Cost-effectiveness of quadrivalent versus trivalent inactivated influenza vaccines for the Portuguese elderly population

Diana Tavares[1¶], Helena Mouriño[1*¶], Cristina Antón Rodríguez[2¶], Carlos Martín Saborido[3¶]

[1]Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal

[2]Facultad de Medicina, Universidad Francisco de Vitoria, Madrid, España

[3]Hospital La Paz Institute for Health Research, IP Research on Evidence and Decision Making Group, Higher Education Center Hygiea. UDIMAMadrid, Madrid. España

* Corresponding author

E-mail: mhnunes@fc.ul.pt

¶ This authors contributed equally to this work.

Abstract

Background

Quadrivalent Inactivated Vaccine (QIV) is expected to replace Trivalent Inactivated Vaccine (TIV) over time. In Portugal, TIV is free of charge for risk groups, which include older adults. In its turn, QIV – which provides broader protection as it includes an additional lineage B strain – was introduced in Portugal in October 2018, but only from the influenza season 2019/20 was provided free of charge for the risk groups. This study evaluates the cost-effectiveness of switching from TIV to QIV from the National Health Service perspective in the Portuguese elderly mainland population (≥ 65 years old).

Methods

A decision tree model was developed to compare TIV and QIV, based on Portuguese hospitalization data for the 2015/16 influenza season. The primary health economic outcome under consideration was the Incremental Cost-Effectiveness Ratio (ICER). In addition, a one-Way Sensitivity Analysis was performed to evaluate the impact of model parameters on the ICER; Probabilistic Sensitivity Analysis was also carried out to analyze the robustness of the base case results.

Results

The high cost of QIV (approximately three times the cost of TIV) would lead to a total increment of 5,283,047 €, and the resulting ICER would be 26,403,007€/QALY, mainly above the usual willingness-to-pay threshold.

Conclusions

From the National Health Service perspective, our findings reveal that QIV is not cost-effective for the Portuguese elderly population due to the high cost. If the QIV costs were the same as the TIV, then QIV would be cost-effective.

Keywords: Influenza vaccines; Decision tree; Cost-Effectiveness analysis; One-way sensitivity analysis; Probabilistic sensitivity analysis

Introduction

Seasonal influenza is an acute respiratory disease caused by infection with influenza viruses(1). There are four types of seasonal influenza viruses: A, B, C and D(1). Only influenza A and B viruses circulate and cause seasonal epidemics of disease(1). The infection may cause signs and symptoms like fever, cough, headache, muscle and joint pain and weakness(1).

Influenza outbreaks are recorded every year. In temperate zones of the northern and southern hemispheres, epidemics occur during the winter, while in the tropics they occur throughout the year(2,3). In Portugal, influenza outbreaks are characterized by significant morbidity in the general population and increased mortality rates. The high-risk groups are: elderly (≥65 years old), patients with chronic or immunosuppressive conditions aged six months or older, pregnant women, health professionals and other healthcare givers(4).

An influenza pandemic can appear when a new and different type of influenza A virus emerges, and it can infect humans who are not immunized(1,5). The most recent pandemic was in 2009, caused by the A(H1N1)2009 virus, after which it became a seasonal influenza serotype(1). In Portugal, 1,189 people were hospitalized, around 10% in intensive care units, resulting in 124 deaths(6).

According to the World Health Organization (WHO), vaccination is the most effective way to prevent seasonal influenza and subsequent severe outcomes(1). Therefore, vaccination should be administered annually to provide optimal protection. Influenza Surveillance System in Portugal is usually activated on week 40 (October) of a given year (*n*) and lasts up to week 20 (April) of the following year (*n*+1) (7,8). Thus, it is recommended to administer the vaccine during autumn and winter, preferably until the end of the year *n* (4). The development of immunity against influenza viruses takes about two weeks after vaccination(9). However, vaccine effectiveness depends on the influenza subtypes included in the vaccines (a mismatch occurs when the viruses in the vaccine are different from the circulating viruses) and the population vaccination coverage. Unfortunately, several European countries reported a decline in vaccination coverage among older people from 2008/09 to 2014/15 seasons. Conversely, Portugal reported an increase in vaccination uptake throughout these seasons(10). In the 2015/16 season, influenza vaccination coverage was 50.1% in Portugal(7). The coverage rate has still increased in the last few years. For instance, in the 2017/18 season, it has increased to 60.8% for people aged 65 years or above(11).

A Cochrane study on this topic concluded that the risk of influenza decreases from 6% to 2.5%, and the risk of Influenza-Like Illness (ILI) reduces from 6% to 3.5%, between unvaccinated and vaccinated

31 groups (≥ 65 years old) during a single season(12). In the European Union, it is estimated that influenza
32 vaccination prevents up to 37,000 deaths each year(13).

33 There are two main types of seasonal influenza vaccines, namely Inactivated Influenza Vaccine (IIV)
34 and Lived Attenuated Influenza Vaccine (this one is not within the scope of the paper)(5,12). The different
35 IIV developed are: trivalent, trivalent adjuvanted and quadrivalent. Trivalent Inactivated Vaccine (TIV) is
36 the most common IIV and protect against three different influenza viruses (two influenza A strains and
37 one influenza B lineage). In some EU/EEA countries, the trivalent adjuvanted vaccine is available for
38 older people to empower immune response(5,14). Quadrivalent inactivated Influenza Vaccine (QIV) is
39 available since the 2014/2015 season in some EU/EEA countries, and it is expected to replace TIV over
40 time(5). It contains one more influenza B strain in addition to those included in TIV, which provides wider
41 protection against influenza viruses. TIV is available in all EU/EEA countries, while QIV is only available
42 in some of them. In Portugal, QIV was launched in October 2018, but only from the influenza season
43 2019/20 it was provided free of charge for the risk groups.

44 Influenza is, thus, a major global health threat that affects all countries, not only from a health
45 perspective but also from economic and social approaches. Therefore, it is crucial to carry out economic
46 evaluations of the influenza vaccination programmes.

47 This work aims to estimate the cost-effectiveness of switching from TIV to QIV based on the National
48 Health Service perspective. The results are presented as incremental cost per unit of effect, described by
49 the Incremental Cost-Effectiveness Ratio (ICER). As far as we know, no cost-effectiveness analysis of
50 Portuguese influenza vaccination has been reported in the literature yet.

51

52 # Methods

Key Features of the Economic Evaluation

The target population is the population of mainland Portugal aged 65 and above because they are one of the most relevant influenza risk groups. In 2015, they represented 21% of the Portuguese population(15). This group is usually retired, so productivity losses are not relevant. The cost-effectiveness evaluation was performed from the National Health Service (NHS) perspective, where only direct costs were considered. Thus, only the medical costs paid by the NHS are considered here.

The Influenza Surveillance System runs from week 40 of a specific year until week 20 of the following year, so the time horizon established for this work was one year. Therefore, data under analysis refers to the 2015/16 influenza season.

