

The Epidemiological and Economic Impact of a Cell-Based Quadrivalent Influenza Vaccine in an Adult Population in the US: A Dynamic Modeling Approach

Van Hung Nguyen (✉ vhnguyen@vhnconsulting.com)

VHN consulting <https://orcid.org/0000-0002-0371-0193>

Yvonne Hilsky

Seqirus Vaccines Ltd

Joaquin Mould-Quevedo

Seqirus Vaccines Ltd

Research article

Keywords: Influenza, cost-effectiveness, Quadrivalent Influenza Vaccine, cell-based influenza vaccine, US

Posted Date: September 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-27872/v2>

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Abstract

Background: Mutations of the H3N2 vaccine strain during the egg-based vaccine manufacturing process seem to partly explain the suboptimal effectiveness of traditional seasonal influenza vaccine. Cell-based influenza vaccines avoid such egg-adaptation, thereby improving antigenic match and vaccine effectiveness. The objective of this study was to evaluate the public health and economic impact of a cell-based quadrivalent influenza vaccine (QIVc) in adult population (18-64 years) compared to the standard egg-based quadrivalent influenza vaccine (QIVe), in the US.

Methods: The impact of QIVc over QIVe in terms of public health and costs outcomes was estimated using a dynamic SEIR transmission model. The model is age-structured and accounts for 4 circulating influenza strains (A/H1N1pdm9, A/H3N2, B(Victoria), and B(Yamagata)). It was calibrated on US attack rate and strain circulation for the influenza seasons 2013-2018. US specific absolute vaccine effectiveness for QIVe, specific hospitalization rate, mortality rate, Quality-Adjusted Life Years (QALYs) and costs were extracted from published literature. Relative vaccine effectiveness of QIVc over QIVe for subjects 18-64 years of age was obtained from a US retrospective cohort study. Robustness of the results was assessed in univariate and probabilistic sensitivity analyses.

Results: Switching from QIVe to QIVc in the 18-64 year-old population may prevent 5.7 M symptomatic cases, 1.8 M outpatient visits; 50K hospitalizations and 5,453 deaths annually. The switch could save 128 K QALYs and US\$ 845M in direct costs, resulting in a cost-saving alternative in a 3-year time horizon analysis. Probabilistic sensitivity analyses confirmed the robustness of the cost-saving result.

Conclusions: The analysis shows that QIVc is expected to prevent a substantial number of hospitalizations and deaths, and would result in substantial savings in health care costs.

Background

With an estimated average of 410,000 deaths yearly (1), the burden of influenza infection still weighs heavily on the world population, despite years of improvement in worldwide immunization policies. In the US only, the US CDC estimates that influenza infections have caused the sickness of 35.5M individuals, 16.5M outpatient visits, 490,600 hospitalizations and 34,200 deaths during the 2018-2019 winter season (2). Vaccination against influenza is generally considered the most effective way to prevent influenza infection and its consequences. However, the complexities of influenza viruses, evading the human immune response with antigenic drift and shift phenomena, competing with a diversity of other strains for dominant circulation, seriously challenge, every year, the effectiveness of influenza immunization campaigns. Recent years have shown advances in influenza vaccination policies, with the adoption by some (mainly high developed) countries of quadrivalent influenza vaccines, containing antigens for two B lineages, instead of a single one, and relatively new adjuvanted and high-dose formulations. Still, conventional egg-based influenza vaccines seem to offer a suboptimal protection during influenza seasons dominated by influenza A(H3N2) circulation. A recent meta-analysis measured a 35% vaccine

effectiveness (VE) against A(H3N2) versus 54–73% for other strains, for working-age adults, vaccinated with egg-based influenza vaccines (3). This poor protection seems to be partially explained by issues related to the production of egg-based vaccines. Mutations of influenza virus strains during the isolation and propagation steps of egg-based vaccine production seem to be leading to a mismatch between the influenza vaccine strain and the circulating one (4,5). Solving this issue may rely on the use of mammalian cells rather than chicken eggs during vaccine virus isolation and propagation. This cell based production process has demonstrated an improved antigenic similarity between the original candidate vaccine virus and the circulating wild-type influenza virus strains, which may translate into an increased VE for new cell-based quadrivalent influenza vaccines (QIVc) (6,7).

