective and other studies used only one perspective. Societal perspective includes all the costs and health effects, like direct medical costs and indirect costs associated with productivity losses. In contrast, payer's perspective may only include medical costs paid by third-party payers (for example the NHS) (7,49,67). The first one is presented in 14 studies, while the last one is presented in 11 studies. Nine studies considered both perspectives (see table 2.3).

Table 2.3 *Review of worldwide health economic studies on seasonal influenza vaccination for the elderly. Adapted from Boer PT De, Maanen BM Van, Damm O, et al. A systematic review of the health economic consequences of quadrivalent influenza vaccination*

Reference	Country	Type of analysis	Type of model	Population	Vaccine type	Perspective	Payer's Perspective Results	Societal Perspective Results
(51)	Canada	CUA	Static	All ages	TIV/QIV	Payer and Society	71,950€/QALY	47,936€/QALY
(52)	United States	CUA	Static	Elderly	TIV/high-dose TIV/QIV	Society	133,883€/QALY	127,868€/QALY
(59)	United States	CUA	Static	All ages	TIV /QIV ≥50y ; TIV/QIV /LAIV <50y	Society	NA	87,430€/QALY
(56)	United States	CUA	Dynamic	All ages	TIV/QIV	Payer and Society	29,343€/QALY	25,628€/QALY
(60)	Germany	CUA	Dynamic	All ages	TIV/QIV	Payer and Society	17,238€/QALY	CS
(61)	Spain	CUA	Static	All ages	TIV/QIV	Society	15,340€/QALY	11,995€/QALY
(57)	Australia	CC – CCA	Static	Elderly and 6mon - 64y with clinical risk conditions	TIV/QIV	Payer and Society	Total savings: 23.2 million (€)	Total savings: 29.8 million (€)
(62)	United States	CC	Static	All ages	TIV/QIV	Payer and Society	Average annual costs: -28 to 316.7 million (€)	Average annual costs of −298.6 to 46 million (€)
(63)	United Kingdom	CUA	Static	Elderly and 18 - 64y with clinical risk conditions	TIV/QIV	Payer and Society	19,861€/QALY	18,305€/QALY
(65)	United States	CUA	Dynamic	All ages	TIV/ adjuvanted TIV/QIV	Society	4,767€/QALY	CS
(64)	Finland	CUA	Dynamic	All ages	TIV /QIV ≥18y ; TIV/QIV /LAIV 2-17y	Payer and Society	CS	CS
(66)	Canada and US	CUA	Dynamic	All ages	Canada: TIV/QIV UK:TIV /QIV, ≥18y ; LAIV, 2-17y	Payer	Can: 6,019€/QALY ; UK1: 10,834€/QALY; UK2: 9,810/QALY	NA
(53)	EU-5 and EU-27	CC – CCA	Static	All ages (≥6mon)	TIV/QIV	Payer and Society	Total savings: EU5: 107,909 million (€); EU27: 165,453 million (€)	Total savings: EU5: 298.956 million (€); EU27: 472.259 million (€)
(58)	United Kingdom	CUA	Static	All ages	TIV/QIV	Payer	7,912€/QALY	NA
(54)	Hong Kong	CUA	Static	Elderly	TIV/QIV	Society	NA	65–79 y: 13,697–233,617€/QALY.≥80 y: CS-64,456€/QALY
(55)	Hong Kong	CUA	Static	All ages	TIV/QIV	Payer and Society	21,442€/QALY	11,913€/QALY

Chapter 3

MATERIALS AND METHODS

3 Materials and Methods

This chapter aims to present all the materials used in the cost-effectiveness evaluation, as well as the methods applied. The first part (sections 3.1, 3.2, 3.3 and 3.4) summarizes the key features of the model, the structure of the decision tree and all sources of information of the model parameters. In section 3.5, it is presented the sensitivity analysis – one-way sensitivity analysis and probabilistic sensitivity analysis - and its statistical basis. Finally, in the section 3.6 it is explained the way how budget impact was performed.

3.1 Cost-effectiveness evaluation

A Cost-effectiveness evaluation (see section 2.10) was performed in order to compare the traditional approach of prevention and control of influenza - trivalent inactivated vaccine - and a more recent vaccine - quadrivalent inactivated vaccine - marketed since 2014/15 season in several countries and recently launched in Portugal. As mentioned before, the model was adapted from a cost-effectiveness evaluation performed for Spain by Universidad Francisco de Vitoria, where four vaccines were compared – TIV, adjuvanted TIV, QIV and intradermal influenza vaccine (8).

3.2 Key features of the economic evaluation

3.2.1 Target Population

The target population of this project is the population of mainland Portugal aged 65 and above. As mentioned before (see section 2.9.3), the elderly are one of the most relevant influenza risk groups. In 2015, they represented 21% of the Portuguese population (68).

3.2.2 Perspective

Changing influenza vaccination program depends on national health authorities. Additionally, people aged over 65 years old are usually retired, so productivity losses are not relevant. With this in mind, the cost-effectiveness evaluation was performed from the National Health Service perspective, where only direct costs were considered.

3.2.3 Time Horizon

According to Drummond et al. (7), "the time horizon should be the period over which the costs and/or effects of the alternative options being compared might be expected to differ". As discussed earlier, every year Influenza Surveillance System works from week 40 until week 20 of the following year (see section 2.9). Therefore, the time horizon established for this project is one year.

3.2.4 Measure of Health Effects

In the present study, health effects are assessed as quality-adjusted life year, which is a health measure of the value of health outcomes (69). QALYs come from the need of measure not only the quantity of life years, (i.e. quantity gains), but also the quality of life (i.e. quality gains), when comparing

different alternatives, and intends to combine both gains in a single index. QALY calculation consists of the product between the health–related quality of life (HRQL) for each health state and the time spent in the same state, followed by the sum of QALYs for all states (equation 3.1). Health-related quality of life (HRQL) is measured as utility, that reports the preference perceived for each health state (7). For instance, the utility associated with a health state is greater as higher the preference for the same (69). This indicator is measured in a 0 to 1 scale where 0 represents the state "Dead" and 1 the "perfect health" (7,70). However, the scale may take negative values, which correspond to states worse than death. The measurement of preferences may be carried out directly on patients or by using pre-scored multi-attribute health status classification systems, which consists of questionnaires with a scoring system. Some of the most used are EQ-5D and Short Form 6D (SF-6D) (7).

$$QALYs = \sum Years\ gain \times HRQL \tag{3.1}$$

Figure 3.1 summarizes the idea. For a patient who did not received any treatment, health-related quality of life would deteriorate faster, and the patient would die earlier (lowest curve) than an individual who received a treatment (highest curve) (71,72). Thus, the QALYs gained by the intervention correspond to the area between the two curves.

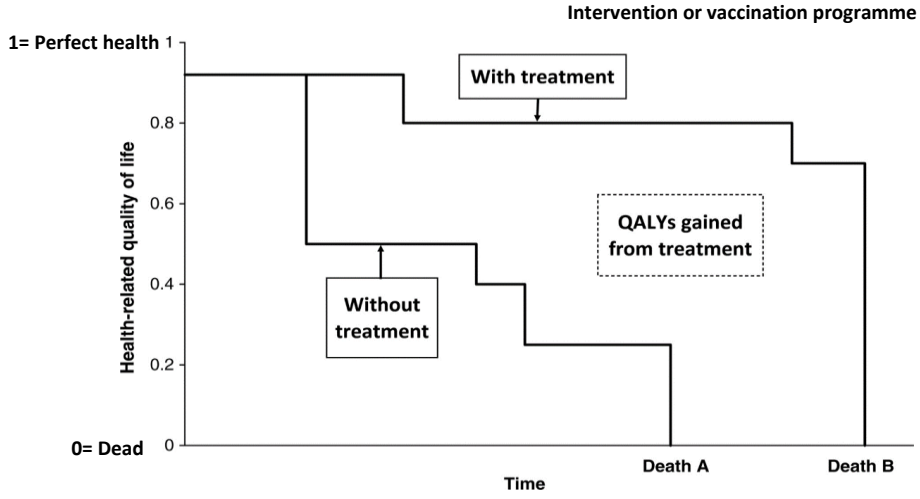


Figure 3.1 *Concept of QALY. Adapted from Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96(1):5-21. doi:10.1093/bmb/ldq033. and Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth. Oxford; 2015.*

On the other hand, the term disutility is associated with the QALY losses, and may instead vary from 0 (for instance, when both health states have similar utilities associated with them) to $+\infty$ (70).

3.2.5 Decision Tree

A decision tree consists of a series of pathways representing possible prognoses for each alternative therapy being evaluated. As the coverage rate was not considered high enough, it was used a static model and no herd effects (for example, as more individuals are immunized, less unvaccinated people get infected with influenza virus) of vaccination were evaluated (see section 2.10).

3.2.5.1 Structure

A. Nodes

Generally, a decision tree starts on the left with a square decision node (■) - see figure 3.2, corresponding to the decision point between alternative options. Moving to right, a sequence of circular chance nodes, (●), appears with several branches issuing from each one. One branch represents one possible event the patient may experience, and a series of branches is a possible pathway each individual may follow. Finally, triangles (◀) represent endpoints (7,70).

B. Probabilities

In decision analysis, the concept of probability is similar to that used in Bayesian analysis - a probability represents the likelihood (or "state of knowledge") of an event happening in the future. In other words, it is represented the strength of belief based on previous knowledge and experience (7). In the decision tree, each event has an associated probability, which allows to obtain the expected costs and effects. The likelihood of the events emerging from chance nodes are represented as branch probabilities.

Several probability concepts are used in a decision model. Conditional probabilities correspond to the probability of an event occurring, given that an earlier event has happened. The notation is $P(A|B)$ and

$$P(A|B) = \frac{P\ (A \cap B)}{P(B)}. \tag{3.2}$$

Branch probabilities are usually conditional probabilities, as they consider previous events the patient may or may not experience. The joint probability describes the probability of two events occurring simultaneously, being noted as $P(A \cap B)$. When the events are independent, it follows that,

$$P(A \cap B) = P(A) \times P(B) \tag{3.3}$$

and

$$P(A|B) = P(A). \tag{3.4}$$

C. Pathway and expected values

The decision tree of this project contains 28 pathways (fig. 3.2). For each one, a pathway probability is calculated by multiplying the corresponding probabilities and it represents the likelihood of a patient experience that set of events. Figure 3.3 summarizes all calculations involved. It is important to note that pathways are mutually exclusive, i.e., a patient follows only one pathway, and exhaustive, meaning that a patient must follow one of the pathways. So, it follows:

$$\sum_{i=1}^{n} P[X = x_i] = 1, \tag{3.5}$$

where *X* is a random variable representing the pathway followed by the individual, *n* corresponds to the total number of pathways and $i=1,2,\ldots,n$.

Each pathway has different costs and effects associated with it, resulting from the sum of event costs, that the patient may experience, and QALYs, that report the quantity and quality gains in each health state, respectively. Therefore, expected values can be obtained by multiplying each pathway

probability by respective pathway cost and QALY, and then summing across all the pathways (7).

3.2.5.2 The rationale

One decision tree model was developed for each alternative therapy (TIV and QIV). For convenience, each decision tree was split into two different diagrams referring to vaccinated and unvaccinated people. An example of a decision tree for vaccinated individuals is shown in figure 3.2. Each model starts by considering whether people was vaccinated or not, as vaccination is a preventive therapy and should be administered in the beginning of the season (see section 2.9). Next, influenza-like-illness (ILI) is considered because it is defined as a set of similar influenza symptoms that may not correspond to influenza (46). It was assumed that influenza confirmation (through diagnostic tests) was carried out in the context of General Practitioner consultation, pneumonia hospitalization, respiratory disease hospitalization or heart disease hospitalization. Although it is known that influenza may be diagnosed in many other situations, pneumonia, respiratory and heart disease are specially associated with complications due to influenza in the elderly as explained before (see section 2.6).

It should be noted that influenza event (secondary diagnoses) may have occurred before or after hospital admission, in which principal diagnoses was pneumonia, respiratory disease or heart disease (see section 3.3.1).

Finally, GP consultation can lead to hospital admission or recover, which corresponds to "Healthy" state. All terminal events lead to one of two states, which are "Death" or "Healthy". It is important to note that "Healthy" state is assumed to include all individuals who did not die, regardless their condition.

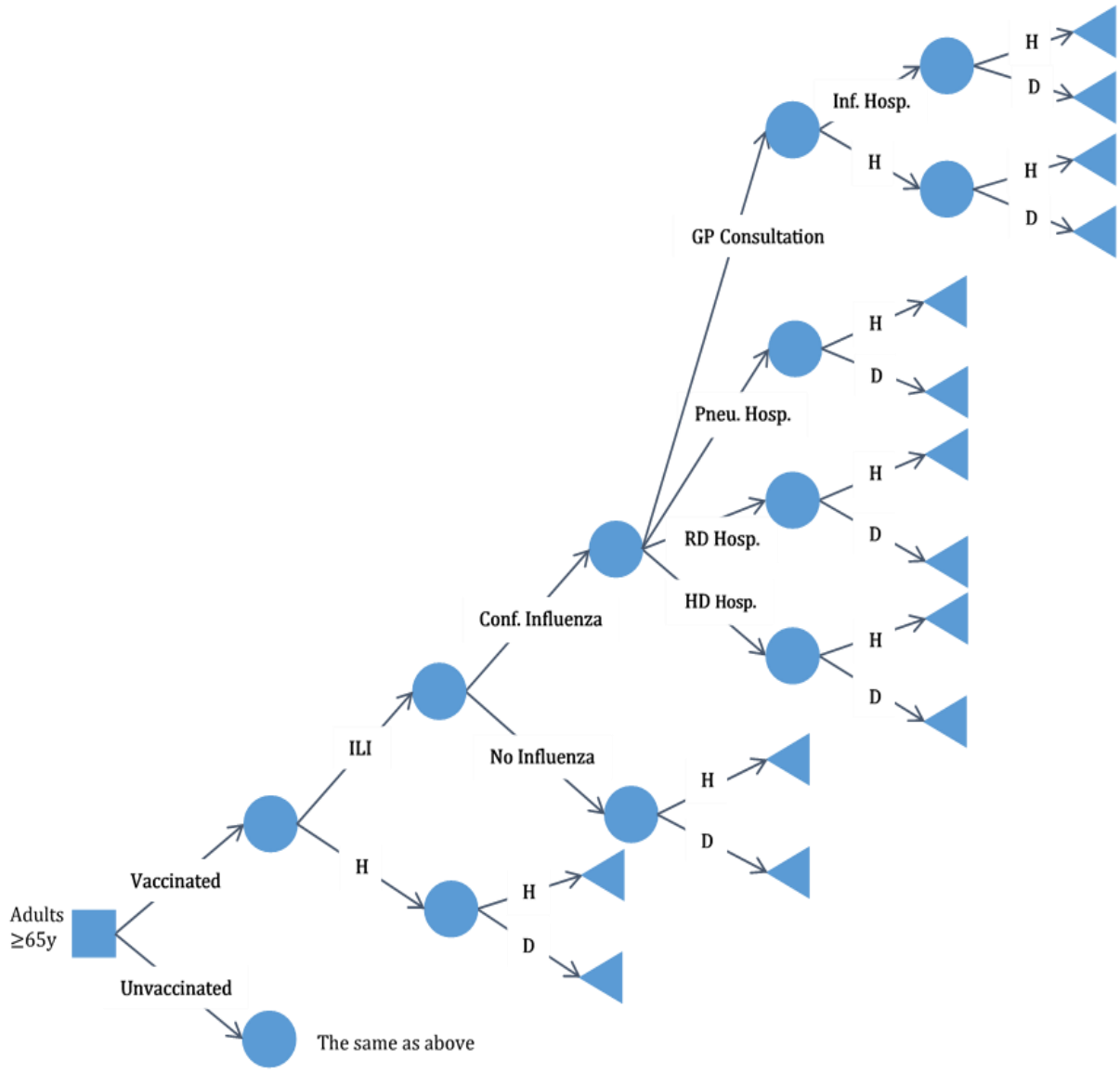


Figure 3.2 *Decision Tree for Trivalent Inactivated Vaccine. ILI, influenza-like-illness; H, healthy; D, death; Conf. Influenza, Confirmed Influenza; GP Consultation, General Practitioner Consultation; Pneu. Hosp., Hospitalization due to pneumonia; RD Hosp., Hospitalization due to respiratory disease; HD Hosp., Hospitalization due to heart disease; Inf. Hosp., Hospitalization due to Influenza.*

3.3 Input Parameters

The decision tree is powered by different types of parameters, namely, probabilities, costs and utilities. In this section, the computation of these parameters will be analysed. It is important to note that no permission had been requested from *Comissão de Ética para Recolha e Proteção de Dados* of the Faculty of Sciences, since no primary data were collected.