As stated above, economic evaluations are performed to identify, measure, value and compare the costs and consequences of different therapeutic alternatives in what respects to influenza vaccination. To perform the cost-effectiveness analysis, health outcomes generated by the two alternative interventions under analysis are assessed through the Quality-Adjusted Life Year (QALY). It measures the length of life-years (i.e., quantity gains) and the quality of life (i.e., quality gains). The quality of life is quantified by the notion of utility: the greater the preference for a particular state, the greater its utility. Utilities incorporate in the analysis the preferences of individuals for different treatment-related outcomes. Another key measure is the concept of quality-of-life loss due to the disease (influenza, in this case), that is, disutility. It corresponds to the reverse of utility, i.e., decrease in utility due to serious health complications. These quantities are obtained by Health-related quality of life (HRQoL) instruments, such as the EQ-5D family of questionnaires. Studies about utilities and disutilities for the Portuguese population are very scarce. In this work, utilities associated with different health states were obtained from a study on *EQ-5D Portuguese Population norms*(16). Data available were stratified by age, but unfortunately, there was no information for people aged 65 or over. Therefore, the utilities for that age group were derived by interpolation (see S1 Appendix). Moreover, no Portuguese studies on disutilities

were found for influenza. Such data were extracted from a Spanish study (17) (see S1 Appendix). All these results were thus combined in a single index, QALY(18,19).

Incremental Cost-Effectiveness Ratio (ICER) is the primary cost-effectiveness outcome used in this work(19). To make recommendations to policymakers, ICER is usually compared with an established threshold, called Willingness-To-Pay (WTP). Some decision-makers have established a Willingness-To-Pay (WTP) threshold, that refers to the maximum ICER accepted for an intervention to be considered cost-effective. In Portugal, there is no established cost-effectiveness threshold for health interventions. Some Portuguese authors refer to a WTP threshold of 30,000€/QALY(20,21), while others consider the cost-effectiveness threshold twice the Gross Domestic Product (GDP) per capita or Gross National Income (GNI) per capita(21,22). In 2015, the Portuguese GNI per capita was 16,887.36€, resulting in a ceiling ratio of approximately 34,000€ (twice the GNI)(23,24). In this paper, the ICER will be used to provide information on the extra amount that is necessary to pay in order to gain an extra QALY when the most effective alternative is chosen(19,25).

Decision Tree

The cost-effectiveness analysis was based on a decision tree model, a very powerful tool in this context because it incorporates probabilities of the outcomes, resource costs, vaccination coverage rate, prices of the vaccines, efficacy, utilities and disutilities. It consists of a series of pathways representing possible prognoses for each alternative therapy being evaluated. A static model was used, and no herd effects of vaccination were evaluated.

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. For illustration, Fig 1 displays the branch of the decision tree for vaccinated individuals.

Fig 1. Decision tree for the cost-effectiveness analysis. Branch for the vaccinated people aged ≥ 65 years old.

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.

It was assumed that influenza confirmation (through diagnostic tests) was carried out in the context of General Practitioner (GP) consultation, pneumonia hospitalization, respiratory disease hospitalization or heart disease hospitalization. Although it is known that influenza may be diagnosed in many other situations, the diseases described above are usually associated with complications due to influenza in the elderly. It should be noted that influenza event (as a secondary diagnosis) may have occurred before or after hospital admission, in which principal diagnoses was pneumonia, respiratory disease or heart disease. It is important to note that the "Healthy" state is assumed to include all individuals who did not die, regardless of their health conditions.

Input Parameters and Computation of the Probabilities

The decision tree is powered by different types of parameters. A detailed description of each of these measures is provided in the S2 Appendix (which includes S1 Table). A summary of the base case values for the parameters under consideration is displayed in Table 1. The computation of the different parameters involved in the decision tree pathways for the TIV – probabilities, costs and QALY – are given in the S1 Fig and S2 Table. Similar calculations are made for the QIV scenario.

121 **Table 1. Input parameters for the decision tree.** Base case values.

Input Parameters	Base Case	Source
Population	2,067,654	(26)
Vaccination Coverage Rate	0.501	(7)
Trivalent Vaccine Effectiveness	0.580	(12)
Quadrivalent Vaccine Effectiveness	0.599	(27–35)
Probability of Influenza-like-illness	0.007	(7,12,26,31,36)
Probability of Confirmed Influenza	0.278	(31)
Probability of GP Consultation	0.952	(31,36)
Probability of Hospitalization due to Influenza	0.091	(37)
Probability of death when Hosp. Influenza	0.079	(37)
Probability of Hospitalization due to Pneumonia	0.008	(37)
Probability of death due to Hosp. Pneumonia	0.381	(37)
Probability of Hospitalization due to Respiratory Disease	0.014	(37)
Probability of death when Hosp. RD	0.050	(37)
Probability of Hospitalization due to Heart Disease	0.026	(37)
Probability of death when Hosp. HD	0.110	(37)
Probability of death when no confirmed influenza	0.043	(26,38)
Cost of GP consultation	31.000	(39)
Cost of Hospitalization due to Influenza	2644.011	(37,39)
Cost of death when Hospitalization due to Influenza	6364.597	(37,39)
Cost of Hospitalization due to Pneumonia	2906.749	(37,39)
Cost of death when Hospitalization due to Pneumonia	11298.219	(37,39)
Cost of Hospitalization due to Respiratory Disease	2534.841	(37,39)
Cost of death when Hospitalization due to RD	1363.460	(37,39)
Cost of Hospitalization due to Heart Disease	2978.842	(37,39)
Cost of death when Hospitalization due to HD	7785.951	(37,39)
Cost of antiviral treatment	18.300	(40,41)
Cost of trivalent vaccine	2.576	(42)
Cost of quadrivalent vaccine	7.692	(43,44)

Cost of vaccine administration	3.700	(39)
Disutility associated with ILI without influenza confirmation	0.009	(17)
Disutility associated with no hospitalized influenza	0.009	(17)
Disutility associated with hospitalization due to influenza	0.031	(17)
Disutility associated with hospitalization due to pneumonia	0.031	(17)
Disutility associated with hospitalization due to respiratory disease	0.031	(17)
Disutility associated with hospitalization due to heart disease	0.031	(17)
Utility associated with healthy population	0.625	(16,26)

Scenario Analysis

The most common ways to characterize parameter uncertainty are: One-way Sensitivity Analysis (OWSA) and Probabilistic Sensitivity Analysis (PSA)(19,25).

OWSA consists of varying the point estimates of the input parameters one at a time within a plausible range of values and assessing the impact on model outcomes(19,25), which corresponds to the ICER. When the Confidence Interval (CI) for a specific parameter was known from the literature, these limits were used as the OWSA range. For parameters with no CI available, a range of ±20% was used to assess model's sensitivity to parameters variation. A tornado diagram was used to report OWSA results.

A scenario analysis of the vaccination coverage rate, TIV effectiveness and QIV effectiveness variation was also carried out. The cost of the quadrivalent vaccine was also studied in detail, as it was identified as a critical parameter(45). For vaccination 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.