The assessment of the public health and economic impact of new influenza immunization policies is routinely done for most countries. Despite WHO recommendations for the assessment of vaccination strategies(8), most of these studies are performed using a simple static epidemiological model(9), unable to grasp the indirect effects of vaccination (herd effects). While the potential impact of improved influenza vaccine effectiveness is generally acknowledged for the pediatric population (10), its impact on the adult population remains unclear. The purpose of the present analysis is to evaluate the cost-effectiveness of QIVc in adults (18-64 years) compared to conventional egg-based quadrivalent influenza vaccines (QIVe) using a dynamic influenza transmission model able to account for the indirect effect of vaccination.

Methods

Epidemiology and vaccine effectiveness

Influenza incidence estimates were extracted from CDC reports for 5 influenza seasons from 2013 to 2018 (Table S1) (11), and combined with WHO FluNet (12) virological data to obtain yearly incidence per strain for the US. The model assumed 66% of people infected with influenza virus were symptomatic (13), that they had an incubation period of 0.8 days, and remained infectious for 1.8 days (14,15).

We used strain specific QIVe VE estimates obtained by Rolfes et al. for the influenza season 2017-2018 (16) assuming VE against A(H3N2) was a mismatch between the vaccine and the circulating strain. To estimate VE conferred by QIVc, we extracted results from a recent study estimating the relative VE (rVE) of QIVc compared to QIVe from electronic medical records, where patients were matched by propensity score for the influenza season 2017-2018 (17), i.e. the same influenza season as in Rolfes et al. This study estimated an overall rVE of 19.3% (95% CI [9.5%;28.0%]) for QIVc compared to QIVe, and age-adjusted rVE for adult population (Table 1). In order to compute the specific QIVc increased effectiveness against A(H3N2) (in 2017-2018, only A(H3N2) antigens are cell-based), we used the total rVE estimated on a US cohort comparing QIVc and QIVe for the same influenza season, and then, we recomputed, the QIVc VE against A(H3N2) using the following equations: **see equations 1, 2, and 3 in the supplementary files.**

Epidemiological and economic model

A four strains compartmental transmission model was developed to provide estimates of the epidemiological impact of the switch from QIVe to QIVc. The model is a classic SEIR model where the population can be either Susceptible to infection with Influenza strain $I(S_i)$, Exposed to the strain (E_i), Infected and infectious (I_i) or Recovered from infection (R_i) (Figure 1). The vaccinated population could still be infected and contribute to the infection dynamic but with a reduced probability corresponding to the vaccine effectiveness against the given influenza strain. The model simulates independently the epidemiological dynamics of A(H1N1)pdm09, A(H3N2), B/Victoria and B/Yamagata for a given influenza season. The model is structured by age-group (6-23mo, 2-4yo, 5-12yo, 13-17yo, 18-49yo, 50-64yo, and more than 65yo) and uses a contact matrix to account for assortative rate of contacts between age-groups. In our analysis, we used in our base case analysis the matrix from Mossong et al.(18) and have conducted sensitivity analysis using Zagenhi et al.(19). Both matrices have provided qualitatively similar results. Probabilities of influenza transmission per influenza strain are estimated for each influenza season to match US reported strain specific attack rate (2013 to 2018 influenza seasons). We assume a pre-immunity of a third of the population based on estimations from Baguelin et al. (20). The estimation process uses the non-linear Nelder-Mead simplex algorithm(21) to maximize a likelihood function.

