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Themed Section: Vaccines

## Cost-Effectiveness of Quadrivalent Versus Trivalent Influenza Vaccination in the Dutch National Influenza Prevention Program



Florian Zeevat, MSc, Pascal Crépey, MD, F. Christiaan K. Dolk, MSc, Arjan J. Postma, MSc, Vidya N.A. Breeveld-Dwarkasing, MD, Maarten J. Postma, MD, PhD

### ABSTRACT

**Objectives:** As of 2019, quadrivalent influenza vaccine (QIV) has replaced trivalent influenza vaccine (TIV) in the national immunization program in The Netherlands. Target groups are individuals of 60+ years of age and those with chronic diseases. The objective was to estimate the incremental break-even price of QIV over TIV at a threshold of €20 000 per quality-adjusted life-year (QALY).

**Methods:** An age-structured compartmental dynamic model was adapted for The Netherlands to assess health outcomes and associated costs of vaccinating all individuals at higher risk for influenza with QIV instead of TIV over the seasons 2010 to 2018. Influenza incidence rates were derived from a global database. Other parameters (probabilities, QALYs and costs) were extracted from the literature and applied according to Dutch guidelines. A threshold of €20 000 per QALY was applied to estimate the incremental break-even prices of QIV versus TIV. Sensitivity analyses were performed to test the robustness of the model outcomes.

**Results:** Retrospectively, vaccination with QIV instead of TIV could have prevented on average 9500 symptomatic influenza cases, 2130 outpatient visits, 84 hospitalizations, and 38 deaths per year over the seasons 2010 to 2018. This translates into 385 QALYs and 398 life-years potentially gained. On average, totals of €431 527 direct and €2 388 810 indirect costs could have been saved each year.

**Conclusion:** Using QIV over TIV during the influenza seasons 2010 to 2018 would have been cost-effective at an incremental price of maximally €3.81 (95% confidence interval, €3.26–4.31). Sensitivity analysis showed consistent findings on the incremental break-even price in the same range.

**Keywords:** cost-effectiveness, influenza, quadrivalent influenza vaccine, vaccination.

VALUE HEALTH. 2021; 24(1):3–10

### Introduction

Seasonal influenza causes one of the highest disease burdens of any infectious disease in The Netherlands.<sup>1</sup> The disease is mostly caused by influenza virus types A and B, which are both subdivided into different strains (for example, H1N1 and H3N2 for type A, and B/Yamagata and B/Victoria for type B).<sup>2</sup> The average annual medical burden associated with influenza infection is estimated at approximately 1000 to 5500 symptomatic cases per 100 000 inhabitants during recent respiratory seasons (2012–2018),<sup>3,4</sup> with a corresponding total estimated annual excess mortality of 3900 to 9444 cases per year in The Netherlands. Despite having a national vaccination program in place, the burden of influenza in The Netherlands is still particularly high among older adults (65 years and older), in which influenza infection attributes to approximately 14 000 hospitalizations per year.<sup>4</sup>

Since 1993, the principal strategy to prevent influenza in The Netherlands has been seasonal vaccination with a trivalent influenza vaccine (TIV). TIV is offered free of charge to individuals in The Netherlands who belong to the risk groups—the older adults (60 years or older) and individuals with chronic diseases, such as recommended.<sup>3,4</sup> With an average vaccination coverage of 21% of the total Dutch population, it has been calculated that an estimated average of 13% of infections, 24% of hospitalizations, and 35% of deaths across the total population have been prevented with TIV vaccination in the influenza seasons of 2003 to 2015.<sup>5</sup> However, the burden associated with influenza is still substantial. The remaining disease burden can be partly attributed to decreasing vaccination coverage rates (49.9% of the total population at risk in 2018 compared to 68.9% in 2010)<sup>6,7</sup> but certainly also by occasional mismatches between the circulating influenza B lineage and the B lineage included in the vaccine. TIV contains 2

influenza type-A strains and 1 of the influenza type-B strains, depending on the prediction of the WHO each season. As these predictions involve inherent uncertainty, a mismatch can occur between the circulating influenza B strain and the B strain included in the vaccine, reducing the vaccine effectiveness of the TIV involved. Moreover, even further in the future, the vaccine effectiveness of the TIV is expected to reduce in mismatched seasons due to antigenic drift of both B-lineages. Antigenic drift is a mechanism that causes small changes of the genes of influenza viruses, which can lead to decreasing cross-reactivity of the B-lineages over time.<sup>8-10</sup>