Instead of representing the parameters as single point estimates as in OWSA, in PSA parameters are represented by random variables following a particular distribution. The S2 Table displays the base case values used for each input parameter of the decision tree models. It also shows the probability distribution

138 (with information on location, shape, scale, when appropriate) used for each parameter under
139 consideration. A total of 1,000 Monte Carlo (MC) simulations were performed.

140 Results

141 *Base Case Analysis*

142 Table 2 summarises the base case results of shifting from TIV to QIV in the elderly, based on the 2015/16
143 influenza season data. Results show a difference in confirmed influenza cases of approximately 37. As a
144 result, about 36 GP consultations could have been averted and, therefore, 1,103€ saved. In addition, five
145 hospitalizations, including hospitalizations due to influenza, pneumonia, respiratory disease and heart
146 disease, could have been averted and one life saved.

147 **Table 2. Base Case.** Results of the cost-effectiveness evaluation comparing TIV and QIV.

	TIV	**QIV**	**Difference (QIV-TIV)**
Events			
GP Consultations	2631.35	2595.77	-35.58
Hospitalizations due to Influenza	239.00	235.77	-3.23
Deaths due to Influenza Hospitalization	19.00	18.74	-0.26
Hospitalizations due to Pneumonia	21.00	20.72	-0.28
Deaths due to Pneumonia Hospitalization	8.00	7.89	-0.11
Hospitalizations due to RD	40.00	39.46	-0.54
Deaths due to RD Hospitalization	2.00	1.97	-0.03
Hospitalizations due to HD	73.00	72.01	-0.99
Deaths due to HD Hospitalization	8.00	7.89	-0.11
Vaccine Doses	1,035,895	1,035,895	0.00
Costs			
GP Consultations	81,572 €	80,469 €	-1,103 €
Hospitalizations due to Influenza	710,464 €	701,189 €	-9,275 €

Deaths due to Influenza Hospitalization	121,552 €	119,934 €	-1,617 €
Hospitalizations due to Pneumonia	128,213 €	126,508 €	-1,705 €
Deaths due to Pneumonia Hospitalization	90,401 €	89,189 €	-1,211 €
Hospitalizations due to RD	99,125 €	97,841 €	-1,285 €
Deaths due to RD Hospitalization	2,731 €	2,697 €	-34 €
Hospitalizations due to HD	256,048 €	252,687 €	-3,361 €
Deaths due to HD Hospitalization	62,303 €	61,471 €	-831 €
Vaccine Doses	2,668,465 €	7,968,557 €	5,300,092 €
Total	8,018,570 €	13,301,618 €	5,283,047 €
QALYs			
Total	1265456.95	1265457.15	0.20
ICER (€/QALY)			26,403,007

Regarding hospitalization and death costs, caution must be taken in the interpretation of the results. The cost of death, when hospitalized, includes all hospitalization costs, and in the same way, the hospitalization costs also include the costs of people who died. Thus, 15,625€ could have been saved in hospitalizations: 9,275 € in hospitalizations due to influenza; 1,705 € in hospitalizations due to pneumonia; 1,285€ in hospitalizations due to respiratory disease; and 3,361 € in hospitalizations due to heart disease. From that value, 3,694€ are related to hospitalizations of patients who died (Table 2).

In what concerns the number of vaccinated people (mentioned in Table 2 as vaccine doses), the value is the same for both strategies. It was an expected result because the vaccination coverage rate applied to TIV and QIV models was the same (the paper's focus is to evaluate the cost-effectiveness of shifting from TIV to QIV). However, there is a difference in the expected costs computed from the two strategies because they depend on the cost of each vaccine. A total of 1,035,895 vaccine doses were expected to have been administered to individuals aged ≥65 years old in the 2015/16 season. For the TIV strategy, this

161 represented spending 2,668,465 €, while for QIV corresponds to 7,968,557 €, that is, shifting from TIV to
162 QIV would result in an additional cost of 5,300,092 € (Table 2).

163 The expected difference in costs between TIV and QIV is 5,283,047 €, while the difference in effects
164 (QALYs) is expected to be 0.20. These values result in a base case ICER of 26,403,007€/QALY (Table
165 2). The plot of the differences in costs and effects on the cost-effectiveness plane shows the value under
166 consideration is in the first quadrant. Thus, for a cost-effectiveness threshold of 34 000€/QALY (twice the
167 GNI per capita), the new vaccine would not be cost-effective.

168 *One-way Sensitivity Analysis*

169 Fig 2 summarizes the one-way sensitivity analysis using the tornado diagram.

170 **Fig 2. One-way sensitivity analysis.** Tornado diagram.

171

172 Fig 2 reveals that the disutility associated with ILI when no confirmed influenza, and the disutility
173 associated with no hospitalized influenza have the highest impact on the ICER. For example, if the first
174 parameter mentioned above assumes the value of 0.007 (lower bound), it results in an ICER of 19,219,556
175 €/QALY; and the value of 0.011 (upper bound) results in an ICER of 42,160,989 €/QALY. This can be
176 explained by the increase in incremental QALYs, yielded by decreasing this parameter, resulting in a
177 reduced ICER and vice-versa. In contrast, the variation of the second parameter within the 95% CI (0.007,
178 0.011) produced ICERs of 39,019,821€/QALY and 19,951,738€/QALY, respectively. Thus, while the
179 pathway corresponding to vaccinated patients with ILI but not confirmed influenza is more populated in
180 the QIV model than in TIV, the same is not valid for the pathway referring to vaccinated patients with no
181 hospitalized influenza. Thus, a reduction in disutility associated with no hospitalized influenza would
182 decrease incremental QALYs and increase ICER.

183 The cost of the quadrivalent vaccine is the third parameter appearing in the tornado diagram (Fig 2).
184 The variation of the cost of the quadrivalent vaccine within a ±20% range results in an ICER of
185 18,438,140 €/QALY (lower bound) and 34,367,874€/QALY (upper bound), respectively. The high impact
186 of QIV's cost on ICER was expected if attention is paid to the difference in costs of QIV and TIV vaccine
187 doses (Table 2). The cost of QIV's vaccines doses is largely above the cost of TIV's vaccine doses.
188 Further analysis was performed, varying the QIV cost within a broader range (Fig 3). For a QIV cost equal
189 to TIV cost, an ICER of -85,182€/QALY was obtained, meaning that shifting from TIV to QIV would be
190 cost-saving, as expected. However, a value higher than 2.576€ would quickly lead to being not cost-
191 effective.

192 **Fig 3. One-way sensitivity analysis of the cost of QIV.** Variation between 2.576€ (the cost of TIV) and
193 9.756€ with increments of 0.05€.

194

195 The probability of ILI and the probability of confirmed influenza also have a high impact on ICER (Fig
196 2). Varying these parameters 20% downward and upward produced ICERs of 33,025,054€/QALY and
197 21,988,309€/QALY, respectively. Thus, as the probability of ILI and/or the probability of confirmed
198 influenza increases, the ICER decreases.