The economic model is based on a decision tree model published in De Boer et al. (22) whose inputs are given in Table S3. We used the same methodology and same health outcomes computed on the whole population. The number of cases per age-group estimated by the epidemiological model, shown in Table 2, are taken as inputs of the economic model. Probabilities of general practitioner visit, hospitalization, and death are applied on the number of cases attributed to a high or low risk group, and then translated into public health outcomes and costs. The economic analysis is performed from a societal perspective without taking into account productivity loss due to death. We consider a willingness to pay per QALY threshold of US\$50 000 to consider a strategy as cost-effective (23).

Economic data

Disease costs and QALYs were extracted from a recent influenza health economic analysis performed in the US context (22). Cost of a work day for the pediatric population are assumed to be related to parental work loss. Vaccine cost for QIVe and QIVc were set at \$17.22 and \$24.22 respectively(24) . We do not consider administration costs since they are assumed to be the same across the different vaccination strategy (no difference in vaccination coverage). Details of the costs per age-groups are given in Table S3.

Scenarios

As a reference strategy, we assume that the US population is vaccinated with conventional QIVe for those aged under 65 years of age and TIV HD for those aged 65 years and above. Then we compare this strategy to a scenario where QIVe is replaced by QIVc for people aged 18–64 years, other age-groups keeping their baseline vaccination. For both scenarios, we use age-based vaccination coverage rate documented by CDC(25), in particular we consider that 34.9% of people aged 18 to 49yo, 47.30% of

people aged 50 to 64yo, and 68.10% of people older than 65 years are vaccinated against influenza (Table S2). In this base case comparison, we consider that a seasonal mismatch between the QIVe A(H3N2) strain and the circulating strain due to egg adaptation occurred during the last 3 years out of 5 years in the analysis scope (26). As a sensitivity analysis we also assessed the impact of QIVc when the mismatch due to egg adaptation occurred over a varying number of years from 1 to 5 years, and randomly picking the influenza season concerned by the mismatch.

We also performed a stochastic probabilistic sensitivity analysis in order to assess the robustness of our results regarding uncertainties in vaccine effectiveness, economic inputs (primary care and hospitalization costs), probability of outcomes, listed in Table S3 and Table S4, with their probability distributions. In this analysis, 1,000 sets of the above-mentioned parameters are randomly drawn from distributions indicated in the Table S2 and Table S3. Clinical and economic results are averaged over the 5 influenza seasons.

Results

In our base case scenario of 3 seasonal A(H3N2) mismatches due to egg adaptation, our analysis shows that using QIVc instead of QIVe in the 18-64yo population would have prevented 5.7M cases of influenza, 1.8M GP visits, almost 50K hospitalizations and more than 5,400 deaths. In total, QIVc would have saved US\$845M in direct costs and saved 128K QALYs. Hence, the switch from QIVe to QIVc in the adult population would be a cost saving strategy (Table 2).

Over 5 influenza seasons of A(H3N2) mismatch, using QIVc instead of QIVe in the 18-64yo population would have a substantial effect but irregular effect, depending on the influenza season, depending on A(H3N2) seasonal circulation (Figure 2). Hence, the choice of the influenza season was also randomly varied in the probabilistic analysis to assess the uncertainty related to the epidemiological context. Varying the number of influenza seasons with an A(H3N2) mismatch of egg-based vaccines between 1 and 5 years still show that QIVc would be cost-saving or very cost effective (Table 3). Probabilistic sensitivity analysis confirms that 95% of the 1,000 simulations gave a cost-saving result (Figure 3).

Discussion

This analysis emphasizes the potentially major public health gain which could be achieved through the use of QIVc. Several studies have highlighted the suboptimal VE of egg-based vaccines against some strains of A(H3N2) (6,27). While the link between VE reduction and egg-related strain mutations is still poorly understood (28) and remains to be fully investigated, recent studies, in different populations, tend to confirm the clinical benefits (7) of QIVc over QIVe regarding A(H3N2) vaccine strain mismatch. Assessing the strain-specific rVE of QIVc compared to QIVe remains a difficult challenge as egg-adaptation phenomena, while most common on A(H3N2), may also occur on B lineages. However, we used QIVc rVE estimated during the 2017-2018 influenza season, when only the A(H3N2) component of QIVc had been grown in cells and we derived our strain specific VE estimations only from this influenza