Several sources of information were used to obtain all parameters. Tables 3.1, 3.2, 3.3 and 3.4 indicate all parameters introduced in the model, their *Excel* names and respective sources of information. These include the National Database on Hospital Morbidity (NDHM) of the *Administração Central do Sistema de Saúde* (ACSS), *Instituto Nacional de Estatística* (INE), reports from *Instituto National de Saúde Doutor Ricardo Jorge* (INSA), among others.

3.3.1 National Database on Hospital Morbidity

The National Database on Hospital Morbidity is located at the ACSS and gathers information about inpatient and outpatient (specifically surgical outpatient) services activity. Data from diagnosis is coded by the International Classification of Diseases (ICD) code and patients are grouped into Diagnosis-related Groups (DRGs) (73). Principal diagnosis represents the condition responsible for admission to the hospital, while secondary diagnosis describes all other conditions that are present at the time of admission, or develop after, and can lead to complications or comorbidities. Only inpatient data were considered.

The data extracted from the NDHM consist of admissions of patients aged 65 or above, with principal diagnosis of influenza, pneumonia, respiratory disease or heart disease in 2015. For hospitalizations due to pneumonia, respiratory disease and heart disease, only subjects who experienced an episode of influenza as secondary diagnosis were considered. Pivot tables in *Excel* were used to obtain counts of episodes, sums of costs, average costs and respective standard deviations.

3.3.2 Event Probabilities

Input probabilities are summarized in table 3.1 as well as the *Excel* name and respective source of information. The probability of confirmed influenza for people aged ≥65 years was based on the National Program for Influenza Surveillance Report for 2015/2016 season (46). Data on GP consultations were extracted from the National Health Service online platform named *Saúde Sazonal* (74). Data were extracted by week, so the total number of GP consultations for influenza ($N_{Total\ GP\ consultations}$) results of the sum of GP consultations per week from week 40 of 2015 to week 20 of 2016. This number was then multiplied by the proportion of patients aged ≥65 years with ILI, $P(\geq 65y\,|ILI)$, (46) times the probability of confirmed influenza, $P(I\text{nfluenza})$, in order to obtain the number of patients (≥65y) who attended to a GP consultation in the context of confirmed influenza ($N_{GP\ consultations}$), as it follows:

$$N_{GP\ consultations} = N_{Total\ GP\ consultations} \times P(\geq 65y\,|ILI) \times P(I\text{nfluenza}). \quad (3.6)$$

The probability of ILI, $P(ILI)$, was subsequently calculated from the probabilities described above and the total number of individuals aged 65 and over ($N_{\geq 65y}$) in 2015, available on INE website (68), vaccination coverage rate (VC) and TIV effectiveness (TIV_{effect}), described in section 3.3.5. TIV effectiveness was considered in the calculation of probability of ILI because data are related to 2015/16 season, when only TIV was administered. In short, probability of ILI is given by

$$P(ILI) = \frac{N_{GP\ consultations}}{N_{\geq 65y} \times VC \times P(Influenza) \times \left(1 - TIV_{effect}\right) + N_{\geq 65y} \times (1 - VC) \times P(Influenz} \quad (3.7)$$

Probabilities of hospitalization due to influenza, pneumonia, respiratory disease and heart disease as well as probabilities of death when hospitalized due to such conditions were obtained from NDHM.

Probability of death when no influenza confirmed was based on the following indicators from INE - *Resident population (Long series, start 1991 - No.) by Place of residence (NUTS - 2013), Sex and Age; Annual* and *Deaths (No.) by Place of residence (NUTS - 2013), Sex and Age; Annual*. The data selected are from 2015 and are stratified by NUTS II regions.

Table 3.1 *Description of the input probabilities and respective sources*

Parameter	Excel Name	Reference
Probability of Influenza-like-illness	p_ili	(46)
Probability of Confirmed Influenza	p_conf_ili	(46)
Probability of GP Consultation	p_gp	(46,74)
Probability of hospitalization due to Influenza	p_hosp_inf	(46,75,76)
Probability of death when Hosp. Influenza	p_death_inf	(75)
Probability of hospitalization due to Pneumonia	p_hosp_pneu	(46,75,76)
Probability of death due to Hosp. Pneumonia	p_death_pneu	(75)
Probability of hospitalization due to Respiratory Disease	p_hosp_RD	(46,75,76)
Probability of death when Hosp. RD	p_death_RD	(75)
Probability of hospitalization due to Heart Disease	p_hosp_HD	(46,75,76)
Probability of death when Hosp. HD	p_death_HD	(75)
Probability of death when no confirmed influenza	p_death_no_inf	(68,77)

3.3.3 Costs

Table 3.2 gives the costs used in the model, respective *Excel* names and references. Costs were calculated in Euros (€) and given in 2015 prices.

Cost of GP consultation and cost of vaccine administration were established by the Government and may be found in *Portaria* No. 234/2015 of 7 August 2015 (73). All costs related to hospitalizations were calculated based on the NDHM. The episode cost results of the product of relative weight, equivalent patient times inpatient base price, as it follows:

$$Cost_{episode} = Relative\ weight\ \times Equivalent\ patient\ \times Base\ price \tag{3.8}$$

Relative weight is available on the price table established by NHS for 2015 (76). Equivalent patient allows to adjust the episode cost according to the episode length, which begins with inpatient admission and ends with inpatient discharge. The inpatient episode may be classified as normal, short or long stay according to the interquartile range of the DRG, (i.e., normal if it falls within the range, short if it is less than the lower bound and long if it is greater than the upper bound). Thus, each inpatient episode is converted into equivalent patient considering the interquartile range defined for each DRG and the duration of inpatient episode (78). Finally, the inpatient base price was defined by ACSS and it corresponds to 2285€ (76). Input costs of hospitalizations and deaths correspond to the average costs. It is important to note that cost of death when hospitalized includes all costs related to the last hospitalization of the patient, so the cost of hospitalization is not considered in the pathways with final events being death.

Cost of antiviral treatment (AT) and cost of TIV for NHS were taken from online public contracts (79,80). According to *Orientação* 007/2015, it was recommended the administration of the oseltamivir 75mg twice daily for 5 days (27). As result, it was considered the total cost of 10 capsules. Cost of AT was considered in all pathways with ILI, as it is recommended to be administered at the earliest stage, preferably in the first 48 hours after the symptoms onset, and laboratorial confirmation is not needed during influenza activity season (27). It was assumed that cost of hospitalization and cost of death when hospitalized include the cost of antiviral treatment, so it was not added in such pathways.

Cost of TIV in 2015 was not available, so it was assumed to be the same as in 2016. Cost of quadrivalent vaccine was estimated from the retail selling price (RSP) that entered into force on 1 October 2018, according to *Infomed* (81). A ratio between the cost of TIV for NHS and its retail selling

price was calculated and then multiplied by the RSP of QIV (81,82).

Cost of ILI when no confirmed influenza and cost of death were set at 0€, as such data were not available for Portugal. However, they were kept in the model to allow for future improvements when further information gets available.

Table 3.2 *Description of the input costs and respective sources*

Parameter	Excel Name	Reference
Cost of ILI without influenza confirmation	c_ili_no_inf	-
Cost of GP consultation	c_GP	(73)
Cost of Hospitalization due to Influenza	c_hosp_inf	(75)
Cost of death when Hosp. Influenza	c_death_inf	(75)
Cost of Hospitalization due to Pneumonia	c_hosp_pneu	(75)
Cost of death when Hospitalization due to Pneumonia	c_death_hosp_pneu	(75)
Cost of Hospitalization due to Respiratory Disease	c_hosp_RD	(75)
Cost of death when Hospitalization due to RD	c_death_hosp_RD	(75)
Cost of Hospitalization due to Heart Disease	c_hosp_HD	(75)
Cost of death when Hospitalization due to HD	c_death_hosp_HD	(75)
Cost of death	c_death	-
Cost of antiviral treatment	c_ant_treat	(27,79)
Cost of trivalent vaccine	c_tiv	(80)
Cost of quadrivalent vaccine	c_qiv	(80,81)
Cost of vaccine administration	c_vac_admin	(73)

3.3.4 Utilities and Disutilities

Table 3.3 gives the description of utilities used in the model. The concept of utility is further described in section 3.2.4. It is important to note that QALYs were calculated annually, as the time horizon chosen was 1 year.

There are few studies published in Portugal about QALY weights calculation (83,84), mainly through EQ-5D measure (see section 3.2.4). Utilities associated with a healthy state were obtained from a study on *EQ-5D Portuguese population norms* (84). Data available were stratified by age, but no stratum corresponded to people aged 65 or over. As result, a weighted value was obtained from "50-69" and "≥70" strata, as it follows:

$$Utility_{\geq 65} = Utilities_{50-69} \times \frac{Population_{65-69}}{Population_{\geq 65}} + Utilities_{\geq 70} \times \frac{Population_{\geq 70}}{Population_{\geq 65}} \quad (3.9)$$

In the same way, no studies were found about disutilities associated with influenza. Such data were extracted from a Spanish study (85), where QALYs losses due to no hospitalized influenza and ILI without influenza confirmation were derived from individual outpatients QALYs losses. On the other hand, disutilities associated with hospitalizations due to influenza, pneumonia, respiratory disease and heart disease were derived from individual inpatient QALYs losses.

In the pathways ending in death, the utility associated with a healthy state was divided by 2 (see figure 3.3). This happens because no time of death is known, so it is assumed to have occurred in the middle of the year.

Table 3.3 *Description of the input utilities/disutilities and respective sources*

Parameter	Excel Name	Reference
Disutility associated with ILI without influenza confirmation	u_ili_no_inf	(85)
Disutility associated with no hospitalized influenza	u_inf_no_hosp	(85)
Disutility associated with hospitalization due to influenza	u_hosp_inf	(85)
Disutility associated with hospitalization due to pneumonia	u_hosp_pneu	(85)
Disutility associated with hospitalization due to respiratory disease	u_hosp_RD	(85)
Disutility associated with hospitalization due to heart disease	u_hosp_HD	(85)
Utility associated with healthy population	u_healthy	(68,84)

3.3.5 Other Parameters

Besides probabilities, costs and utilities, the model also needs other parameters, namely, the total number of individuals aged 65 and over, vaccines effectiveness and vaccination coverage. These parameters are given by table 3.4.

As mentioned in section 3.3.2, the total population aged ≥65-year-old was derived from a INE indicator, named *Resident population (Long series, start 1991 - No.) by Place of residence (NUTS - 2013), Sex and Age; Annual*. Data on vaccination coverage in 2015/2016 season were taken from the INSA report *Vacinação antigripal da população portuguesa na época 2015/2016* (35). Such data were not stratified by region.

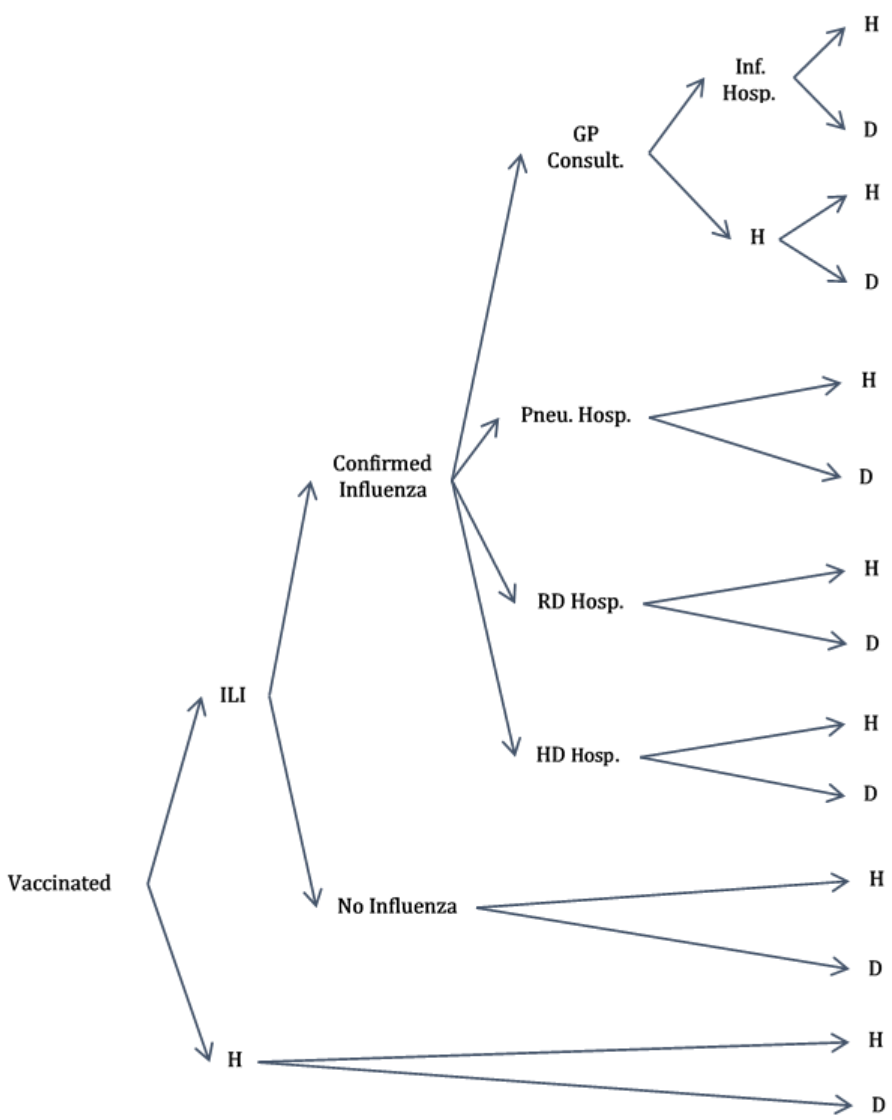
Trivalent vaccine effectiveness was established at 58% according to Demicheli et al. (36). It was calculated as 1-RR, where RR (Risk Ratio) corresponds to the ratio between the proportions of patients who developed influenza in vaccinated and unvaccinated patients. The latter correspond to patients who received placebo (36). Quadrivalent vaccine effectiveness was estimated through the study of the proportion of circulating B strains not included in TIV across several seasons, summarized in table 3.5. The methodology was adapted from Petri and Ruiz-Aragón (86). Such data were taken from the National Influenza Surveillance Programme (NISP) annual report for seasons from 2010/11 to 2016/17 (46,87–92). Only data related to season 2017/18 were derived from the last weekly report on influenza surveillance published by INSA, as NISP was not yet available (93). On average, 8.69% of the circulating strains corresponds to mismatched TIV strains. Next step was to obtain the relative gain in effectiveness of using QIV instead of TIV, which was calculated as 8.69% × 0.38 = 3.30%, where 0.38 indicates the mean reduction in VE due to B lineage mismatch (86).