199 One-way sensitivity analyses of the effectiveness of QIV and TIV are displayed in S2 Fig and S3 Fig,
200 respectively. If the TIV effectiveness is equal to QIV effectiveness, the ICER is not defined as it results in
201 a difference in effects equal to zero and, therefore, a division by zero, and a vertical asymptote at 59.91%
202 is shown (S2 Fig). As TIV effectiveness approaches 59.91% from the left, the ICER tends to positive
203 infinity. Otherwise, as TIV effectiveness approaches 59.91% from the right, the ICER tends to negative
204 infinity. Such behavior is explained by the difference in effects close to zero when TIV and QIV
205 effectiveness are close. A negative ICER is produced for TIV effectiveness values higher than QIV
206 effectiveness as the incremental QALYs value is negative. Similarly, S3 Fig shows a vertical asymptote

207 when QIV effectiveness equals 58%; ICER tends to infinity when it approaches the vertical asymptote
208 from the right. Finally, the higher the effectiveness of quadrivalent vaccines (>58%), the lower the ICER.

209 Although vaccination coverage rate does not significantly impact ICER as the above parameters do, a
210 detailed study was also performed for this parameter (S4 Fig). A higher coverage rate would result in
211 decreased ICER. As recommended by the World Health Assembly, for a coverage rate of 75%,
212 21,010,680 €/QALY would be obtained, corresponding to a reduction of 20,42%.

213 *Probabilistic Sensitivity Analysis*

214 Probabilistic sensitivity analysis allows one to evaluate the robustness of the base case results. To attain
215 this goal, a probability distribution was assigned to each parameter of the model to reflect parameter
216 uncertainty due to sampling errors. Parameters values were then sampled 1,000 times; expected costs and
217 QALY were recorded from the 1,000 MC simulations. Finally, some empirical statistics such as mean,
218 standard deviation and confidence intervals were computed.

219 In general, the results from PSA (S3 Table) are similar to those obtained from the base case analysis
220 (Table 2). The estimated mean costs difference between QIV and TIV is 5,293,456 € with an interval
221 estimate of (4,375,217€; 6,088,637€), while the estimated mean effect difference corresponds to 0.20
222 QALYs with an interval varying from 0.06 to 0.43 QALYs. On its turn, mean ICER is estimated at
223 34,501,793€/QALY (13,052,665€/QALY; 87,418,632€/QALY). This value is about 31% higher than in
224 the base case result.

225 S5 Fig displays the scatterplot of the 1,000 MC simulations to compare TIV and QIV, that is, the
226 graphical representation of costs against QALYs. The base case results are also shown. QALY of both
227 interventions varies within a similar range of values (it varies between 1,155,190 and 1,375,507). On the
228 other hand, the difference between TIV and QIV in terms of costs is very well delimited, being QIV more
229 costly than TIV (QIV: mean=13,323,148€; SD=987,347€; TIV: mean=8,029,692€; SD=548,739€).

230 Fig 4 shows the results of the simulations in a cost-effectiveness plane, where the incremental costs are
231 plotted against the incremental effects. According to Fig 4, the cost-effectiveness results are robustly
232 located in the first quadrant of the cost-effectiveness plane, and all simulated ICERs are higher than CE
233 thresholds previously established.

234 **Fig 4. Probabilistic sensitivity analysis for TIV and QIV.** Cost-effectiveness plane based on data from
235 the 2015/16 influenza season.

236 Discussion

237 To the best of our knowledge, this is one of the first published studies performing a cost-effectiveness
238 evaluation of seasonal influenza vaccination in Portugal. Only a few papers studied the burden of disease
239 and vaccination effectiveness in the Portuguese population, for instance, the international I-MOVE+
240 project(46–50).

241 We evaluated the cost-effectiveness of switching from TIV to QIV based on the 2015/16 influenza
242 season data. Base case results revealed that the universal substitution of TIV with QIV would result in an
243 ICER of 26,403,007€ per QALY gained. As such, for the cost-effectiveness thresholds of 30,000€/QALY
244 or 34,000€/QALY, QIV is not cost-effective. Probabilistic sensitivity analysis enhanced the robustness of
245 the base case results. The ICER is much higher than any possible ceiling ratio established by NHS. Such
246 results are comparable to those obtained for the first year of QIV administration to Hong Kong elderly
247 (≥80 years old) when a cost-effectiveness analysis over nine seasons was performed(51). The need for a
248 longer time horizon study is here emphasized.

249 The majority of the published international papers(45,52–60)does not report such a high ICER, and
250 QIV is usually identified as cost-effective compared with TIV. As cited above, one of the reasons might
251 be using of a long time horizon to calculate QIV effectiveness, which allowed to assume a few seasons
252 that match the TIV with the circulating strains and therefore low mismatching (see S2 Appendix). Another

253 reason might be the cost of QIV, which in this study is about three times the TIV. Regarding the
254 quadrivalent vaccine, its cost is here 200% higher than TIV. However, in the literature, the additional cost
255 of QIV is rarely higher than 100% of the TIV cost(52,54–56), which might be one of the reasons why QIV
256 is cost-effective in some studies. To be cost-effective, the cost of QIV would need to be the same as TIV
257 in our case.

258 In the literature, the probability of influenza-like-illness and the probability of confirmed influenza was
259 found to be higher than those used here. For example, Capri et al.(60) applied a probability of influenza of
260 6.4%, resulting from the product of ILI attack rate (16.8%) by influenza virus isolation rate (32.1%), while
261 Van Bellinghen et al.(55) used a probability of symptomatic influenza infection of 6.17%. In our study,
262 the probability of confirmed influenza was derived from a Portuguese report on influenza surveillance,
263 and the probability of ILI was determined from other input values. It is comparable to the value reported
264 by INSA for the 2015/16 influenza season(31).

265 One-way sensitivity analysis demonstrated that our model is more sensitive to disutility associated with
266 ILI, disutility associated with no hospitalized influenza, cost of quadrivalent vaccine and probabilities of
267 confirmed influenza and ILI. The most relevant input parameters obtained from the OWSA are in line
268 with other OWSA results in the literature(52,55,56). Considering the PSA, the results are in line with the
269 base case conclusions and confirm their robustness.

270 A limitation of our study has to do with the fact that the model is static in a way that herd effects of
271 immunization are not considered, and only direct protection is captured. Thus, the impact of vaccination
272 on the burden of the disease might be underestimated. In the future, a dynamic transmission model might
273 be a possible approach to account for the impact of vaccination on influenza transmission(45,56). In
274 addition, side effects of vaccination were not included in this study, but QIV safety is assumed to be
275 comparable to that of TIV, and side effects are assumed to be mild and temporary. Thus, no impact is
276 expected on the ICER(56).

Summing up, this study contributes to understanding the impact of annual influenza epidemics on health economics and public health in Portugal.

Acknowledgments

H. Mouriño was supported by the National Funding from FCT – Fundação para a Ciência e Tecnologia, under the project: UIDB/04561/2020.