season. Our analysis relies on retrospective studies (7,17) performed during the 2017-2018 influenza season when A(H3N2) represented 66% of the influenza positive samples (12). By construction, these analyses were only able to assess non-strain specific QIVc rVE compared to QIVe, and we had to estimate QIVc strain specific VE, assuming that the increased total VE was only linked to an increase of VE against A(H3N2). Also, variations in QIVc rVE are likely to occur due to the changing distribution patterns of circulating influenza strains. Namely, influenza seasons with a highly dominant A(H1N1)pdm09 circulation (2015-2016) will see a low benefit to QIVc compared to QIVe, while others, like 2014-2015, 2016-2017, or 2017-2018, may see a significant one. Hence, analysis on multiple influenza seasons is necessary in order to fully assess the potential “averaged” impact of cell-based vaccines across various realistic epidemiological contexts.

We chose to consider as a base case scenario that a mismatch occurred between the A(H3N2) circulating strain and the egg-based vaccine strain during three influenza seasons. We considered this choice a median scenario between a systematic yearly mismatch and no mismatch at all. In addition, this assumption has a limited impact on our results since 1) we consider the observed influenza strain distribution, and 2) we have analyzed situation when the number of mismatched years was varied from 1 to 5 years and reached qualitatively similar results. In addition, our results are consistent with previous health-economic analysis of QIVc in Europe (UK, Spain, Italy, Germany) (29–31), where QIVc has been shown to be either cost-saving or highly cost-effective.

Our analysis uses a 4-strain SEIR compartmental model with an age-structure. This kind of approach, previously used in several similar analysis (9,32–34), is key to capture the potential indirect effects of influenza vaccination, accounting for prevented chains of transmission. However, it relies on assumptions regarding age-related contact rate which may be difficult to measure for specific countries. Despite its advantages, our approach suffers from limitations inherent to any modeling exercise. In absence of better estimates, our transmission model assumes that 30% of the population benefits from remaining immunity against influenza based on a British modeling study(14). In addition, uncertainties regarding surveillance-based influenza incidence estimates, or influenza strains circulations in the US will directly impact the epidemiological dynamics reproduced by the model.

Finally, our analysis shows the potential public health benefits of the use of QIVc in the 18-64yo US population during the 2013-2018 period. Results obtained retrospectively may be different from what may be achieved in the future as influenza strain circulation is currently challenging to predict. In particular, given the potential expected benefits, and on-going clinical trials, it is likely that QIVc would be also recommended for the pediatric population, which would certainly reinforce its impact.

Conclusions

Estimated public health benefits related to the use of QIVc in the US adult population, indicate that the use of QIVc could be clinically superior and cost-saving compared to the current vaccination practice

(QIVe). Sensitivity analyses on vaccine effectiveness, costs and number of influenza seasons of egg-based strain mismatch show the robustness of QIVc cost-effectiveness.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing Interests

J.M.Q. and Y.H. are employees of Seqirus USA Inc. V.H.N. was contracted by Seqirus and received fees for conducting the study.

Funding

The study was funded by Seqirus. The funder had no role in the study design, data collection, analysis, decision to publish or preparation of the manuscript.

Authors' contribution

V.H.N., J.M.Q. and Y.H. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors have read and approved the manuscript.

Abbreviations

QIVe: egg-based Quadrivalent Influenza Vaccine

QIVc: cell-based Quadrivalent Influenza Vaccine

VE: Vaccine Effectiveness

RVE: Relative Vaccine Effectiveness

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Tables

Table 1: Vaccine effectiveness (VE) for QIVe and QIVc, per age-group, based on estimates of relative vaccine effectiveness (rVE) between the two vaccines. VE estimates are taken from Rolfes et al. (16), and rVE from Boikos et al.(17), both studies were performed in the US during the 2017-2018 influenza season.