Table 3.4 *Description of other parameters and respective sources*

Parameter	Excel Name	Reference
Population	Pop	(68)
Vaccination Coverage Rate	Coverage	(35)
Trivalent Vaccine Effectiveness	tiv_effect	(36)
Quadrivalent Vaccine Effectiveness	qiv_effect	(46,86–93)

Table 3.5 *Proportion of B lineage influenza virus not included in the seasonal trivalent vaccines from 2010-11 to 2017/18 seasons*

Season	Proportion of Influenza B	Proportion of B/Victoria	Proportion of B/Yamagata	B - lineage in TIV	Proportion of B lineage mismatch	Standard Error	Ref.
2010-11	43,20%	42,70%	0,50%	Victoria	0,50%	0,00022	(87)
2011-12	2,30%	0,00%	2,30%	Victoria	2,30%	0,00058	(88)
2012-13	51,30%	1,80%	49,50%	Yamagata	1,80%	0,00038	(89)
2013-14	0,80%	0,10%	0,70%	Yamagata	0,10%	0,00011	(90)
2014-15	0,36%	0,00%	0,36%	Yamagata	0,00%	0,00000	(91)
2015-16	8,30%	7,80%	0,50%	Yamagata	7,80%	0,00084	(46)
2016-17	0,20%	0,20%	0,00%	Victoria	0,00%	0,00000	(92)
2017-18	66,00%	9,00%	57,00%	Victoria	57,00%	0,00354	(93)
2010/11-2017/18	21,56%				8,69%	0,00213	



Probability	Costs	QALY
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_gp × p_hosp_inf × (1-p_death_inf)	c_tiv + c_vac_admin + c_GP + c_hosp_inf	u_healthy - u_hosp_inf
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_gp × p_hosp_inf × p_death_inf	c_tiv + c_vac_admin + c_GP + c_death_inf	(u_healthy/2) - u_hosp_inf
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_gp × (1-p_hosp_inf) × (1-p_death_no_inf)	c_tiv + c_vac_admin + c_GP + c_ant_treat	u_healthy - u_inf_no_hosp
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_gp × (1-p_hosp_inf) × p_death_no_inf	c_tiv + c_vac_admin + c_GP + c_death + c_ant_treat	(u_healthy/2) - u_inf_no_hosp
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_hosp_pneu × (1-p_death_pneu)	c_tiv + c_vac_admin + c_hosp_pneu	u_healthy - u_hosp_pneu
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_hosp_pneu × p_death_pneu	c_tiv + c_vac_admin + c_death_hosp_pneu	(u_healthy/2) - u_hosp_pneu
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_hosp_RD × (1-p_death_RD)	c_tiv + c_vac_admin + c_hosp_RD	u_healthy - u_hosp_RD
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_hosp_RD × p_death_RD	c_tiv + c_vac_admin + c_death_hosp_RD	(u_healthy/2) - u_hosp_RD
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_hosp_HD × (1-p_death_HD)	c_tiv + c_vac_admin + c_hosp_HD	u_healthy - u_hosp_HD
coverage × p_ili × p_conf_ili × (1-tiv_effect) × p_hosp_HD × p_death_HD	c_tiv + c_vac_admin + c_death_hosp_HD	(u_healthy/2) - u_hosp_HD
coverage × p_ili × [1- (p_conf_ili × (1-tiv_effect)] × (1-p_death_no_inf)	c_tiv + c_vac_admin + c_no_inf + c_ant_treat	u_healthy - u_ili_no_inf
coverage × p_ili × [1- (p_conf_ili × (1-tiv_effect)] × p_death_no_inf	c_tiv + c_vac_admin + c_no_inf + c_death + c_ant_treat	(u_healthy/2) - u_ili_no_inf
coverage × (1-p_ili) × (1-p_death_no_inf)	c_tiv + c_vac_admin	u_healthy
coverage × (1-p_ili) × p_death_no_inf	c_tiv + c_vac_admin + c_death	u_healthy/2

Figure 3.3 *Probability, cost and QALY calculations by decision tree pathway for individuals aged ≥65 years old who received TIV*

3.4 Outcomes of the Cost-effectiveness Evaluation

3.4.1 Incremental Cost-Effectiveness Ratio

Incremental Cost-Effectiveness Ratio (ICER) is a widely used outcome measure in health economic evaluations that summarizes the additional costs that one health intervention imposes over another per unit of health effects gained. In this case, the ICER provides information about the extra amount that is necessary to pay in order to gain an extra QALY when a more effective alternative is chosen (7,70).

$$ICER = \frac{Costs_{QIV} - Costs_{TIV}}{Effects_{QIV} - Effects_{TIV}} \tag{3.10}$$

3.4.2 The cost-effectiveness plane

The aim of the cost-effectiveness plane consists of making the choice clearer. The difference in effect (or incremental effect) is represented by the horizontal axis (see figure 3.4), while the vertical axis corresponds to the difference in costs (or incremental cost). This way, the slope of the line OA, where O represents the conventional treatment and A represents the new alternative, designates the cost-effectiveness ratio.

Looking at the plane, if point A is placed in quadrant I or III, the choice is not clear. In quadrant I, the new intervention is more effective, but also more costly, while in quadrant III the opposite is true – less effective and less costly than conventional option. In such case, the willingness-to-pay (WTP) threshold should be considered. As the name suggest, a WTP threshold (also referred to as cost-effectiveness threshold) consists of a maximum acceptable cost per QALY gained that the decision maker is willing to pay (7).

In Portugal, there is no established cost-effectiveness threshold for health interventions. Some Portuguese authors refers a WTP threshold of 30,000€/QALY (94,95), while others consider the cost-effectiveness threshold as twice the Gross Domestic Product (GDP) per capita or Gross National Income (GNI) per capita (96,97). In 2015, the Portuguese GNI per capita was 16,887.36€, resulting in a ceiling ratio of approximately 34,000€ (98,99).

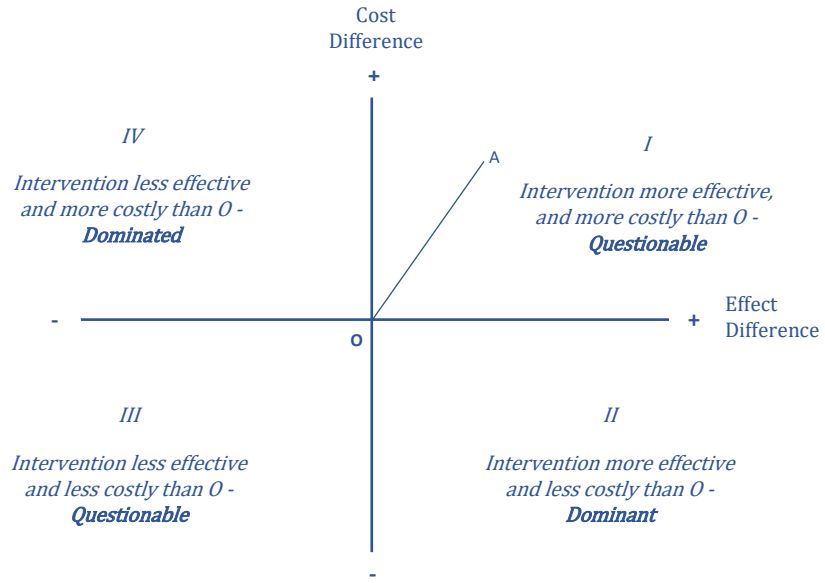


Figure 3.4 *The cost-effectiveness plane. Adapted from Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes, page 55, Fourth. Oxford; 2015.*

3.5 Sensitivity Analysis

3.5.1 Uncertainty

There are several sources of uncertainty in a decision model. Uncertainty types usually present in a model are variability, heterogeneity, structural and parameter uncertainty (7,70).

Variability is related to the differences in outcome that occurs between identical patients by chance. Some authors call it *first-order uncertainty*, but the preferred term is stochastic uncertainty. Heterogeneity consists of the variability that occurs between patients that can be explained by patient characteristics. Structural uncertainty refers to the scientific judgements made when the model is constructed, which might be associated, for example, with the assumptions inherent to the decision model structuring. Parameter uncertainty, also called *second-order uncertainty*, refers to uncertainty inherent to the parameter's estimation. The most used ways of characterizing parameter uncertainty are Deterministic Sensitivity Analysis (DSA) and Probabilistic Sensitivity Analysis (PSA) (7,70).

In the present project, DSA was performed as a measure of sensitivity, i.e., to identify the most sensitive parameters (100), while PSA allowed to characterize parameter uncertainty in combination within the model (7,70,100), as described below.

3.5.2 Deterministic Sensitivity Analysis

One-Way Sensitivity Analysis (OWSA) consists of varying the point estimates of the input parameters one at a time within a plausible range and assess the impact on model outcomes (7,70) – in this case, the ICER.

Regarding the plausible range, when the confidence interval was known from the original source it was used as DSA range. For coverage rate, it was applied the 95% CI (Confidence Interval) available on the INSA report mentioned above (see section 3.3.4). The DSA range for disutilities were also taken from the aforementioned studies (85). For parameters with no CI available, a range of ±20% was used to assess the sensitivity of the model to parameter variation. In other words, univariate sensitivity analysis was used as a measure of sensitivity, as far as it is intended to identify to what input change the ICER is most sensitive and what inputs yields the biggest changes.

All, except four parameters were included in the DSA. The parameters not included are probability of GP consultation, probability of hospitalization due to Pneumonia, probability of hospitalization due to RD and probability of hospitalization due to HD, because these probabilities sum to 1 and varying one of these values would result in a sum different from 1.

As recommended by the task force of Modelling Good Research Practices (100), a tornado diagram was used to report OWSA results, where the horizontal bars, showing the outcome range of variation associated with each parameter, are displayed vertically and sorted by descending order of length. A vertical line is displayed across all bars, indicating the base case result.

To carry out the OWSA, an *Excel* macro was developed in order to switch the input values and record the ICER for the lower and upper bounds of the range. Then, parameters are sorted by length of ICER range and data are introduced to the model according to that order.

Additionally, it was found relevant the detailed study of coverage rate, TIV effectiveness and QIV effectiveness variation. This way, coverage rate varied from 0% to 100% and TIV effectiveness varied within the 95% CI. It was assumed that QIV effectiveness is higher than TIV effectiveness and as such, it varied from 58% to 100%. The cost of quadrivalent vaccine was also studied in more detail, as it was identified as a key parameter and no official cost is available (56). For coverage rate and QIV cost, a sequence of parameters values was generated with an increment of 0.05. For TIV and QIV

effectiveness, the increment used was 0.005. An ICER value was obtained for each parameter value by altering such value in the model and recording the consequent ICER, as described before for tornado diagram.

3.5.3 Probabilistic Sensitivity Analysis

Instead of representing the parameters as single point estimates as in DSA, parameters are represented by random variables following a certain distribution (7). It is important to be aware that inputs like costs, probabilities and vaccination coverage rate are related to season 2015/16. As such, PSA aims to evaluate the robustness of base case results for 2015/16 season.

Only parameters based on samples were accounted for PSA, since parameters based on the population are not uncertain (58). In what regards the probabilities, there are two inputs calculated from samples that influence other probabilities. Such parameters are "probability of confirmed influenza" and "probability of being ≥ 65 years when ILI" and were taken from INSA reports, as mentioned previously (see section 3.3.2). Probability distributions are assigned to these parameters and the generated probabilistic values are included in the calculation of probabilities that these two parameters inform. With respect to costs, only quadrivalent vaccine cost was assumed to be uncertain, since the remaining were either obtained from 2015/16 population or established by the Government. However, as there is no data available on this topic for Portugal, assigning a distribution would add uncertainty to the PSA results. This parameter was fully explored in OWSA. Disutilities and utilities were included in the PSA, as they are not related to 2015/16 season. In the same way, TIV and QIV effectiveness were also considered. Finally, vaccination coverage was also assigned to a probability distribution, as it was derived from a sample.

3.5.3.1 Monte Carlo Simulations

As explained before, in PSA distributions are assigned to parameters in order to reflect uncertainty around them. Monte Carlo (MC) simulations sample the distributions at random in order to generate a random vector **X** of independent and identically distributed variables in some space $\mathbb{R}^n$ from a given probability distribution (101). This involves two steps:

1. Draw uniform random numbers $U_1, \dots, U_k$ for $k = 1, 2, \dots$,
2. Transform $U_1, \dots, U_k$ to $\mathbf{X} = g\ (U_1, \dots, U_k)$ where g is some function from $(0,1)^k$ to $\mathbb{R}^n$ (101).

The first step is hold by the random number generator (RNG) in *Excel* that gives pseudo random numbers on the interval (0,1), through RAND() function. They are called "pseudo random" numbers, because the generated sequence is based on an initial value. Values are sampled from a uniform distribution and so they are equally likely (70).

From the uniformly distributed random values, it is necessary to get random values from different specified distributions (70). The Probability Integral Transformation Theorem is the methodology underlying this work (102).

Probability Integral Transformation Theorem

Given a continuous random variable X with cumulative distribution function (cdf) $F_X(x)$ and defining the random variable Y as $Y = F_X(X)$, then Y has a uniform distribution on (0,1), that is, $P(Y \leq y) = y,\ 0 < y < 1$ (102). This theorem is proved by,

$$
\begin{aligned}
&F_Y(y) = P(Y \leq y) \\
&= P(F_X(X) \leq y) \\
&= P\left(F_X^{-1}[F_X(X)] \leq F_X^{-1}(y)\right) \\
&= P\left(X \leq F_X^{-1}(y)\right) \\
&= F_X\left(F_X^{-1}(y)\right) \\
&= y.
\end{aligned}
\tag{3.11}
$$

where, F_X^{-1} defines the inverse function of F_X. This way, a uniform random value, u, is transformed into a random value from a specified distribution, x, by solving for x in the equation $F_X(x) = u$.