References

1. WHO | Influenza (Seasonal). WHO [Internet]. 2018; Available from: http://www.who.int/mediacentre/factsheets/fs211/en/

2. Shi A, Zeng D, Lin S-S, Caldwell L. Harrison's - Principles of Internal medicine. 16th ed. McGraw-Hill; 2011. 515 p.

3. Villacampa T. Manual Curso Intensivo Mir Asturias - Enfermedades Infecciosas. 2017.

4. Direção Geral de Saúde. Orientação Vacinação contra a gripe. Época 2017/2018. 2017;1–6.

5. Types of Influenza Viruses | Seasonal Influenza (Flu) | CDC [Internet]. [cited 2018 Mar 6]. Available from: https://www.cdc.gov/flu/about/viruses/types.htm

6. George F. História da gripe. 2014;1–28.

7. Sousa Uva M, Kislaya I, Roquette R, Rodrigues AP, Machado A. Vacinação antigripal da população portuguesa na época 2015/2016: estudo na amostra ECOS. 2016 Oct 13 [cited 2018 Sep 1]; Available from: http://repositorio.insa.pt/handle/10400.18/4013

8. Instituto Nacional de Saúde Dr. Ricardo Jorge. Influenza Vaccine Effectiveness in Portugal. Season 2015-16 Report. 2017. 44 p.

9. Key Facts About Influenza (Flu) | Seasonal Influenza (Flu) | CDC [Internet]. [cited 2018 Mar 9]. Available from: https://www.cdc.gov/flu/keyfacts.htm

10. Jorgensen P, Mereckiene J, Cotter S, Johansen K, Tsolova S, Brown C. How close are countries of the WHO European Region to achieving the goal of vaccinating 75% of key risk groups against influenza? Results from national surveys on seasonal influenza vaccination programmes, 2008/2009 to 2014/2015. Vaccine [Internet]. 2017;36(4):442–52. Available from: https://doi.org/10.1016/j.vaccine.2017.12.019

11. Machado A, Torres AR, Kislaya I, Neto M. Vacinação antigripal da população portuguesa em 2016/2017 e 2017/2018. Cobertura e características do ato vacinal. [Internet]. Lisboa; 2019. Available from: http://repositorio.insa.pt/bitstream/10400.18/5700/3/INSA_Relatorio_Vacinacao-antigripal-epocas-2016-2017_2017-2018.pdf

12. Demicheli V, Jefferson T, C DP, Ferroni E, Thorning S, Re T, et al. Vaccines for preventing influenza in the elderly (Review). 2018;(2).

13. Influenza - European Commission [Internet]. [cited 2018 Mar 15]. Available from: https://ec.europa.eu/health/vaccination/influenza_en

14. Types of seasonal influenza vaccine |WHO. 2018 Mar 22 [cited 2018 Mar 22]; Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/influenza/vaccination/types-of-seasonal-influenza-vaccine

15. Krahn M, Kuntz KM, Meltzer DO, Owens DK, Russell LB, Siegel JE, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016;316(10):1093–103.

16. Ferreira LN, Ferreira PL, Pereira LN, Oppe M. EQ-5D Portuguese population norms. Qual Life Res. 2014;23(2):425–30.

320 17. Hollmann M, Garin O, Galante M, Ferrer M, Dominguez A, Alonso J. Impact of Influenza on
321 Health-Related Quality of Life among Confirmed (H1N1)2009 Patients. PLoS One. 2013;8(3):1–
322 10.

323 18. Greenland S. Sensitivity analysis, Monte Carlo risk analysis, and Bayesian uncertainty assessment.
324 Risk Anal [Internet]. 2001;21(4):579–83. Available from:
325 http://www.ncbi.nlm.nih.gov/pubmed/11726013

326 19. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic
327 Evaluation of Health Care Programmes. Fourth. Oxford; 2015.

328 20. Laires PA, Ejzykowicz F, Hsu T-Y, Ambegaonkar B, Davies G. Cost–effectiveness of adding
329 ezetimibe to atorvastatin vs switching to rosuvastatin therapy in Portugal. J Med Econ [Internet].
330 2015;18(8):565–72. Available from:
331 http://www.tandfonline.com/doi/full/10.3111/13696998.2015.1031794

332 21. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set?
333 Clashing opinions and an absence of data: a systematic review. Glob Health Action [Internet].
334 2018;11(1). Available from: https://doi.org/10.1080/16549716.2018.1447828

335 22. Marques A, Lourenço Ó, Ortsäter G, Borgström F, Kanis JA, da Silva JAP. Cost-Effectiveness of
336 Intervention Thresholds for the Treatment of Osteoporosis Based on FRAX®in Portugal. Calcif
337 Tissue Int. 2016;99(2):131–41.

338 23. Areia M, Spaander MCW, Kuipers EJ, Dinis-Ribeiro M. Endoscopic screening for gastric cancer:
339 A cost-utility analysis for countries with an intermediate gastric cancer risk. United Eur
340 Gastroenterol J. 2018;6(2):192–202.

341 24. World Development Indicators | DataBank [Internet]. [cited 2018 Sep 15]. Available from:
342 http://databank.worldbank.org/data/reports.aspx?source=2&country=PRT

25. Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press; 2006. 445 p.

26. Portal do Instituto Nacional de Estatística [Internet]. [cited 2018 May 4]. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0000256&contexto=bd&selTab=tab2&xlang=en

27. Guiomar R, Conde P, Cristóvão P, Pechirra P, Nunes B. Programa Nacional de Vigilância da Gripe - Relatório da Época 2012/2013. Inst Nac Saúde Doutor Ricardo Jorge, IP. 2013;

28. Guiomar R, Conde P, Cristóvão P, Pechirra P, Nunes B. Programa Nacional de Vigilância da Gripe - Relatório da Época 2013/2014. Inst Nac Saúde Doutor Ricardo Jorge, IP. 2015;

29. Guiomar R, Costa I, Cristóvão P, Pechirra P, Rodrigues AP, Nunes B. Programa Nacional de Vigilância da Gripe - Relatório da época 2014/2015. Inst Nac Saúde Doutor Ricardo Jorge, IP. 2015;

30. Guiomar R, Pechirra P, Cristóvão P, Costa I, Conde P, Rodrigues AP, et al. Programa Nacional de Vigilância da Gripe - Relatório da época 2016/2017. Inst Nac Saúde Doutor Ricardo Jorge, IP. 2017;

31. Guiomar R, Pechirra P, Rodrigues AP, Silva SP, Machado A, Nunes B. Programa Nacional de Vigilância da Gripe - Relatório da época 2015/2016. Instituto Nacional de Saúde Doutor Ricardo Jorge, editor. Inst Nac Saúde Doutor Ricardo Jorge, IP [Internet]. 2016; Available from: http://repositorio.insa.pt//handle/10400.18/4044

32. Gonçalves P, Pechirra P, Conde P, Guiomar R, Nunes B. Programa Nacional de Vigilância da Gripe - Relatório da Época 2010/2011. Inst Nac Saúde Doutor Ricardo Jorge, IP. 2013;

33. Gonçalves P, Pechirra P, Conde P, João I, Guiomar R, Nunes B. Programa Nacional de Vigilância da Gripe - Relatório da Época 2011/2012. Inst Nac Saúde Doutor Ricardo Jorge, IP. 2013;

34. Petri E, Ruiz-aragón J. A Comparison of Cost Effectiveness of Seasonal Influenza vaccines in Spain. In: IVW conference, Albufeira, 6th -9th October 2015. 2015. p. 7015.