Age group	Match (16)			Mismatch (16)	Match (computed)	rVE(17)
	A/H1N1pdm09	B Victoria	B Yamagata	A(H3N2)	A(H3N2)	
18-49yrs	48% (18%-67%)	57% (43%-69%)	57% (43%-69%)	14% (0%-30%)	43%	26.8% (14%-37%)
50-64yrs	36% (0%-67%)	44% (24%-60%)	44% (24%-60%)	21% (0%-41)	50%	

Note: We report 95% confidence intervals (CI) in parenthesis. We have assumed a 0% in the lower bound 95% CI in vaccine effectiveness when negative percentage was reported by Rolfes et al (16). We used VE estimates against influenza B (all lineages), as age-specific estimates were not available by B lineages.

Table 2 - Base case results - 3 years of mismatch out of 5 years. The 3 years of mismatch considered are the 3 most recent influenza seasons.

	QIVe	QIVc	Difference
Number of doses	118 818 800	118 818 800	0
Number of cases	27 240 600	21 556 900	-5 683 700
Number of GP* visits	8 595 300	6 751 400	-1 843 900
Lost work days	29 390 500	22 983 500	-6 407 000
Hospitalizations	199 916	150 191	-49 725
Deaths	22 436	16 983	-5 453
Life years lost	371 040	277 635	-93 405
Life years lost (discounted)	269 745	202 268	-67 477
QALY lost due to sickness	165 410	129 151	-36 259
QALY lost due to death	367 118	274 906	-92 212
QALY lost due to death (discounted)	266 001	199 575	-66 426
Total QALY lost	532 527	404 057	-128 470
Total QALY lost (discounted)	431 410	328 726	-102 684
Cost of GP visits	1 028 822 400	775 428 700	-253 393 700
Cost of hospitalizations	3 794 189 100	2 775 660 700	-1 018 528 400
Cost of lost workdays	2 105 378 600	1 648 894 900	-456 483 700
Vaccine cost	2 610 747 400	3 037 887 500	427 140 100
Total direct costs	7 433 759 000	6 588 976 900	-844 782 100
ICER		-10400 [-17400 ; 11000] (cost saving)	

* General practitioner

Table 3: Sensitivity analysis on the number of mismatch years

Number of mismatch years	Medical costs*			QALY** gained			ICER***		
	Median	Lower bound	Upper bound	Median	Lower bound	Upper bound	Median	Lower bound	Upper bound
1	-136 179 800	-2 176 061 100	821 374 700	74 800	10 300	205 900	-1 800	-12 000	67 900
2	-1 570 682 800	-4 916 394 100	577 624 600	164 100	26 800	396 300	-8 600	-16 000	15 000
3	-2 749 808 800	-7 530 202 100	351 732 800	241 200	42 200	600 100	-10 500	-18 000	3 400
4	-3 999 641 400	-9 658 482 100	182 466 200	325 700	50 400	732 600	-11 600	-18 800	100
5	-5 222 697 300	-12 426 192 400	21 380 200	412 000	64 600	920 200	-12 200	-19 400	-3 200