The Dutch national authorities responded to the recent mismatches by switching from the TIV to the quadrivalent influenza vaccine (QIV) as of the 2019 to 2020 influenza season.<sup>11</sup> QIV may provide better health outcomes compared to TIV because QIV contains both B-type strains in the vaccine, potentially avoiding future mismatches; however, QIV is also more expensive than TIV. The clinical and economic effects of replacing TIV with QIV for The Netherlands have so far only been captured by a straightforward static model, which estimated the cost-effectiveness of QIV if it had been implemented in The Netherlands during the last 8 influenza seasons.<sup>12</sup> An integrated analysis designed to fully capture the complexity of the dynamics of infections in humans, including the indirect effects of herd protection on unvaccinated individuals, is yet to be realized. As these factors may considerably influence the cost-effectiveness of a national immunization program against influenza, this study aimed to assess the incremental price at which the switch from TIV to QIV is still cost-effective using a dynamic modeling approach.

## Method

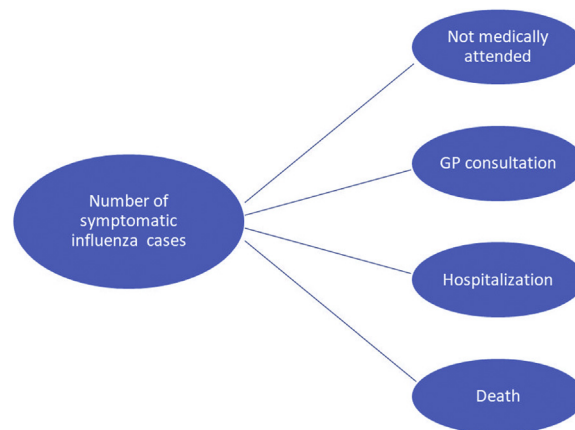
### Overview

An age-structured compartmental model with a dynamic retrospective framework was used over an 8-year time horizon (covering the seasons 2010-2011 through 2017-2018) to compare the effects of QIV versus TIV on both clinical and economic outcomes for the entire population of The Netherlands. In our base case, we used our model to simulate the vaccination strategy if TIV had been replaced by QIV in the total population eligible for vaccination (adults 60 years or older, and individuals with chronic diseases), by modeling the QIV coverage rate as the actual TIV coverage rates reported for each season.<sup>5,13</sup> The clinical outcomes of the simulation include the annual incidence of symptomatic influenza infection, general practitioner (GP) consultations, hospitalizations, and deaths over a time horizon of 8 years. Costs were assessed from the third-party payer (TPP) perspective, which includes direct medical costs, as well as from the societal perspective, which also considers over-the-counter medication and indirect costs due to productivity losses. The incremental break-even price of QIV over TIV is calculated from the societal perspective because this perspective is recommended for economic evaluations in The Netherlands.<sup>14</sup> This is calculated by using a threshold of €20 000 per QALY, which is frequently applied as the threshold for preventive interventions in The Netherlands.<sup>15</sup>

### Dynamic Transmission Model

To estimate age-stratified numbers of symptomatic influenza cases, a published dynamic transmission model was used. This model was originally developed and published by Crepey et al<sup>16</sup> and has been adapted to The Netherlands. It was considered that a complex dynamic model was to be preferred, to adequately include all impacts on transmission of the virus, inclusive among

**Figure 1.** Decision tree of health economic model.



nonvaccinated groups or those where the vaccine was not effective.<sup>17</sup> Ergo, indirect effects of herd effects as well the complexity of dynamic human behavior (interactions within- and between-hosts) were included.<sup>18-20</sup> Given the major distinction between QIV and TIV concerning influenza B, the model explicitly distinguished between influenza A and both types of influenza B (Victoria and Yamagata). The dynamic transmission model, including model inputs (eg, influenza incidence, vaccine efficacy, and coverage), are described in the [Supplemental Materials](https://doi.org/10.1016/j.jval.2020.11.002) found at <https://doi.org/10.1016/j.jval.2020.11.002>.