35. Instituto Nacional de Saúde Doutor Ricardo Jorge. Boletim de Vigilância Epidemiológica da Gripe - semana 20. 2018.

36. Inverno e Saúde - Evolução Semanal [Internet]. [cited 2018 May 9]. Available from: http://saudesazonal.min-saude.pt/#consultaSindromeGripal/149/757

37. Administração Central do Sistema de Saúde I.P. Base de dados Central de Morbilidade Hospitalar.

38. Portal do Instituto Nacional de Estatística [Internet]. [cited 2018 May 4]. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0008180&contexto=bd&selTab=tab2

39. Coelho PP, Morgado C, Albuquerque D De, Rodrigues M. Diário da República 1.ª série, Nº153 - Portaria 234/2015 de 7 de agosto - Anexo-II. 2015.

40. BASE:contratos públicos online [Internet]. [cited 2018 May 4]. Available from: http://www.base.gov.pt/Base/pt/Homepage

41. Direção Geral de Saúde. Orientação 007/2015 Terapêutica e quimioprofilaxia da gripe sazonal. 2014;1–7.

42. Serviços Partilhados do Ministério da Saúde. Contrato Fornecimento de V13 - Vacina Contra a Gripe Inativada [UDOSE] à Administração Regional de Saúde do Alentejo. 2016.

43. BASE:contratos públicos online [Internet]. [cited 2020 Jan 27]. Available from: http://www.base.gov.pt/Base/pt/Pesquisa/Contrato?a=5864096

44. Portal do INE - Índice de preços no consumidor (Taxa de variação média dos últimos 12 meses - Base 2012 - %) por Localização geográfica e Agregados especiais; Mensal [Internet]. [cited 2020

388 Jan 13]. Available from:
389 https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0002390&co
390 ntexto=pi&selTab=tab0

391 45. Boer PT, Crépey P, Pitman RJ, Macabeo B, Chit A, Postma MJ. Cost-Effectiveness of
392 Quadrivalent versus Trivalent Influenza Vaccine in the United States. Value Heal [Internet].
393 2016;19(8):964–75. Available from: http://dx.doi.org/10.1016/j.jval.2016.05.012

394 46. Rondy M, Kissling E, Gherasim A, Pebody R, Trebbien R, Pozo F, et al. Interim 2017 / 18
395 influenza seasonal vaccine effectiveness : combined results from five European studies. Euro
396 Surveill. 2018;23(9):1–12.

397 47. Rondy M, Gherasim A, Casado I, Launay O, Rizzo C, Pitigoi D, et al. Low 2016/17 season vaccine
398 effectiveness against hospitalised influenza A(H3N2) among elderly: awareness warranted for
399 2017/18 season. Eurosurveillance. 2017 Oct 12;22(41).

400 48. Rondy M, Larrauri A, Casado I, Alfonsi V, Pitigoi D, Launay O, et al. 2015 / 16 seasonal vaccine
401 effectiveness against hospitalisation with influenza A (H1N1) pdm09 and B among elderly people
402 in Europe : results from the I-MOVE + project. Euro Surveill. 2015;

403 49. Nunes B, Machado A, Pechirra P, Falcão I, Gonçalves P, Conde P, et al. Efetividade da vacina
404 antigripal na {é}poca 2010-2011 em Portugal: resultados do projeto EuroEVA. Rev Port Med
405 Geral E Fam. 2012;28(4):271–84.

406 50. Kissling E, Valenciano M, Pozo F, Vilcu A-M, Reuss A, Rizzo C, et al. 2015/16 I-MOVE/I-
407 MOVE+ multicentre case control study in Europe: moderate vaccine effectiveness estimates
408 against influenza A(H1N1)pdm09 and low estimates against lineage mismatched influenza B
409 among children. Influenza Other Respi Viruses. 2017 Nov 10;

410 51. You JHS, Ming WK, Chan PKS. Cost-effectiveness analysis of quadrivalent influenza vaccine

411 versus trivalent influenza vaccine for elderly in Hong Kong. BMC Infect Dis. 2014;14(1):1–7.

412 52. You JHS, Ming WK, Chan PKS. Cost-effectiveness of quadrivalent influenza vaccine in Hong
413 Kong - A decision analysis. Hum Vaccines Immunother. 2015;11(3):564–71.

414 53. Chit A, Roiz J, Aballea S. An assessment of the expected cost-effectiveness of quadrivalent
415 influenza vaccines in Ontario, Canada using a static model. PLoS One [Internet]. 2015;10(7):1–15.
416 Available from: http://dx.doi.org/10.1371/journal.pone.0133606

417 54. Chit A, Roiz J, Briquet B, Greenberg DP. Expected cost effectiveness of high-dose trivalent
418 influenza vaccine in US seniors. Vaccine [Internet]. 2015;33(5):734–41. Available from:
419 http://dx.doi.org/10.1016/j.vaccine.2014.10.079

420 55. Van Bellinghen LA, Meier G, Van Vlaenderen I. The potential cost-effectiveness of quadrivalent
421 versus trivalent influenza vaccine in elderly people and clinical risk groups in the UK: A lifetime
422 multi-cohort model. PLoS One. 2014;9(6).

423 56. Dolk C, Eichner M, Welte R, Anastassopoulou A, Van Bellinghen LA, Poulsen Nautrup B, et al.
424 Cost-Utility of Quadrivalent Versus Trivalent Influenza Vaccine in Germany, Using an Individual-
425 Based Dynamic Transmission Model. Pharmacoeconomics. 2016;34(12):1299–308.

426 57. García A, Ortiz de Lejarazu R, Reina J, Callejo D, Cuervo J, Morano Larragueta R. Cost–
427 effectiveness analysis of quadrivalent influenza vaccine in Spain. Hum Vaccines Immunother.
428 2016;12(9):2269–77.

429 58. Meier G, Gregg M, Poulsen Nautrup B. Cost-effectiveness analysis of quadrivalent influenza
430 vaccination in at-risk adults and the elderly: an updated analysis in the UK. J Med Econ [Internet].
431 2015;18(9):746–61. Available from:
432 http://www.tandfonline.com/doi/full/10.3111/13696998.2015.1044456

433 59. Mullikin M, Tan L, Jansen JP, Van Ranst M, Farkas N, Petri E. A Novel Dynamic Model for

Health Economic Analysis of Influenza Vaccination in the Elderly. Infect Dis Ther. 2015;4(4):459–87.

60. Capri S, Barbieri M, de Waure C, Boccalini S, Panatto D. Cost-effectiveness analysis of different seasonal influenza vaccines in the elderly Italian population. Hum Vaccin Immunother. 2018;14(6):1331–41.

61. MC W, G T, Mcguire A. QALYs : The Basics. Value Heal. 2009;12(1):S5–9.

62. Uva MS, Kislaya I, Roquette R, Rodrigues AP, Machado A. Vacinação antigripal da população portuguesa na época 2015/2016. Estudo na amostra ECOS. 2016; Available from: http://www.onsa.pt/conteu/estud_vacina-anti-gripal_onsa.pdf

Supporting Information

S1 Appendix.