* Medical costs include cost of GP visits and hospitalizations

** Quality-adjusted life year

*** Incremental cost effectiveness ratio

Figures

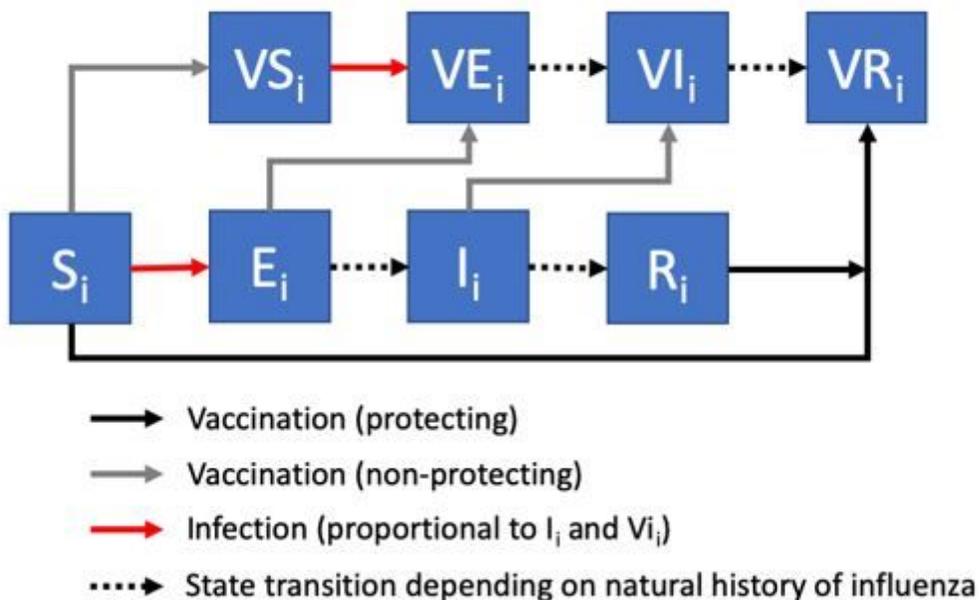


Figure 1

Diagram of the influenza transmission model. S_i , E_i , I_i , and R_i stand for susceptible, exposed, infectious, and recovered individuals respectively regarding the influenza strain i ; VS_i , VE_i , and VI_i stand for susceptible, exposed and infectious individuals experiencing a non-protective vaccination respectively regarding influenza strain i , VR_i are individuals protected and vaccinated against influenza strain i ; i stands for influenza strains: A/H1N1, A/H3N2, B Victoria, B Yamagata

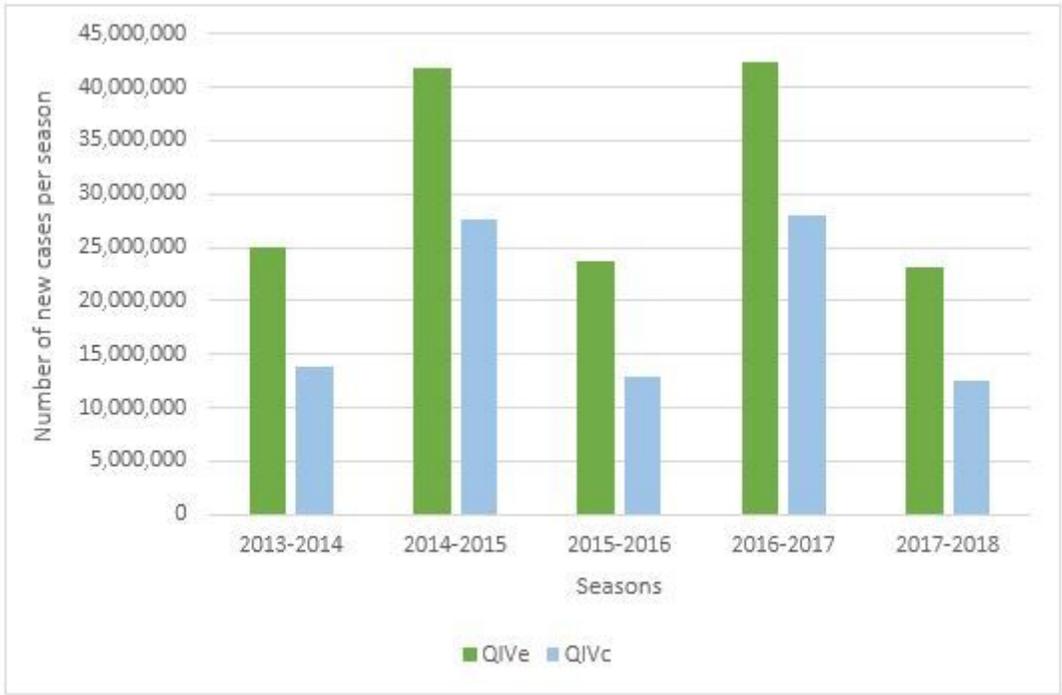


Figure 2

Number of influenza cases over the 5 studied influenza seasons considering systematic A(H3N2) mismatch