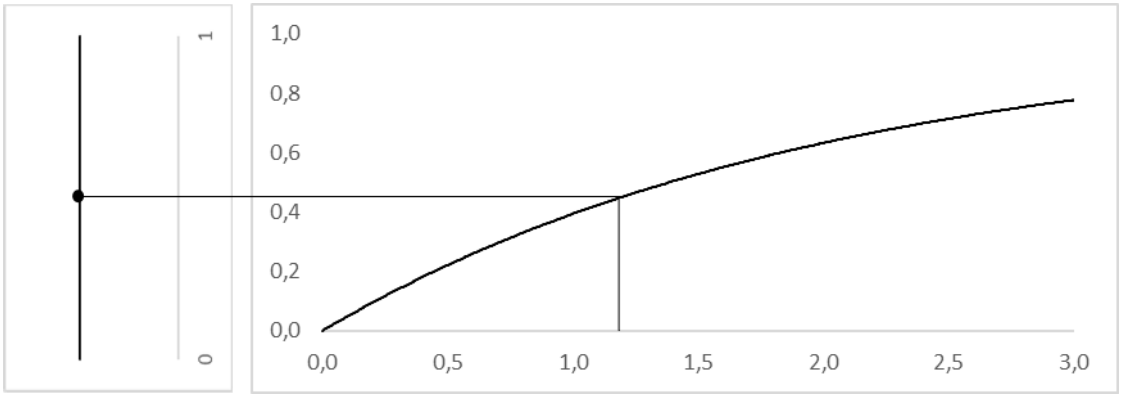


Figure 3.5 *Generating random samples from a Gamma distribution using uniform random value generator (left panel) and the inverse cumulative distribution function of the Gamma (1,2) (right panel).*

Figure 3.5 summarizes the idea. If we consider a random draw from the uniform distribution on the interval (0,1) (shown on the left), it is possible to obtain a random draw from the $Gamma(1,2)$ distribution (horizontal axis of the cdf curve), by using the inverse of the cdf function.

A random value is obtained for all parameters of the model and the results are recorded in each iteration through an *Excel* macro (7,8,70). A total of 1,000 iterations were performed in the present project (56,58).

3.5.3.2 Probability Distributions

The choice of the distributions to be assigned to input parameters should take into account three important aspects – the nature of the parameter, the method used to estimate it, and the summary statistics available (7). This way, the number of appropriate probability distributions for each parameter is very limited. Table 3.6 summarizes the applied distributions according to the data types, which are explained in more detail in the following sections. On its turn, table 3.7 presents the base case values and the parameters (parameter 1 and parameter 2) of the probability distributions applied, obtained through the methods explored in the following sections.

Table 3.6 *Parameter types and candidate distributions.*

Parameter Description	Distribution
Probability ($0 \leq x \leq 1$)	Beta
Utility Decrement ($x \geq 0$)	Gamma Lognormal
Relative Risk ($x \geq 0$)	Lognormal

Table 3.7 *Base case values and distributions assigned to the input parameters of the model*

Input Parameters	Base Case	SD	Distribution	Parameter 1	Parameter 2
Probability of Confirmed Influenza	0.278	0.037	Beta	39.72	103.28
Probability of being ≥65years when ILI	0.130	0.0095	Beta	162.87	1089.13
Disutility associated with ILI without influenza confirmation	0.009	0.0010	Gamma	77.79	0.00012
			Lognormal	-4.72	0.013
Disutility associated with no hospitalized influenza	0.009	0.0010	Gamma	77.79	0.00012
			Lognormal	-4.72	0.013
Disutility associated with hospitalization due to influenza	0.031	0.0031	Gamma	102.55	0.00030
			Lognormal	-3.48	0.010
Disutility associated with hospitalization due to pneumonia	0.031	0.0031	Gamma	102.55	0.00030
			Lognormal	-3.48	0.010
Disutility associated with hospitalization due to respiratory disease	0.031	0.0031	Gamma	102.55	0.00030
			Lognormal	-3.48	0.010
Disutility associated with hospitalization due to heart disease	0.031	0.0031	Gamma	102.55	0.00030
			Lognormal	-3.48	0.010
Utility associated with healthy population	0.625	0.0163	Gamma	525.41	0.00071
			Lognormal	-0.98	0.002
Vaccination coverage rate	0.501	0.041	Beta	74.68	74.38
Proportion of B lineage viruses not included in TIV	0.087	0.002	Beta	15.77	165.81
1 - Trivalent Vaccine Effectiveness	0.421	0.228	Lognormal	-0.865	0.228

3.5.3.2.1 Distribution for the Probabilities: Beta Distribution

Beta distribution is the natural choice for probability parameters, as they consist of proportions (70) and they are constrained on the interval (0,1). To assess the uncertainty associated with 2015/16 data, a beta distribution was assigned to the probability of confirmed influenza, probability of being ≥ 65y when ILI, proportion of B lineage viruses not included in TIV and vaccination coverage rate. The standard error was estimated from the data available. As there are no closed-form expressions for the estimates of α and β based on the maximum likelihood (ML) method, the parameters α and β were estimated by the method of moments.

The probability density function (pdf) of the Beta distribution is defined as (102):

$$f(x|\alpha,\beta) = \frac{1}{\mathrm{B}(\alpha,\beta)} x^{\alpha-1}(1-x)^{\beta-1}, \qquad 0 < x < 1, \qquad \alpha > 0, \qquad \beta > 0 \tag{3.12}$$

where $\mathrm{B}(\alpha,\beta)$ corresponds to the beta function, defined by (102):

$$\mathrm{B}(\alpha,\beta) = \int_0^1 x^{\alpha-1}(1-x)^{\beta-1}dx\,, \qquad \alpha > 0, \qquad \beta > 0. \tag{3.13}$$

It also can be written in terms of the gamma function, as it follows,

$$B(\alpha,\beta)=\frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha+\beta)}\,,\qquad \alpha,\beta\in(0,\infty). \tag{3.14}$$

It should be stressed that if X is a continuous random variable and has pdf $f(x)$, then $E\left(X^k\right)$ is given by

$$E\left(X^k\right)=\int_{-\infty}^{\infty}x^k f(x)dx. \tag{3.15}$$

Applying this result to the beta distribution,

$$E\left(X^k\right)=\int_0^1 x^k\frac{1}{\mathrm{B}(\alpha,\beta)}x^{\alpha-1}(1-x)^{\beta-1}dx=\frac{1}{\mathrm{B}(\alpha,\beta)}\int_0^1 x^{\alpha+k-1}(1-x)^{\beta-1}dx=\frac{B(\alpha+k,\beta)}{B(\alpha,\beta)}. \tag{3.16}$$

For the first moment, $k=1$, and considering the property of the gamma function, $\Gamma(\alpha+1)=\alpha\Gamma(\alpha),\ \alpha>0$, it comes:

$$E(X)=\frac{B(\alpha+1\,,\beta)}{B(\alpha,\beta)}=\frac{\Gamma(\alpha+1)\Gamma(\beta)}{\Gamma(\alpha+\beta+1)}\times\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}\ \ \therefore\ \ E(X)=\frac{\alpha}{\alpha+\beta}. \tag{3.17}$$

For $k=2$,

$$E(X^2)=\frac{B(\alpha+2\,,\beta)}{B(\alpha,\beta)}\therefore\ \ E(X^2)=\frac{\alpha(\alpha+1)}{(\alpha+\beta)(\alpha+\beta+1)}. \tag{3.18}$$

The formula for the variance follows from $Var(X)=E(X^2)-[E(X)]^2$ (102,103),

$$Var(X)=\frac{\alpha(\alpha+1)}{(\alpha+\beta)(\alpha+\beta+1)}-\left(\frac{\alpha}{\alpha+\beta}\right)^2=\frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}. \tag{3.19}$$

This way, if the sample moments are known, then:

$$\bar{X}=\frac{\alpha}{\alpha+\beta}\ ;\ \ S^2=\frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}. \tag{3.20}$$

After solving for the two parameters, the estimators for α and β based on the method of moments are given by

$$\hat{\alpha}=\frac{\bar{X}^2(1-\bar{X})}{S^2}-\ \bar{x}\ ;\ \ \hat{\beta}=\hat{\alpha}\cdot\frac{1-\bar{X}}{\bar{X}}. \tag{3.21}$$

3.5.3.2.2 Distributions for the Utilities and Disutilities

In theory, utilities range from $-\infty$ to 1. These values represent the worse possible health state (i.e. worse than death, as death corresponds to 0) and perfect health state, respectively. On the other hand, disutilities may range from 0 to $+\infty$ (70). In practice, utilities vary between -0.50 and 1, and disutilities are constrained to the interval $(0, 1.65)$, according to the literature (84,85).

This way, gamma and lognormal distributions are possible distributions for disutility data, as shown in table 3.6. For disutilities, mean and confidence intervals are available (see section 3.3.4), which allows to derive the standard error.

For utilities, mean and standard error are available (see section 3.3.4). In order to apply gamma and lognormal distributions to utility data, the transformation $disutility = 1 - utility$ was used to have these parameters constrained on the interval $(0, +\infty)$.

3.5.3.2.2.1 Gamma Distribution

In order to derive the estimates for the parameters of the gamma distribution, the method of moments was applied in a manner analogous to that used for beta distribution, as it is not possible to obtain closed-form expressions for both parameters α and β using the ML method. Doing so, the kth moment of the random variable X is given by (102)

$$\begin{aligned} E(X^K) &= \int_0^\infty x^k \frac{1}{\beta^\alpha \Gamma(\alpha)} x^{\alpha-1} e^{-\frac{x}{\beta}} dx, \quad 0 < x < \infty \\ &= \frac{1}{\beta^\alpha \Gamma(\alpha)} \int_0^\infty x^{\alpha+k-1} e^{-\frac{x}{\beta}}. \end{aligned} \tag{3.22}$$

Applying the property of the gamma function, $\int_0^\infty x^{\alpha-1}\, e^{-\beta x} dx = \frac{\Gamma(\alpha)}{\beta^\alpha},\ \beta > 0$, it follows that

$$E(X^K) = \frac{1}{\beta^\alpha \Gamma(\alpha)} \beta^{\alpha+k}\, \Gamma(\alpha + k). \tag{3.23}$$

For $k = 1$,

$$E(X) = \frac{1}{\beta^\alpha \Gamma(\alpha)} \beta^{\alpha+1} \Gamma(\alpha + 1) = \frac{\alpha\beta\Gamma(\alpha)}{\Gamma(\alpha)} = \alpha\beta \tag{3.24}$$

and for $k = 2$,

$$E(X^2) = \frac{1}{\beta^\alpha \Gamma(\alpha)} \beta^{\alpha+2} \Gamma(\alpha + 2) = \frac{\beta^2(\alpha + 1)\Gamma(\alpha + 1)}{\Gamma(\alpha)} = \alpha\beta^2(\alpha + 1). \tag{3.25}$$

The variance is thus obtained through:

$$var(X) = \alpha\beta^2(\alpha + 1) - (\alpha\beta)^2 = \alpha\beta^2. \tag{3.26}$$

Based on the method of moments, the sample mean and variance equate to the mean and variance of the distribution as follows:

$$\bar{X} = \alpha\beta\ ;\ S^2 = \alpha\beta^2. \tag{3.27}$$

Now, it is possible to obtain the method of moments' estimators for the parameters α and β:

$$\hat{\alpha} = \frac{\bar{X}^2}{S^2}\ ;\quad \hat{\beta} = \frac{S^2}{\bar{X}}. \tag{3.28}$$

3.5.3.2.2.2 Lognormal Distribution

As mentioned before, the lognormal distribution is one of the candidate distributions for disutilities and risk ratios. A continuous random variable X has a lognormal distribution with parameters $\mu \in \mathbb{R}$ and $\sigma^2 \in (0, \infty)$ if $\ln(X)$ follows a normal distribution with mean μ and variance σ^2. The pdf of lognormal distribution is given by (102,103)

$$f(x|\mu, \sigma^2) = \frac{1}{x\sqrt{2\pi}\sigma} e^{-(\ln(x)-\mu)^2/(2\sigma^2)}, \qquad 0 < x < +\infty. \tag{3.29}$$

If only the mean and the standard deviation of a dataset are available, method of moments allows one to find equations of lognormal parameters. The expected value of X^k is given by

$$\begin{aligned} E(X^k) &= \int_0^\infty x^k \frac{1}{x\sqrt{2\pi}\sigma} e^{\frac{-(\ln(x)-\mu)^2}{2\sigma^2}} dx \\ &= \int_0^\infty x^{k-1} \frac{1}{\sqrt{2\pi}\sigma} e^{\frac{-(\ln(x)-\mu)^2}{2\sigma^2}} dx. \end{aligned} \tag{3.30}$$

If we consider $y = \ln(x) - \mu$, then $lnx = y + \mu$ and $x = e^{y+\mu}$. Therefore, $\frac{dy}{dx} = \frac{1}{x}$. Then substituting into expression (3.30), it follows that

$$\begin{aligned} E(X^k) &= \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\infty} (e^{y+\mu})^{k-1} \cdot e^{\frac{-y^2}{2\sigma^2}} \cdot e^{y+\mu} \cdot dy \\ &= \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\infty} (e^{y+\mu})^{k} \cdot e^{\frac{-y^2}{2\sigma^2}} dy \\ &= e^{k\mu} \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\infty} e^{\frac{-y^2}{2\sigma^2} + ky} dy. \end{aligned} \tag{3.31}$$

As $ax^2 + bx + c = a\left(\left(x + \frac{b}{2a}\right)^2 + \frac{c}{a} - \frac{b^2}{4a^2}\right)$, expression (3.31) takes the form

$$\begin{aligned} E(X^k) &= e^{k\mu} \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\infty} e^{-\frac{1}{2\sigma^2}\left((y-k\sigma^2)^2 - k^2\sigma^4\right)} dy \\ &= e^{k\mu} \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\infty} e^{-\frac{(y-k\sigma^2)^2}{2\sigma^2}} e^{\frac{k^2\sigma^2}{2}} dy \\ &= e^{k\mu} e^{\frac{k^2\sigma^2}{2}} \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\infty} e^{-\frac{(y-k\sigma^2)^2}{2\sigma^2}} dy \\ &= e^{k\mu} e^{\frac{k^2\sigma^2}{2}}, \end{aligned} \tag{3.32}$$

because $\frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-\frac{(y-k\sigma^2)^2}{2\sigma^2}} dy = 1$.