S2 Appendix. Model input parameters.

S1 Table. Proportion of B lineage influenza virus not included in the seasonal trivalent vaccines from 2010/11 to 2017/18 influenza seasons.

S2 Table. Description of the variables that take part of S1 Fig.

S3 Table. Input parameters. Base case value; SD; parameters of the probability distribution.

S4 Table. Probabilistic sensitivity analysis. Assessing the 2015/16 influenza season-related uncertainty.

454 **S1 Fig. Probability, cost and QALY calculations by decision tree pathway for individuals**
455 **aged ≥65 years old who received TIV.**

456 **S2 Fig. One-way sensitivity analysis of TIV effectiveness.** Variation between 34% and 74%
457 with increments of 0.005.

458 **S3 Fig. One-way sensitivity analysis of QIV effectiveness.** Variation between 58% (TIV
459 effectiveness) and 100% with increments of 0.005.

460 **S4 Fig. One-way sensitivity analysis of vaccination coverage rate.** Variation between 0% and
461 100% with increments of 0.05.

462 **S5 Fig. Probabilistic sensitivity analysis for TIV and QIV.** Scatter plot based on the 2015/16
463 influenza season.

464

465

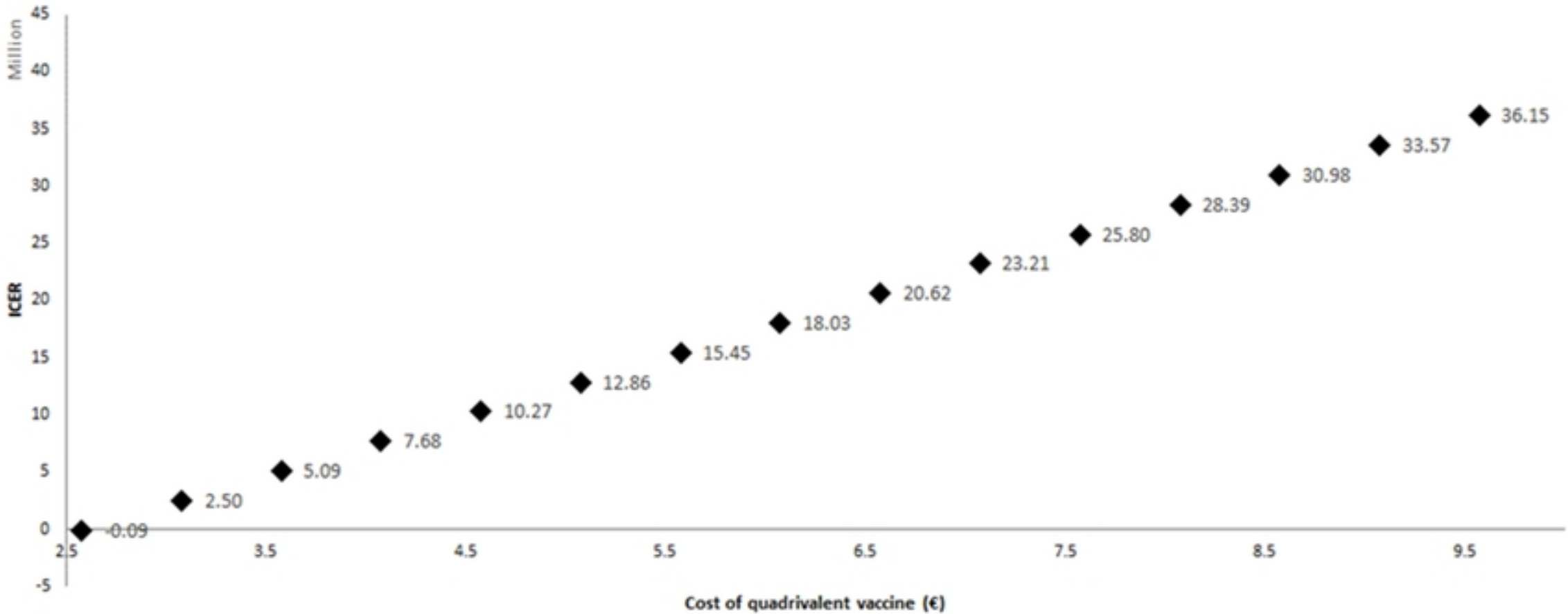
Million
ICER
45
40
35
30
25
20
15
10
5
0
-5
-0.09
2.50
5.09
7.68
10.27
12.86
15.45
18.03
20.62
23.21
25.80
28.39
30.98
33.57
36.15
2.5
3.5
4.5
5.5
6.5
7.5
8.5
9.5
Cost of quadrivalent vaccine (€)

Figure 3

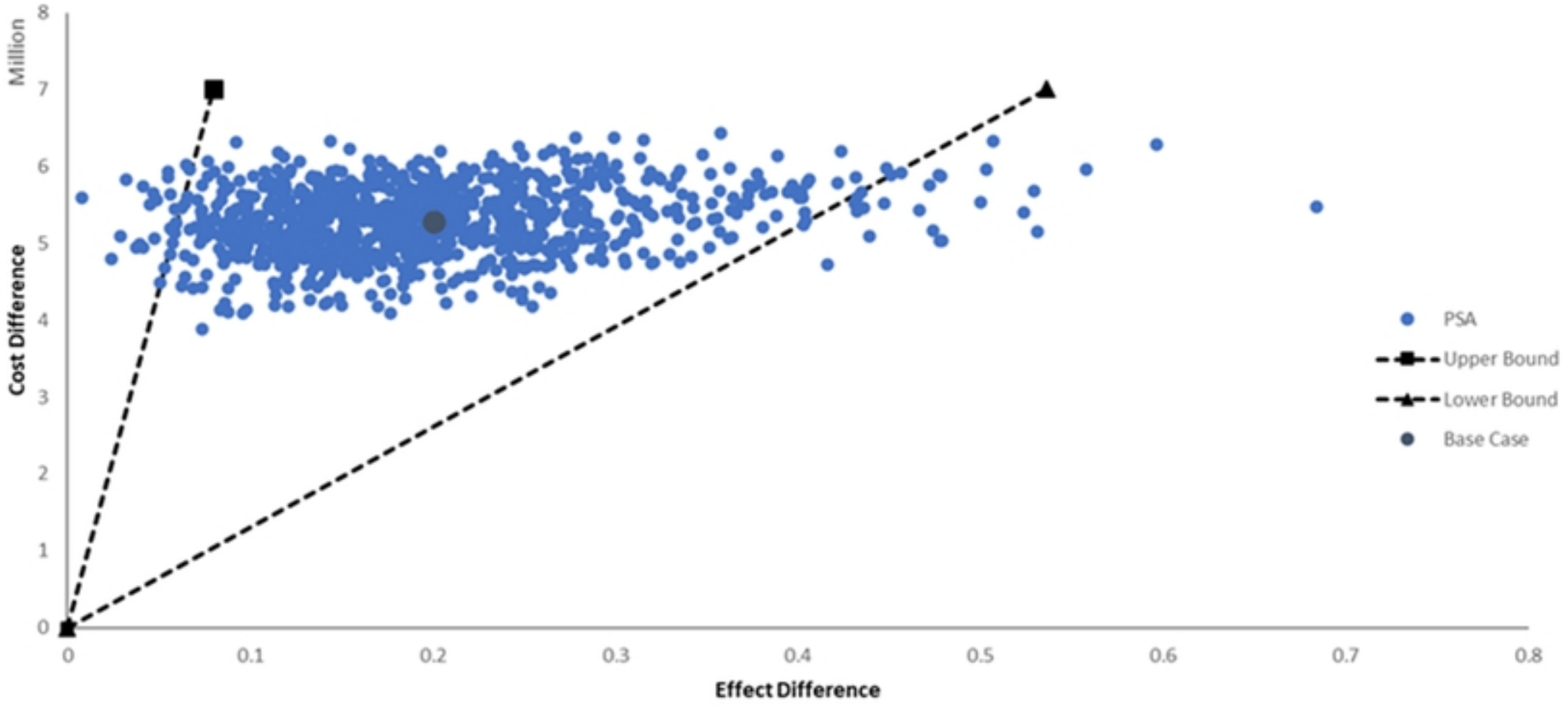
Million
Cost Difference
Effect Difference
0
1
2
3
4
5
6
7
8
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
PSA
Upper Bound
Lower Bound
Base Case