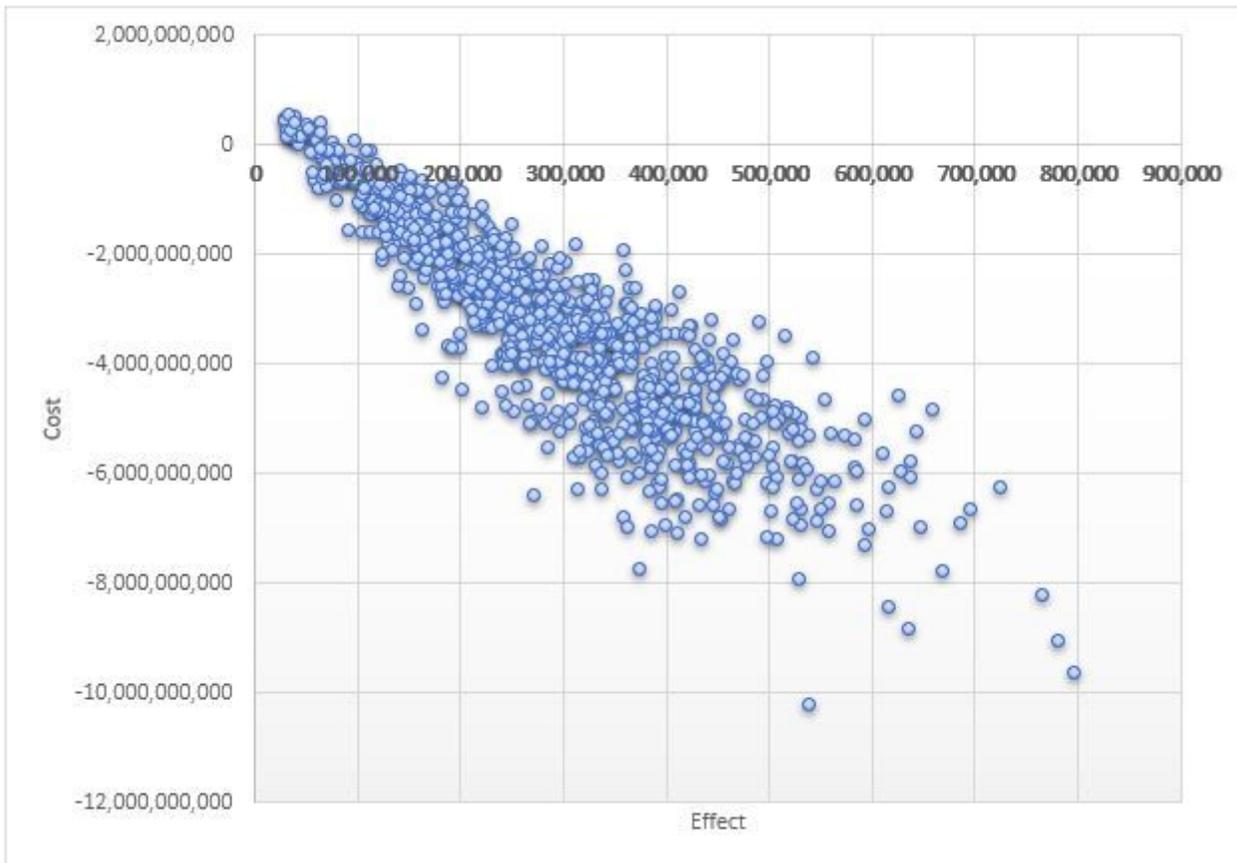


Figure 3

Probabilistic sensitivity analysis of the QIVc scenario compared to QIVe. Health is measured in QALY and cost in US\$.