For $k = 1$,

$$E(X) = e^{\mu} e^{\frac{\sigma^2}{2}} \tag{3.33}$$

and for $k = 2$,

$$E(X^2) = e^{2\mu} e^{2\sigma^2}. \tag{3.34}$$

As $var(X) = E(X^2) - [E(X)]^2$, then

$$\begin{aligned} var(X) &= e^{2\mu}e^{2\sigma^2} - \left(e^{\mu}e^{\frac{\sigma^2}{2}}\right)^2 \\ &= e^{2\mu}e^{2\sigma^2} - e^{2\mu}e^{\sigma^2} \\ &= e^{2\mu}e^{\sigma^2}\left(e^{\sigma^2} - 1\right). \end{aligned}$$

Therefore, μ and σ^2can be expressed as functions of the mean and the variance of X:

$$\mu = \ln\left(\frac{E(X)^2}{\sqrt{E(X)^2 + var(X)}}\right); \quad \sigma^2 = \ln\left(\frac{var(X)}{E(X)^2} + 1\right). \tag{3.36}$$

Equating the sample moments with the respective theorical moments, it follows:

$$\hat{\mu} = \ln\left(\frac{\bar{X}^2}{\sqrt{\bar{X}^2 + S^2}}\right); \quad \hat{\sigma}^2 = \ln\left(\frac{S^2}{\bar{X}^2} + 1\right). \tag{3.37}$$

3.5.3.2.3 Distribution of the Effectiveness

As referred to before, vaccine effectiveness is calculated based on $1 - RR$. Relative risk results of the ratio between two proportions, namely, the proportion of patients infected by influenza when vaccinated and the proportion of patients infected when not vaccinated. Thus, it may vary between 0 and $+\infty$. Generally, the relative risk calculation is supported by a two-by-two table, as shown in table 3.8.

Table 3.8 – *Two-by-two table showing results from a prospective study*

	Influenza	**Not Influenza**	**Total**
Vaccine	A	b	a + b
Placebo	C	d	c + d
Total	a + c	b + d	n

The RR is given by:

$$RR = \frac{\frac{a}{a+c}}{\frac{b}{b+d}}. \tag{3.38}$$

Risk ratios are analysed on a log scale, i.e. the log risk ratio, the standard error and confidence intervals of a log risk ratio are computed in log units and then converted to the original metric (70,104). Data for TIV effectiveness was taken from a Cochrane meta-analysis, where Mantel-Haenszel methods were used (36). Using this method, the log risk ratio is given by

$$\ln(RR_{MH}) = \ln\left(\frac{\sum w_{MH,i} RR_i}{\sum w_{MH,i}}\right), \tag{3.39}$$

where $w_{MH,i}$ corresponds to the weight of each study of the meta-analysis and it is given by

$$w_{MH,i} = \frac{c_i(a_i + b_i)}{N_i}. \tag{3.40}$$

It is possible to obtain the standard error of the log risk ratio by

$$se[\ln(RR_{MH})] = \frac{P}{RS} \tag{3.41}$$

where,

$$P = \sum \frac{n_{1i}n_{2i}(a_i + c_i) - a_i c_i N_i}{N_i^2}$$
$$R = \frac{a_i n_{2i}}{N_i}$$
$$S = \frac{c_i n_{1i}}{N_i}. \tag{3.42}$$

As the log risk ratio and the standard error of log risk ratio are easily obtained from the meta-analysis study, the lognormal distribution was assigned to the RR and, as mentioned before, TIV effectiveness was obtained as 1-RR. The probabilistic value of QIV effectiveness is obtained from TIV effectiveness and the proportion of B lineage viruses not included in TIV, which follows a beta distribution (see section 3.5.3.3.1).

3.5.3.3 Net Benefits

Net benefits (NB) allow to place both costs and effects in the same scale, which may be net monetary benefit (NMB) or net health benefit (NHB) (7). These measures are derived from ICER expression (see equation 3.10), which represents the quotient of the difference between QIV and TIV in costs (ΔC) and the difference in effects (ΔE). In fact, this expression can be rearranged to obtain the ΔC as a function of the ICER, which can be any CE threshold (105), λ,

$$\Delta C = \Delta E \times \lambda. \tag{3.43}$$

Then, the NMBs result of the subtraction of expected costs from the product of expected effects (QALYs) times a given CE threshold (105), as given by

$$NMB = (\Delta E \times \lambda) - \Delta C. \tag{3.44}$$

In the same way, the NHB can be derived from the ICER equation and consists of the difference between expected effects and expected costs rescaled to health effects units, which means that the expected costs are divided by CE threshold, as follows:

$$NHB = \Delta E - \big(\Delta C \times (1/\lambda)\big). \tag{3.45}$$

Thus, net benefits allow to use the CE thresholds as a function of costs and effects (105), which allow to draw the Cost-effectiveness acceptability curve (7,105), described in more detail in section 3.5.3.3.7.

3.5.3.4 Interval Estimates

Each iteration of the 1000 MC simulations, generates a value for costs and effects of both alternatives and, therefore, a cost effectiveness ratio. Thus, interval estimates can be obtained by taking the $\alpha/2$ and $(1-\alpha/2)$ quantiles of the simulation vector, where α=0.05 for a 95% confidence interval. Such limits will be displayed on the cost-effectiveness plane.

3.5.3.5 Scatter plot

Scatter plots are used to represent PSA results. Each simulated estimate of the expected incremental costs and effects is placed in the cost-effectiveness plane, described in section 3.4.2 for the base case. Additionally, a chart with scattered results of total costs and total QALYs, rather than the increments, is constructed to better understand how these outputs differ between interventions (7).

3.5.3.6 Cost-Effectiveness Acceptability Curve

In addition to the scatter plot and uncertainty intervals, a cost-effectiveness acceptability curve (CEAC) is also reported. The CEAC aims to help the decision-maker to better characterize uncertainty related to the decision to approve or reject a new health strategy (7,106).

The graph gives the probability of each strategy being cost-effective for a given cost-effectiveness threshold (or ceiling ratio) shown on the horizontal axis. It is important to note that the sum of the probabilities of being cost-effective at a given ceiling ratio is equal to 1. In other words, the sum of the area under the two curves is 160,000, as the CE threshold (€/QALY) varies from 0 to 160,000 in the present study.

The probability of each alternative being cost-effective is calculated from the stored results of the MC simulations. For each simulation, the expected NMB is calculated and recorded based on the expected costs, expected effects and a given CE threshold. An *Excel* macro replaces the CE threshold on the NMB formula by a given value from a range between 0€/QALY and 160,000€/QALY. For each iteration, a value of 1 is assigned to TIV and 0 to QIV if the NMB is negative, which means that the NMB are higher for TIV than QIV. If the NMB is positive, a value of 1 is assigned to QIV and 0 to TIV. This allows to record the number of times each strategy offers the highest expected NB. The average of these values gives the probability of each strategy being cost-effective for a given threshold, i.e., the proportion of times that an intervention has the highest expected NB (7).

3.6 Individualizing expected costs by NUTS II regions

Expected costs were individualized by region according to population characteristics, as data derived from National Database on Hospital Morbidity were stratified by NUTS II regions (municipal data were aggregated in NUTS II (Nomenclature of Territorial Units for Statistics, second level) regions according to "Carta Administrativa Oficial de Portugal – Versão 2015"(28)). It is important to be aware that some data were not stratified by region and, therefore, it was applied the aggregated value. Probability of ILI, probability of confirmed influenza, costs of vaccines, GP consultation, antiviral treatment and vaccine administration are examples of that.

3.6.1 Market Share

Although QIV is now commercialized in Portugal, from the NHS perspective TIV still controls 100% of the market, as QIV is not reimbursed. Based on data from 2015/16 season, the expects costs for different market shares, also including QIV, were computed. New scenarios considered include market share of 50%-50% and 100% controlled by QIV. Results are presented for Portugal (Mainland) and NUTS II regions, namely, *Norte, Centro, Lisboa e Vale do Tejo*, *Alentejo* and *Algarve*.

To perform this analysis, an *Excel* macro was created to change key values in the model (namely, the NUTS II region and respective population) in order to use data parameters disaggregated by region, and then record the main results. Each time the macro is run, results from current and new scenario are presented as well as the difference in costs between both, for all regions. A loop was created to copy and paste the results for each region. After the results from the current scenario are copied, the population input value of each strategy is changed, according to the market share, and results from the new scenario are recorded as well.

Chapter 4

RESULTS

4 Results

Chapter 4 summarizes the main results of the decision tree model when the base case values of the parameters for 2015/16 season were considered and shows a detailed sensitivity analysis. The results include the number of hospitalizations and deaths averted by switching from TIV to QIV, the related costs and QALYs and the consequent ICER. The tornado diagram for OWSA, the cost-effectiveness plane and cost-effectiveness acceptability curve are also presented. Finally, costs were individualized by NUTS II regions for different hypothetical market share scenarios.

4.5 Base Case Analysis

Table 4.1 gives a summary of the base case results of shifting from TIV to QIV in the elderly, based on 2015/16 season data. Results show a difference in confirmed influenza cases of approximately 37, resulting in a cost saving of 20,695€. About 36 GP consultations could have been averted and, therefore, 1,103€ saved. Five hospitalizations, including hospitalizations due to influenza, pneumonia, respiratory disease and heart disease, could have been averted and one life saved.

Regarding hospitalization and death costs, caution must be taken in the interpretation of the results. The cost of death, when hospitalized, include all hospitalization costs, and in the same way, the hospitalization costs showed also include costs of people who died. Thus, 15, 873€ could have been saved in hospitalizations, specifically: 9, 434 € in hospitalizations due to influenza; 1, 718 € in hospitalizations due to pneumonia; 1, 311€ in hospitalizations due to respiratory disease; and 3, 409 € in hospitalizations due to heart disease. From that value, 3, 719 € are related to hospitalizations of patients who died.

In what concerns to the number of vaccinated people (mentioned in the table 4.1 as vaccine doses), the value is the same for both strategies. This was an expected result, because the coverage applied to TIV and QIV models was the same, as we are estimating the cost-effectiveness of shifting from TIV to QIV. However, expected costs differ, depending on the vaccine cost. A total of 1,035,895 vaccine doses were expected to have been administered to individuals aged ≥65 years old in 2015/16 season. For TIV strategy, this represented a spending of 2,668,465 €, while for QIV corresponds to 5,535,397 €, meaning that shifting from TIV to QIV would result in an additional cost of 2,866,933 €.

The expected difference in costs between TIV and QIV is 2,849,888 €, while the difference in effects (QALYs) is expected to be 0.20. These values result in a base case ICER of 14,242,844 €/QALY. Plotting the differences in costs and effects on the cost-effectiveness plane, such value is located at the first quadrant. According to section 3.4.2, a cost-effectiveness threshold should be considered, as the new intervention is more costly and more effective. Considering a CE threshold of 34 000€/QALY (see section 3.4.2), the new approach would not be cost-effective.

Table 4.1 *Base Case results of the cost-effectiveness evaluation comparing TIV and QIV.*

	TIV	QIV	Difference (QIV-TIV)	Difference (%)
Events				
GP Consultations	2631.35	2595.77	-35.58	-1.35%
Hospitalizations due to Influenza	239.00	235.77	-3.23	-1.35%
Deaths due to Influenza Hospitalization	19.00	18.74	-0.26	-1.37%
Hospitalizations due to Pneumonia	21.00	20.72	-0.28	-1.33%
Deaths due to Pneumonia Hospitalization	8.00	7.89	-0.11	-1.38%
Hospitalizations due to RD	40.00	39.46	-0.54	-1.35%
Deaths due to RD Hospitalization	2.00	1.97	-0.03	-1.50%
Hospitalizations due to HD	73.00	72.01	-0.99	-1.36%
Deaths due to HD Hospitalization	8.00	7.89	-0.11	-1.38%
Vaccine Doses	1,035,895	1,035,895	0.00	-
Costs				
GP Consultations	81,572 €	80,469 €	-1,103 €	-1.35%
Hospitalizations due to Influenza	710,464 €	701,030 €	-9,434 €	-1.33%
Deaths due to Influenza Hospitalization	121,552 €	119,922 €	-1,630 €	-1.34%
Hospitalizations due to Pneumonia	128,213 €	126,494 €	-1,718 €	-1.34%
Deaths due to Pneumonia Hospitalization	90,401 €	89,184 €	-1,217 €	-1.35%
Hospitalizations due to RD	99,125 €	97,814 €	-1,311 €	-1.32%
Deaths due to RD Hospitalization	2,731 €	2,695 €	-35 €	-1.30%
Hospitalizations due to HD	256,048 €	252,639 €	-3,409 €	-1.33%
Deaths due to HD Hospitalization	62,303 €	61,466 €	-837 €	-1.34%
Vaccine Doses	2,668,465 €	5,535,397 €	2,866,933 €	107.44%
Total	8,018,570 €	10,868,459 €	2,849,888 €	35.54%
QALYs				
Total	1265456.95	1265457.15	0.20	0.00002%
ICER (€/QALY)			14,242,844	

4.6 Deterministic Sensitivity Analysis

After the base case analysis, OWSA allows to identify the most sensitive parameters of the model, i.e. the ones that produce the biggest variation of the ICER. Figure 4.1 summarizes the one-way sensitivity analysis by means of the tornado diagram (see section 3.5.2). Considering the 95% CI, when available, and a variation of ±20% for the remaining parameters, OWSA shows that the disutility associated with ILI when no confirmed influenza, and the cost of quadrivalent vaccine have the highest impact on the ICER.

If the first above mentioned parameter assumes the value of 0.007 (lower bound), it results in an ICER of 10,367,801 €/QALY, and the value of 0.011 (upper bound) results in an ICER of 22,743,332 €/QALY. This can be explained by the increase in incremental QALYs, yielded by decreasing this parameter, that consequently results in a reduced ICER, and vice-versa. In contrast, the variation of the cost of the quadrivalent vaccine within a ±20% range, results in an ICER of 8,710,009 €/QALY (lower bound) and 19,775,678€/QALY (upper bound), respectively.

Figure 4.1 *Tornado diagram showing One-Way Sensitivity Analysis results*

The high impact of QIV cost on ICER was expected if attention is paid to the difference in costs of QIV and TIV doses, which is given by table 4.1. The cost of QIV doses is largely above the cost of TIV doses. Further analysis was performed varying the QIV cost within a wider range (figure 4.2). For a QIV cost equal to TIV cost, an ICER of -85,182€/ QALY was obtained, meaning that shifting from QIV to TIV would be cost-saving, as expected. However, a value higher than 2,576€ would easily lead to not being cost-effective.