Figure 4

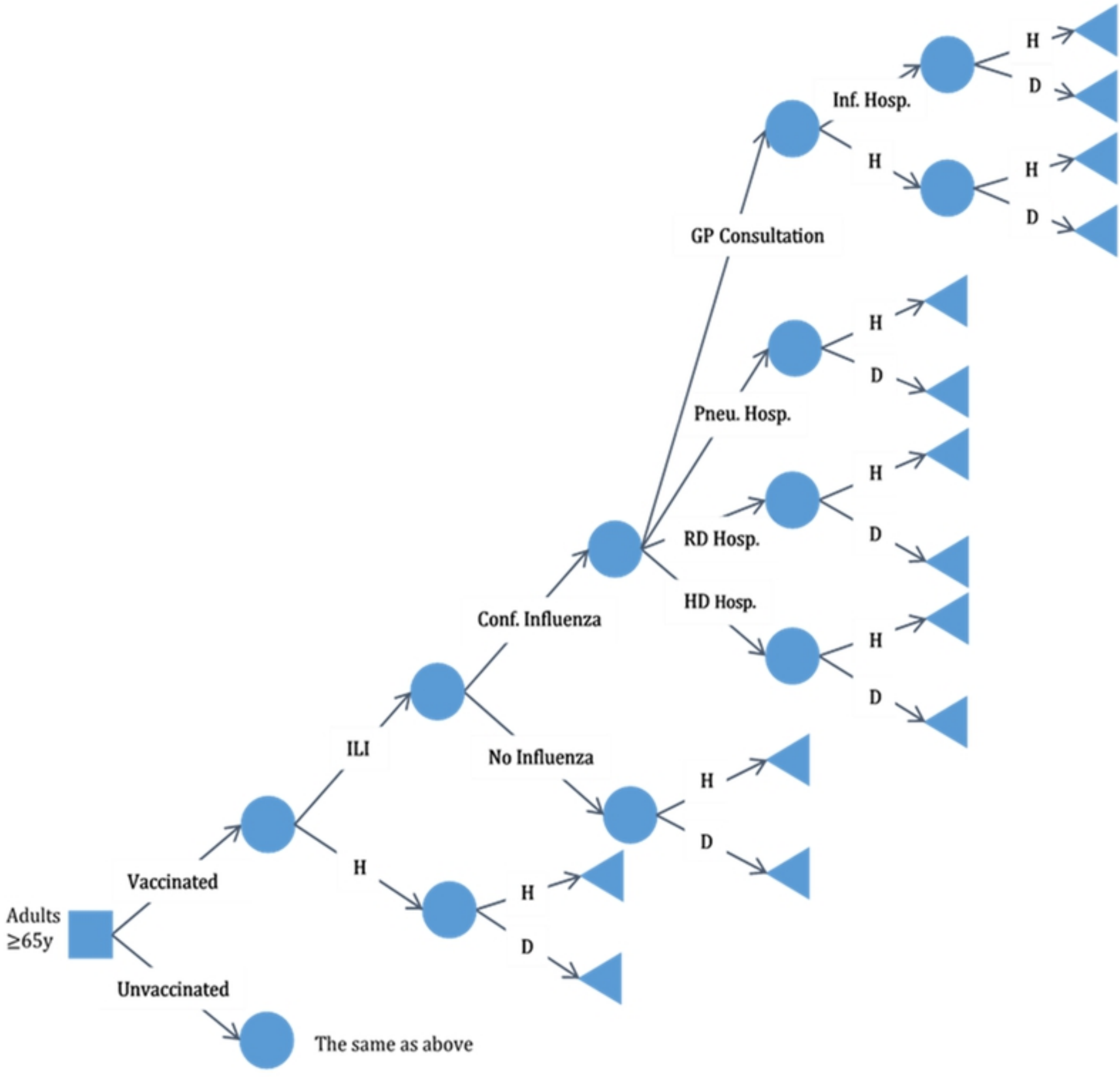
Adults
≥65y
Vaccinated
Unvaccinated
The same as above
ILI
H
Conf. Influenza
No Influenza
H
D
H
D
GP Consultation
Inf. Hosp.
H
D
H
D
Pneu. Hosp.
H
D
RD Hosp.
H
D
HD Hosp.
H
D

Figure 1

One-Way Sensitivity Analysis
Disutility associated with ILI wihout influenza confirmation
Disutility associated with no hospitalized influenza
Cost of quadrivalent vaccine
Probability of Influena-like-illness
Probability of Confirmed Influenza
Probability of Hospitalization due to Influenza
Cost of trivalent vaccine
Disutility associated with hospitalization due to influenza
Utility associated with healthy population
Probability of death when Hosp. Influenza
Probability of death when no confirmed influenza
Vaccination Coverage Rate
Probability of death due to Hosp. Pneumonia
Probability of death when Hosp. HD
Disutility associated with hospitalization due to heart disease
Disutility associated with hospitalization due to respiratory disease
Disutility associated with hospitalization due to pneumonia
Probability of death when Hosp. RD
Cost of Hospitalization due to Influenza
Cost of Hospitalization due to Heart Disease
Cost of death when Hospitalization due to Influenza
Cost of Hospitalization due to Respiratory Disease
Cost of death when Hospitalization due to Pneumonia
Cost of GP consultation
Cost of death when Hospitalization due to HD
Cost of Hospitalization due to Pneumonia
Cost of antiviral treatment
Cost of death when Hospitalization due to RD
Cost of vaccine administration
0
50
100
150
200
250
300
350
400
450
ICER
x 100000

Figure 2