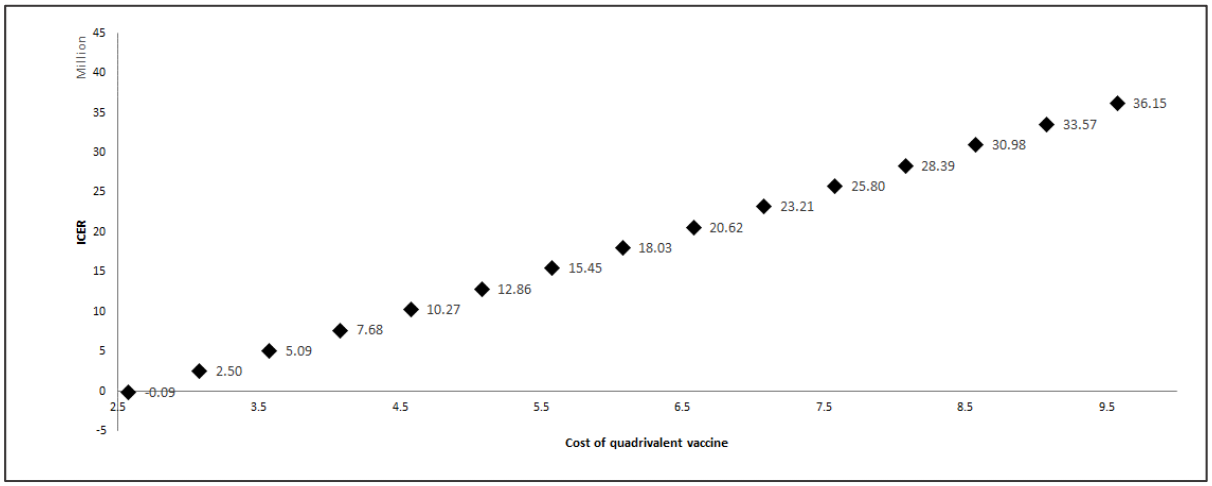


Figure 4.2 *One-way sensitivity analysis of cost of quadrivalent vaccine. Variation between 2.576€ (=TIV cost) and 9.756€ with increments of 0.05€.*

The disutility associated with no hospitalized influenza is the third parameter appearing on the tornado diagram. The variation of this parameter within its 95%CI (0.007, 0.011) produced ICERs of 21,048,861€/QALY and 10,762,770€/QALY, respectively. While the pathway corresponding to vaccinated patients with ILI but not confirmed influenza is more populated in QIV model than in TIV, the same is not true for the pathway referring to vaccinated patients with no hospitalized influenza. Thus, a reduction in disutility associated with no hospitalized influenza would decrease incremental QALYs and therefore, increase ICER.

Probability of ILI and probability of confirmed influenza also have high impact on ICER. Varying these parameters 20% downward and upward produced ICERs of 11,854,839€/QALY and 17,824,850€/QALY, respectively. Thus, as probability of ILI and/or probability of confirmed influenza increases, the ICER decreases.

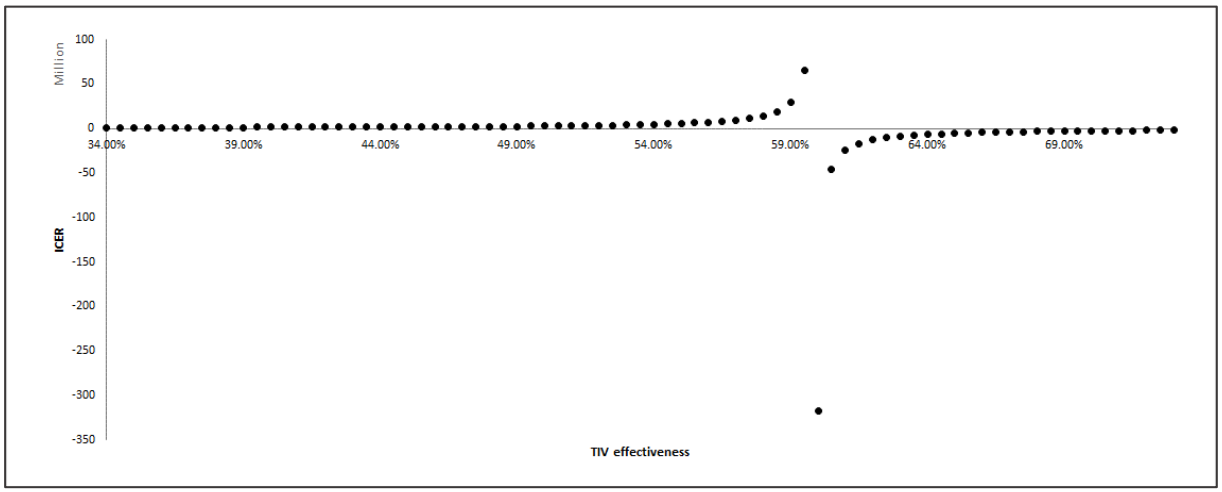


Figure 4.3 *One-way sensitivity analysis of trivalent vaccine effectiveness. Variation between 34% and 74% with increments of 0.005.*

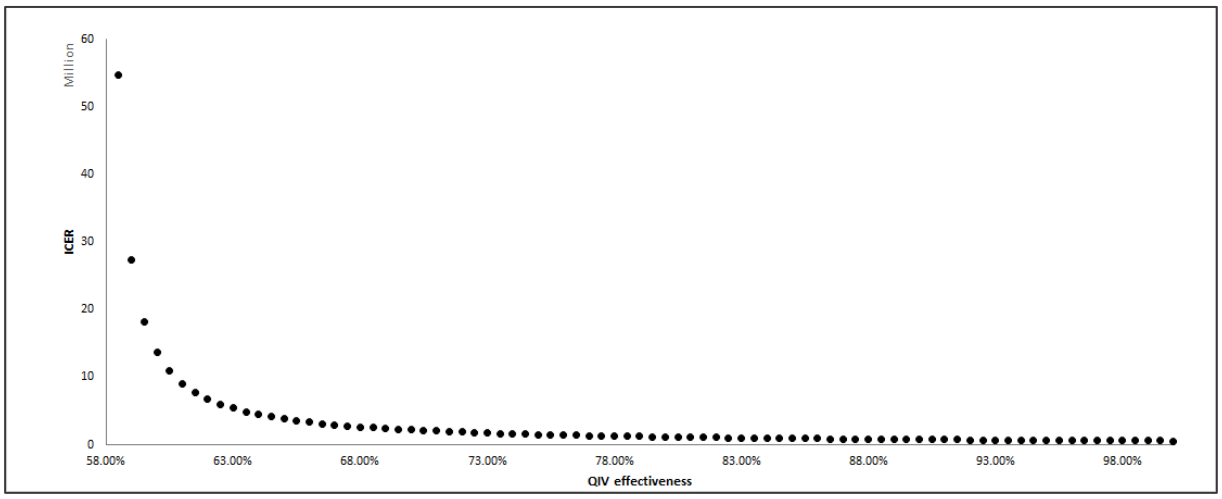


Figure 4.4 *One-way sensitivity analysis of quadrivalent vaccine effectiveness. Variation between 58% (=TIV effectiveness) and 100% with increments of 0.005.*

Regarding QIV and TIV effectiveness, if the TIV effectiveness is equal to QIV effectiveness, the ICER is not defined, as it results in a difference in effects equal to zero and, therefore a division by zero, and a vertical asymptote at 59.91% is shown (fig.4.3). As TIV effectiveness approaches 59.91% from the left, the ICER tends to infinity. Otherwise, as TIV effectiveness approaches 59.91% from the right, the ICER tends to negative infinity. Such is explained by the difference in effects close to zero when TIV and QIV effectiveness are close. For TIV effectiveness values higher than QIV effectiveness, a negative ICER is produced, as the incremental QALYs value is negative.

Similarly, fig. 4.4 shows a vertical asymptote when QIV effectiveness is equal to 58% and ICER tends to infinity when such parameter approaches this value from the right. Finally, the higher the effectiveness of quadrivalent vaccines ($> 58\%$), the lower the ICER.

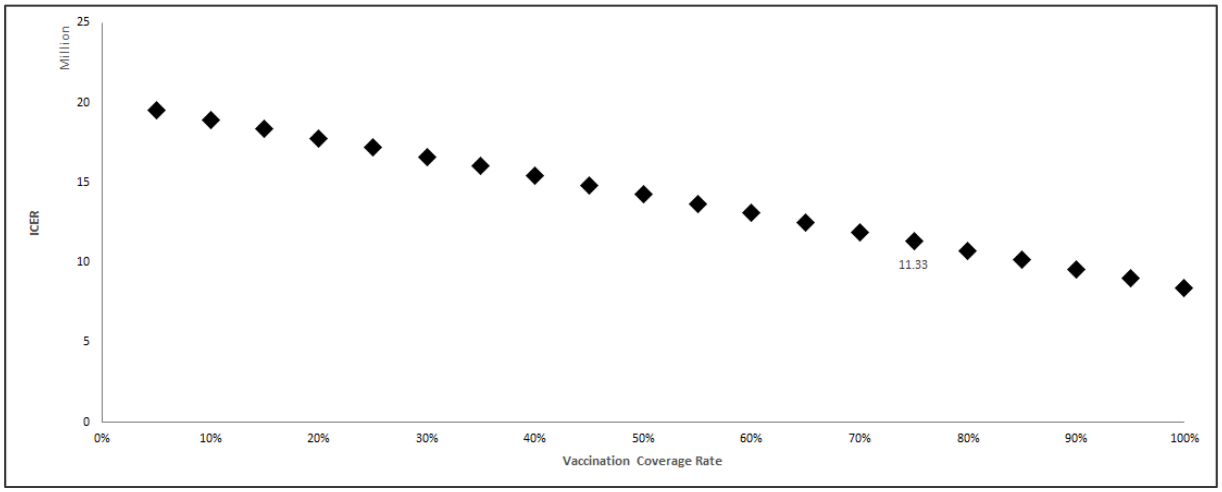


Figure 4.5 *One-way sensitivity analysis of vaccination coverage rate. Variation between 0% and 100% with increments of 0.05.*

Although vaccination coverage rate does not have such a large impact on ICER, as the previous analysed parameters do, a detailed study was also performed for this parameter (fig.4.5). An higher

coverage rate would result in a decreased ICER. For a coverage rate of 75%, as recommended by the World Health Assembly, 11,326,019 €/QALY would be obtained corresponding to a reduction of 20,48%.

4.3 Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis allowed to evaluate the robustness of the base case results. For that, a probability distribution was assigned to the parameters in order to reflect parameter uncertainty, when parameters are estimated based on samples. Parameters values were then sampled 1,000 times and total costs and QALYs were recorded in each iteration. Some empirical statistics such as mean, standard deviation and confidence intervals were then calculated.

As described in section 3.5.3.3.2, two different probability distributions may be assigned to disutilities, which are lognormal and gamma distributions. Both distributions were applied, and main results are presented below.

Table 4.2 *Comparison of the main results of PSA for gamma and lognormal distributions applied to disutility parameters.*

	Distribution for Disutilities	
	Gamma	**Logormal**
Difference in costs	2,848,924€	2,854,253€
Standard Deviation	233,724€	237,518€
CI 95%	(2,401,864€; 3,313,772€)	(2,397,449€; 3,328,321€)
Difference in effects	0.20	0.20
Standard Deviation	0.09	0.07
CI 95%	(0.06; 0.44)	(0.08; 0.36)
ICER (€/QALY)	18,301,554	16,414,766
Standard Deviation	13,240,831	7,468,689
CI 95%	(7,047,221; 46,191,560)	(8,078,889; 33,605,370)

As given by table 4.2, the ICER interval obtained when gamma distribution was used is given by (7,047,221; 46,191,560), which is wider than that obtained from the lognormal distribution (8,078,889; 33,605,370). As such, only gamma results are presented in the following pages of this section, since the conclusions of the study are the same for both distributions.

In general, the results from PSA, given by table 4.3, are similar to those obtained from the base case analysis (table 4.1). The estimated mean cost difference is 2,848,924 € with an interval estimate of (2,401,864€; 3,313,772€), while the estimated mean effect difference corresponds to 0.20 QALYs with an interval varying from 0.06 to 0.44 QALYs. On its turn, mean ICER is estimated at 18,301,554€/QALY (7,047,221; 46,191,560). This value revealed to be about 36% higher than base case result.

Table 4.3 *Probabilistic Sensitivity Analysis results assessing 2015/16 season-related uncertainty*

	TIV	QIV	Difference (QIV-TIV)	Difference (%)
Events				
GP Consultations	2,641.08	2,605.92	-35.16	-1.33%
Hospitalizations due to Influenza	239.00	235.81	-3.19	-1.33%
Deaths due to Influenza Hospitalization	19.00	18.75	-0.25	-1.33%
Hospitalizations due to Pneumonia	21.00	20.72	-0.28	-1.33%
Deaths due to Pneumonia Hospitalization	8.00	7.89	-0.11	-1.33%
Hospitalizations due to RD	40.00	39.47	-0.53	-1.33%
Deaths due to RD Hospitalization	2.00	1.97	-0.03	-1.33%
Hospitalizations due to HD	73.00	72.03	-0.97	-1.33%
Deaths due to HD Hospitalization	8.00	7.89	-0.11	-1.33%
Vaccine Doses	1,035,462	1,035,462	0.00	-
Costs				
GP Consultations	81,874 €	80,783 €	-1,090 €	-1.33%
Hospitalizations due to Influenza	710,470 €	701,170 €	-9,300 €	-1.31%
Deaths due to Influenza Hospitalization	121,552 €	119,945 €	-1,607 €	-1.32%
Hospitalizations due to Pneumonia	128,213 €	126,519 €	-1,695 €	-1.32%
Deaths due to Pneumonia Hospitalization	90,401 €	89,201 €	-1,200 €	-1.33%
Hospitalizations due to RD	99,126 €	97,834 €	-1,293 €	-1.30%
Deaths due to RD Hospitalization	2,731 €	2,696 €	-35 €	-1.28%
Hospitalizations due to HD	256,050 €	252,689 €	-3,361 €	-1.31%
Deaths due to HD Hospitalization	62,303 €	61,478 €	-825 €	-1.32%
Vaccine Doses	2,667,352 €	5,533,090 €	2,865,737 €	107.44%
Total	8,017,027 €	10,865,951 €	2,848,924 €	35.54%
CI lower bound	6,998,818 €	9,398,862 €		
CI upper bound	9,141,942 €	12,472,711 €		
QALYs				
Total	1,263,350.23	1,263,350.43	0.20	0.00002%
CI lower bound	1,199,761.94	1,199,762.09		
CI upper bound	1,328,408.79	1,328,409.29		
ICER (€/QALY)				18,301,554
CI lower bound				7,047,221
CI upper bound				46,191,560

Figure 4.6 shows the average costs and QALYs produced from the 1,000 Monte Carlo simulations for TIV and QIV. While total QALYs of both interventions vary within a small range, the difference in costs between TIV and QIV is well defined, being QIV more costly than TIV.

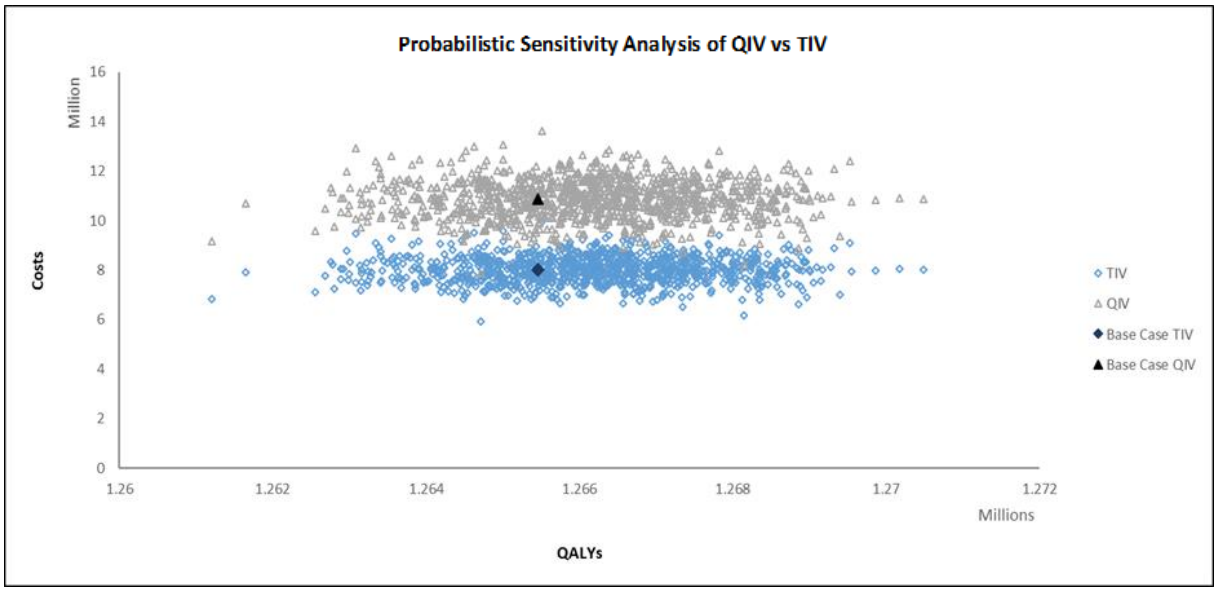


Figure 4.6 *Probabilistic sensitivity analysis for TIV and QIV: Scatter plot based on 2015/16 season*

According to figure 4.7, the cost-effectiveness results are robustly located in the first quadrant of the cost-effectiveness plane (see section 3.4.2) and all simulated ICERs are higher than CE thresholds previously established. This conclusion is enhanced by CEAC (fig.4.8), which demonstrates that the probability of QIV being cost-effective is equal to zero for any threshold value between 0 and 160,000€/QALY (see section 3.5.3.3.7).

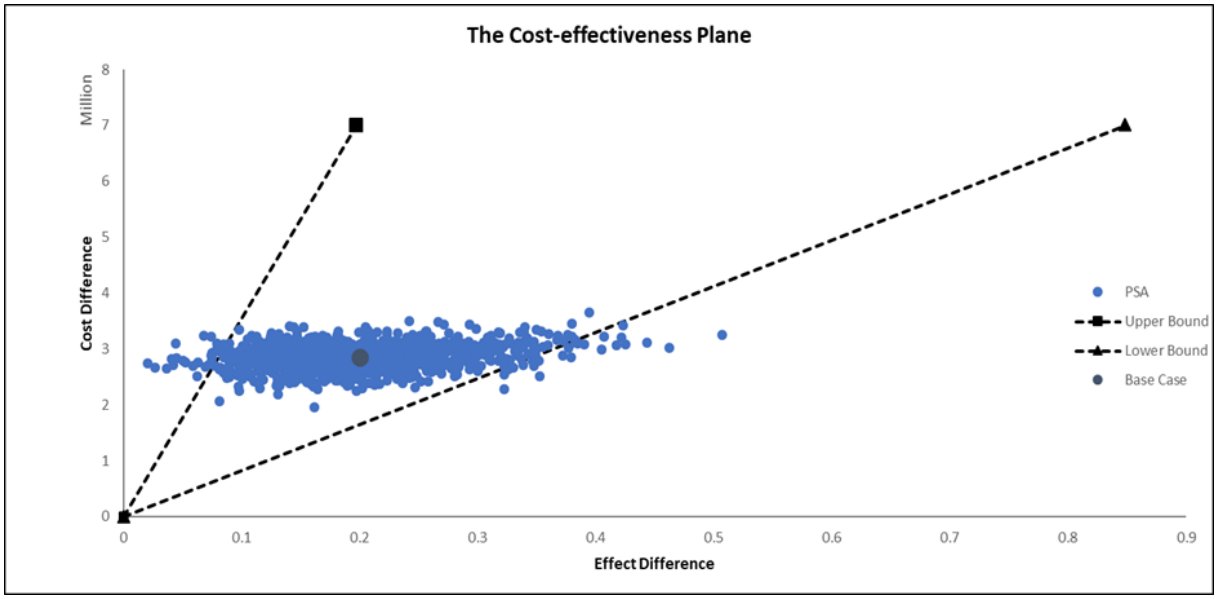


Figure 4.7 *Probabilistic sensitivity analysis for TIV and QIV: Cost-effectiveness plane based on data from 2015/16 season*

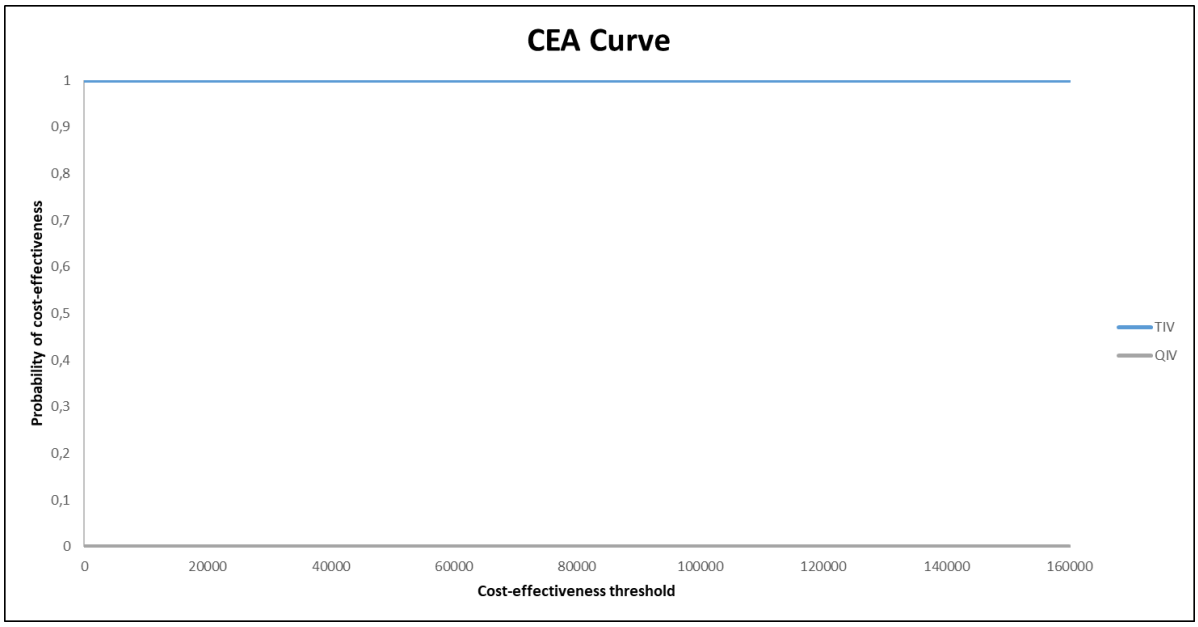


Figure 4.8 *Cost-effectiveness acceptability curve*

4.4 Individualizing expected costs by NUTS II regions

This section provides the expected costs results individualized by the five Portuguese NUTS II regions, which are *Norte*, *Centro*, *Lisboa e Vale do Tejo*, *Alentejo* e *Algarve*. Although QIV is now available in Portugal, only the trivalent Inactivated vaccine is reimbursed by NHS, so the "Current Scenario" is set as TIV having 100% of market share. Beyond the current scenario, two new scenarios were presented, namely: market share of 50%, and market 100% controlled by QIV. Figure 4.9 shows the expected costs by regions for the three computed scenarios and table 4.4 summarizes individualized expected costs, QALYs and differences between scenarios. The results are set out in more detail in the appendices (tables 1, 2, 3, 4, 5 and 6).

Norte region revealed to have the highest expected costs (incremental costs of 471,637€ for 50%-50% scenario and 943,274 € for 100% QIV scenario), which is expected as *Norte* is the most populated region. On its turn, *Centro* is the region with the highest number of QALYs saved (incremental effects of 0.033 QALYs for 50%-50% scenario and 0.066 QALYs for 100% QIV scenario). This can be explained by the higher probabilities of hospitalization and consequent death, recorded for *Centro* than for *Norte*.

Alentejo and *Algarve* have the lowest incremental costs and incremental effects, what is justified by the lowest population level. The expected incremental costs for these regions are 123,903€ and 63,881€ for 50% scenario, and 247,806€ and 127,763€ for 100% QIV scenario, respectively. In contrast, the expected difference in effects are 0.007 and 0.002 QALYs for the first scenario, and 0.013 and 0.003 QALYs for the last scenario, respectively. In particular, *Algarve* region did not record neither hospitalization due to pneumonia (and therefore, deaths when pneumonia hospitalization) nor deaths when hospitalized due to respiratory and heart diseases. *Centro* is the only region that recorded deaths when RD hospitalization (see appendices).

The expected incremental costs for *Lisboa e Vale do Tejo* are 405,335€ for 50% scenario, and 810,671€ for 100% QIV scenario, while the incremental effects are 0.017 and 0.034 QALYs, respectively.

Figure 4.9 *Expected costs by NUTS II regions for the three different scenarios of market share: 100%TIV, 50%-50% and 100%QIV.*

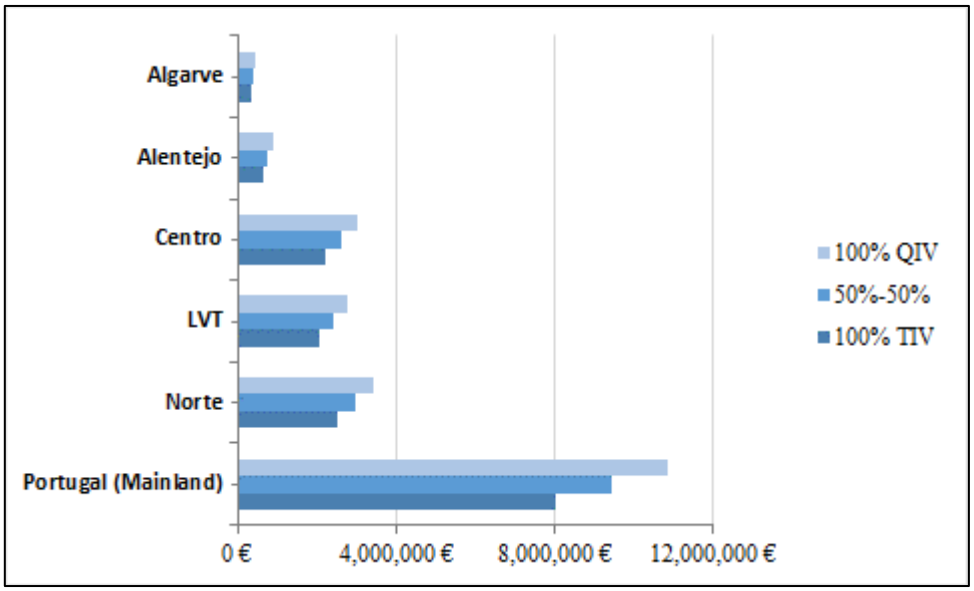


Table 4.4 *Expected costs and incremental costs for Portugal (Mainland) considering a scenario of 50% market share and 100% QIV market share*

		100% TIV (Current Scenario)	50%-50% Scenario	Difference	100% QIV Scenario	Difference
Portugal (Mainland)	QALYs	1,265,456.953	1,265,457.053	0.100	1,265,457.153	0.200
	Costs	8,018,570 €	9,443,515 €	1,424,944 €	10,868,459 €	2,849,888 €
Norte	QALYs	418,299.3093	418,299.3219	0.0127	418,299.3346	0.0254
	Costs	2,499,204 €	2,970,841 €	471,637 €	3,442,478 €	943,274 €
Centro	QALYs	321,412.925	321,412.958	0.033	321,412.991	0.066
	Costs	2,030,467 €	2,393,039 €	362,572 €	2,755,611 €	725,143 €
LVT	QALYs	360,144.306	360,144.323	0.017	360,144.340	0.034
	Costs	2,189,978 €	2,595,313 €	405,335 €	3,000,649 €	810,671 €
Alentejo	QALYs	109,196.921	109,196.928	0.007	109,196.934	0.013
	Costs	637,282 €	761,185 €	123,903 €	885,088 €	247,806 €
Algarve	QALYs	56,407.791	56,407.792	0.002	56,407.794	0.003
	Costs	308,946 €	372,827 €	63,881 €	436,709 €	127,763 €

Chapter 5
DISCUSSION

5 Discussion and limitations of the study

To the best of our knowledge, this is the first published study performing a cost-effectiveness evaluation of seasonal influenza vaccination in Portugal. Only a few papers studied the burden of disease (3,107) and vaccination effectiveness in the Portuguese population. The latter was performed within the scope of the international I-MOVE+ project (30,108–112).

The present project constitutes an adaptation of the cost-effectiveness model constructed by Universidad Francisco de Vitoria to compare the four marketed vaccines in Spain (8,9). For Portugal, the potential cost-effectiveness of switching from trivalent inactivated vaccine to quadrivalent inactivated vaccine was evaluated based on 2015/16 season data. Additionally, the expected costs were individualized by NUTS II regions and different market share scenarios were considered.

Base case results revealed that the universal substitution of TIV with QIV would result in an ICER of 14,242,844€ per QALY gained. As such, for the cost-effectiveness thresholds of 30,000€/QALY and 34,000€/QALY, QIV is not cost-effective. Probabilistic sensitivity analysis enhanced the robustness of the base case results. Uncertainty interval estimates and CEAC highlighted that the potential ICER is much higher than any possible ceiling ratio established by NHS. Such results are comparable to those obtained for the first year of QIV administration to Hong Kong elderly (≥80 years old), when a CE analysis over 9 seasons was performed (54). As consequence, the need for a longer time horizon study is emphasized, as discussed later in this chapter.

In contrast, the generality of published international papers (see section 2.10) does not report such an high ICER, and QIV is usually identified as cost-effective when compared with TIV (see table 2.3). This inconsistency between this model and the published papers is mainly due to the use of long time-horizon to calculate QIV effectiveness. This allowed them to assume a few seasons that match the QIV with the circulating strains and low mismatching. Other reason is the cost of QIV which in this study is about three times the one of TIV, as discussed below.

Univariate sensitivity analysis demonstrated that the model is most sensitive to disutility associated with ILI, cost of quadrivalent vaccine, disutility associated with no hospitalized influenza, and probabilities of confirmed influenza and ILI. However, when comparing these inputs values with those used in other studies, large differences are identified. Regarding the cost of quadrivalent vaccine, lower differences between strategies costs were considered. Specifically, the additional cost of QIV is rarely higher than 100% of the TIV cost (52,55,58,60,66). In addition, the probability of influenza-like-illness and the probability of confirmed influenza were found to be higher than those applied in this model. Capri et al. (113) applied a probability of influenza of 6.4%, resulting from the product of ILI attack rate (16.8%) by influenza virus isolation rate (32.1%), while Van Bellinghen et al. (58) used a probability of symptomatic influenza infection of 6.17%. It is important to remember that the probability of confirmed influenza was derived from a national report on influenza surveillance and probability of ILI was determined from other input values and it is comparable to the value reported by INSA for 2015/16 season (46).

The fact that the number of influenza-related deaths is roughly the same as that reported by INE for 2015 (*Óbitos (N.º) por Local de residência (NUTS - 2013)* (114), *Sexo, Grupo etário e Causa de morte (Lista OCDE adaptada); Anual*) may validate the assumed model structure – i.e., confirmed influenza was only diagnosed in either GP consultation, pneumonia, respiratory disease or heart disease hospitalization context. Moreover, although the number of influenza and pneumonia hospitalizations is not in accordance with the excess hospitalizations estimated by Rodrigues et al. (3), it can be explained by the low influenza activity recorded in 2015/16 season (46). Even so, QIV impact may be underestimated.

Regarding the sensitivity analysis, it must be strengthened that univariate sensitivity analysis was performed to identify the factors of greatest influence on the model, instead of assessing parameter

uncertainty (60,86,100). Such sensitive inputs revealed to be in line with other DSA results found in the literature (55,58,66,115). For probabilistic sensitivity analysis, probability distributions were assigned only to parameters based on samples, as the population-based ones do not add uncertainty to the model. Ideally, distributions should have been fitted to patient-level data. However, this was not possible as uncertain parameters were taken from literature. Thus, distributions for describing the data were chosen based on commonly used distributions (70). The cost-effectiveness plane, interval estimate and CEAC were in line with the base case conclusions.

With respect to the region individualized costs, *Norte* was identified as the region with higher expected costs, while *Centro* reported the highest expected effects. In contrast, *Algarve* is the region with the lowest incremental costs and effects. In general, these results are in accordance with the expectative.

The presented model is limited to the 2015/16 season data. Low influenza activity was reported for this season and, therefore, it may not be representative of other seasons. A model developed with data from several seasons would be desirable, as it would allow a better knowledge about the vaccine cost-effectiveness behaviour over time (54). Additionally, a lifetime horizon instead of 1-year horizon would help to better reflect health policy in the real world, as it would account for the repeated vaccination and other interventions (58,61).

The present project employed a static model, where the herd effects of immunization are not considered, and only direct protection is captured. Thus, the impact of vaccination on the burden of disease might be underestimated. As more patients are immunized against more influenza virus, the probability of an individual gets infected by influenza decreases. A dynamic transmission modelling approach would be better to account for the impact of vaccination on the influenza transmission (56,60,64,66,116).

Side effects of vaccination were not included in this study, but QIV safety is assumed to be comparable to that of TIV and side effects are assumed to be mild and temporary. Thus, no impact is expected on the ICER (60).

In order to assess the cost-effectiveness of influenza vaccination for the all population, a model stratified by age and risk groups would be desirable. As average life expectancy is increasing over time, the group of individuals aged 65 and over is also increasing, being an important risk group that must be studied in detail. However, the analysis of full health-economic impact of seasonal influenza vaccination must include the entire population.

As cost of quadrivalent vaccine is one of the influential factors of the model, different results might be obtained from a hypothetical societal perspective, because influenza vaccination is free for the elderly and, therefore, the cost of QIV is not expected to be borne by the patient. In turn, additional indirect costs including productivity loss of caregivers and patients and over-the-counter medicines, would be considered.

Another limitation of this project is related to international sources of information. Although Portuguese data were usually preferred over international data, because it characterizes the study population in a better way, some input parameters were not available for Portugal and, therefore, information was taken from foreign published studies. Data on disutilities are an example of that.

One main strength of the model is the use of real data extracted from the National Database on Hospital Morbidity. This constitutes an improvement over the Spanish model, which is largely based on data from literature. In addition, the model constructed on *Excel* can easily be adapted to compare other strategies.

Chapter 6
CONCLUSIONS

6 Conclusions

The present study investigated the cost-effectiveness of switching from trivalent inactivated vaccine to quadrivalent inactivated vaccine for individuals aged 65 and over in Portugal. The model was based on that developed by *Universidad Francisco de Vitoria* for Spain. Additionally, expected costs were also individualized by NUTS II regions.

In conclusion, quadrivalent vaccine revealed not to be cost-effective for the elderly population in Portugal from the NHS perspective. Some parameters were identified as being highly different from those used in the literature, what may explain large differences in the main outcome, that is, ICER. Probabilistic sensitivity analysis validated the robustness of the base case results. Even though QIV was not concluded to be cost-effective, results are consistent with findings from literature which indicate that QIV would be expected to avert more influenza cases, hospitalizations and deaths than TIV.

Although QIV is already marketed in Portugal, the vaccine is not yet reimbursed by NHS. Further investigation is required to fully understand the cost-effectiveness of QIV versus TIV in Portugal. However, as this study is the first published paper performing an economic analysis of the influenza vaccination in Portugal, it could be a useful basis and tool for future developments. The use of a dynamic model, which accounts for herd immunity, a longer lifetime horizon, the stratification by age and risk groups and an entire population approach are some of the improvements that could be done in the future to complement this analysis. Furthermore, the inclusion of productivity losses and over-the-counter costs could allow to better characterize the societal impact.

To conclude, the present project results could be important to inform manufacturers and national authorities in respect to influenza vaccines production and pricing, as well as policy makers in what concerns to the adoption of new strategies. Moreover, this study gave its contribution to understand the impact of annually influenza epidemics on health economics and public health in Portugal.

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APPENDICES

Appendices

Table 1 *Expected costs for Portugal (Mainland) considering a scenario of 50% market share and 100% QIV market share*

Portugal (Mainland)					
Events	**100% TIV (Current Scenario)**	**50%-50% Scenario**	**Difference**	**100% QIV Scenario**	**Difference**
GP Cons.	81,571.87 €	81,020.37 €	-551.51 €	80,468.86 €	-1,103.01 €
Infl. Hosp.	710,463.60 €	705,746.65 €	-4,716.95 €	701,029.70 €	-9,433.90 €
Infl. Deaths	121,551.71 €	120,736.78 €	-814.93 €	119,921.84 €	-1,629.87 €
Pneu. Hosp.	128,212.58 €	127,353.33 €	-859.25 €	126,494.09 €	-1,718.49 €
Pneu. Deaths	90,400.65 €	89,792.34 €	-608.30 €	89,184.04 €	-1,216.61 €
RD Hosp.	99,125.33 €	98,469.62 €	-655.71 €	97,813.91 €	-1,311.42 €
RD Deaths	2,730.64 €	2,712.90 €	-17.74 €	2,695.17 €	-35.48 €
HD Hosp.	256,048.23 €	254,343.51 €	-1,704.72 €	252,638.78 €	-3,409.45 €
HD Deaths	62,302.50 €	61,884.17 €	-418.33 €	61,465.84 €	-836.66 €
Vaccine Doses	2,668,464.63 €	4,101,930.96 €	1,433,466.33 €	5,535,397.28 €	2,866,932.65 €
Total QALY	1265456.9532	1265457.0533	0.1000	1265457.1533	0.2001
Total Costs	8,018,570.39 €	9,443,514.53 €	1,424,944.14 €	10,868,458.67 €	2,849,888.29 €

Table 2 *Expected costs for Norte region considering a scenario of 50% market share and 100% QIV market share*

Norte					
Events	**100% TIV (Current Scenario)**	**50%-50% Scenario**	**Difference**	**100% QIV Scenario**	**Difference**
GP Cons.	27,367.77 €	27,182.74 €	-185.03 €	26,997.70 €	-370.07 €
Infl. Hosp.	152,984.84 €	151,969.76 €	-1,015.08 €	150,954.69 €	-2,030.15 €
Infl. Deaths	18,153.94 €	18,032.23 €	-121.71 €	17,910.52 €	-243.42 €
Pneu. Hosp.	4,126.85 €	4,099.46 €	-27.39 €	4,072.08 €	-54.78 €
Pneu. Deaths	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
RD Hosp.	23,394.63 €	23,239.80 €	-154.83 €	23,084.97 €	-309.67 €
RD Deaths	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
HD Hosp.	62,618.24 €	62,202.07 €	-416.17 €	61,785.89 €	-832.35 €
HD Deaths	5,524.83 €	5,487.73 €	-37.10 €	5,450.64 €	-74.19 €
Vaccine Doses	881,336.93 €	1,354,780.27 €	473,443.34 €	1,828,223.62 €	946,886.69 €
Total QALY	418299.3093	418299.3219	0.0127	418299.3346	0.0254
Total Costs	2,499,204.16 €	2,970,841.26 €	471,637.11 €	3,442,478.37 €	943,274.22 €

Table 3 *Expected costs for Centro region considering a scenario of 50% market share and 100% QIV market share*

Centro					
Events	**100% TIV (Current Scenario)**	**50%-50% Scenario**	**Difference**	**100% QIV Scenario**	**Difference**
GP Cons.	20,885.11 €	20,743.91 €	-141.20 €	20,602.71 €	-282.41 €
Infl. Hosp.	177,527.69 €	176,349.25 €	-1,178.44 €	175,170.80 €	-2,356.88 €
Infl. Deaths	29,097.69 €	28,903.27 €	-194.42 €	28,708.85 €	-388.84 €
Pneu. Hosp.	47,307.39 €	46,989.85 €	-317.53 €	46,672.32 €	-635.07 €
Pneu. Deaths	35,444.42 €	35,205.56 €	-238.87 €	34,966.69 €	-477.74 €
RD Hosp.	24,779.78 €	24,615.58 €	-164.20 €	24,451.38 €	-328.40 €
RD Deaths	1,937.17 €	1,924.59 €	-12.58 €	1,912.00 €	-25.17 €
HD Hosp.	44,388.67 €	44,093.69 €	-294.98 €	43,798.71 €	-589.95 €
HD Deaths	18,316.96 €	18,194.41 €	-122.56 €	18,071.85 €	-245.11 €
Vaccine Doses	678,861.04 €	1,043,536.83 €	364,675.79 €	1,408,212.62 €	729,351.58 €
Total QALY	321412.9250	321412.9582	0.0332	321412.9913	0.0663
Total Costs	2,030,467.11 €	2,393,038.86 €	362,571.75 €	2,755,610.61 €	725,143.50 €

Table 4 *Expected costs for Lisboa e Vale do Tejo region considering a scenario of 50% market share and 100% QIV market share*

Lisboa e Vale do Tejo					
Events	**100% TIV (Current Scenario)**	**50%-50% Scenario**	**Difference**	**100% QIV Scenario**	**Difference**
GP Cons.	23,557.97 €	23,398.70 €	-159.28 €	23,239.42 €	-318.55 €
Infl. Hosp.	153,130.94 €	152,113.08 €	-1,017.86 €	151,095.22 €	-2,035.72 €
Infl. Deaths	29,477.57 €	29,279.29 €	-198.27 €	29,081.02 €	-396.54 €
Pneu. Hosp.	37,476.15 €	37,224.57 €	-251.58 €	36,972.99 €	-503.16 €
Pneu. Deaths	27,758.01 €	27,571.11 €	-186.90 €	27,384.21 €	-373.80 €
RD Hosp.	14,039.61 €	13,947.25 €	-92.35 €	13,854.90 €	-184.71 €
RD Deaths	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
HD Hosp.	45,183.27 €	44,882.67 €	-300.61 €	44,582.06 €	-601.21 €
HD Deaths	1,413.88 €	1,404.58 €	-9.30 €	1,395.28 €	-18.61 €
Vaccine Doses	757,953.99 €	1,165,117.54 €	407,163.55 €	1,572,281.09 €	814,327.10 €
Total QALY	360144.3061	360144.3230	0.0169	360144.3400	0.0338
Total Costs	2,189,977.82 €	2,595,313.16 €	405,335.34 €	3,000,648.50 €	810,670.68 €

Table 5 *Expected costs for Alentejo region considering a scenario of 50% market share and 100% QIV market share*

Alentejo					
Events	**100% TIV (Current Scenario)**	**50%-50% Scenario**	**Difference**	**100% QIV Scenario**	**Difference**
GP Cons.	7,188.71 €	7,140.11 €	-48.60 €	7,091.51 €	-97.21 €
Infl. Hosp.	31,470.95 €	31,260.49 €	-210.46 €	31,050.02 €	-420.93 €
Infl. Deaths	1,766.40 €	1,754.71 €	-11.69 €	1,743.03 €	-23.37 €
Pneu. Hosp.	2,652.76 €	2,635.60 €	-17.17 €	2,618.43 €	-34.33 €
Pneu. Deaths	929.59 €	923.82 €	-5.77 €	918.04 €	-11.54 €
RD Hosp.	4,996.39 €	4,963.38 €	-33.01 €	4,930.37 €	-66.02 €
RD Deaths	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
HD Hosp.	5,674.03 €	5,636.95 €	-37.08 €	5,599.87 €	-74.16 €
HD Deaths	1,201.69 €	1,193.82 €	-7.87 €	1,185.95 €	-15.74 €
Vaccine Doses	231,299.61 €	355,550.91 €	124,251.30 €	479,802.22 €	248,502.60 €
Total QALY	109196.9211	109196.9277	0.0066	109196.9342	0.0131
Total Costs	637,281.71 €	761,184.83 €	123,903.12 €	885,087.95 €	247,806.24 €

Table 6 *Expected costs for Algarve region considering a scenario of 50% market share and 100% QIV market share*

Algarve					
Events	**100% TIV (Current Scenario)**	**50%-50% Scenario**	**Difference**	**100% QIV Scenario**	**Difference**
GP Cons.	3,779.37 €	3,753.82 €	-25.55 €	3,728.27 €	-51.10 €
Infl. Hosp.	1,277.31 €	1,269.18 €	-8.12 €	1,261.06 €	-16.24 €
Infl. Deaths	638.65 €	634.59 €	-4.06 €	630.53 €	-8.12 €
Pneu. Hosp.	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
Pneu. Deaths	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
RD Hosp.	1,379.84 €	1,370.77 €	-9.07 €	1,361.70 €	-18.14 €
RD Deaths	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
HD Hosp.	1,201.69 €	1,193.82 €	-7.87 €	1,185.95 €	-15.74 €
HD Deaths	0.00 €	0.00 €	0.00 €	0.00 €	0.00 €
Vaccine Doses	119,013.05 €	182,945.39 €	63,932.34 €	246,877.73 €	127,864.69 €
Total QALY	56407.7905	56407.7922	0.0017	56407.7939	0.0033
Total Costs	308,946.09 €	372,827.48 €	63,881.39 €	436,708.86 €	127,762.77 €