### Economic Model

For the economic component of the model, an age-structured decision tree model was used, developed in Excel 2010 and linked to the dynamic transmission model.<sup>16,21</sup> The output of the epidemiological component in terms of age-stratified symptomatic influenza cases served as input for the economic component. Subsequently, the age groups of the epidemiological model were recategorized in the economic model to align with available data on economic parameters. The symptomatic influenza cases were divided into 4 categories concerning outcomes: no medical attention, GP visit, hospital admission, and death (Fig. 1).<sup>21</sup> The input parameters of the economic model, including probabilities, costs, and QALYs, can be found in the [Supplemental Materials](https://doi.org/10.1016/j.jval.2020.11.002) found at <https://doi.org/10.1016/j.jval.2020.11.002>.

### Outcomes

Outcomes were expressed in health effects and incremental costs. Costs were expressed in 2018 price levels and were not discounted because the analysis was retrospective and the costs of influenza in our model occurred within the same year as the infection.<sup>22</sup> Health effects were discounted at 1.5% per annum.<sup>14</sup> The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental QALYs. Because influenza vaccination is offered through a public program in which the vaccines are centrally procured via EU tender procedures, net prices of the vaccines are usually lower than the official list prices. Hence, the list prices are not representative for the actual costs of the vaccination program. In addition, the National Institute for Public Health in The Netherlands (Rijksinstituut voor Volksgezondheid & Milieu; RIVM), who is responsible for the procurement of vaccines, awards the supply contracts to 2 vaccine producers in a 60:40 volume ratio, which may also result in 2 different price offers. Therefore, because the contract prices remain confidential

**Table 1.** Base-case results of the annually estimated number of influenza B cases, hospitalizations, and deaths; QALYs lost because of influenza B related death; and total costs of the quadrivalent influenza vaccine (QIV) compared with the trivalent influenza vaccine (TIV) after a switch from TIV to QIV in the population eligible for vaccination, over the period 2010 to 2018.

	TIV		Complete switch from TIV to QIV	
	Current situation		New situation	Difference
<b>Clinical influenza B outcomes</b>				
Total number of symptomatic cases (input from dynamic transmission model)	171 877		162 408	−9469
Total number outpatient visits	38 049		35 919	−2130
Total number of hospitalizations	1018		934	−84
Total number of deaths	235		196	−38
<b>Health effects</b>				
Total QALYs lost because of influenza illness	792		746	−46
Total QALYs lost because of influenza-associated death	2112		1774	−339
Total life-years lost because of influenza-associated death	2483		2085	−398
<b>Costs</b>				
Vaccination	€47 025 273		€58 128 673	€11 103 400
Outpatient visit	€1 633 769		€1 523 365	€−110 404
Hospitalized	€4 462 192		€4 085 987	€−376 205
Productivity losses	€41 504 703		€38 582 142	€−2 922 561

QALY indicates quality-adjusted life-year; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine.

and unknown, the incremental break-even price of QIV over TIV was calculated from a societal perspective by using a threshold of €20 000 per QALY in the base case. This threshold is often applied for vaccines that are used in public programs in The Netherlands.<sup>23</sup>

### Sensitivity and Scenario Analysis

Sensitivity and scenario analyses were performed using the incremental break-even price obtained in the base-case analysis. A deterministic sensitivity analysis was conducted to assess the impact of individual parameters on the results. For the hospitalization costs, the minimum and maximum values were based on the reported boundaries of the 95% confidence intervals (CI). Probabilities and utilities varied by  $\pm 25\%$  from the base-case value.

To describe the impact of the combined parameter uncertainty on the model outcomes, a probabilistic sensitivity analysis (PSA) was performed. A distribution was created for all uncertain parameters, depending on the underlying data. A beta distribution was used for the probabilities and QALY losses, and a gamma distribution for the costs (hospitalization, outpatient visit, productivity losses) in which the parameter's range depends on the minimum and maximum values. The PSA was performed by recalculating the ICER 1000 times, while all input variables were varied simultaneously over their distribution.

Moreover, to further explore the variation in the base case, 6 scenario analyses were performed. In scenario 1, the relatively high TIV coverage rates of the year 2010 were applied for the entire period from 2010 to 2018 for QIV only (see [Supplemental Materials](https://doi.org/10.1016/j.jval.2020.11.002) found at <https://doi.org/10.1016/j.jval.2020.11.002> for the vaccination coverage) to show the impact on the ICER of such a higher coverage rate. This scenario assumed that since 2010 the declining vaccination coverage rate could have been averted.<sup>24</sup>

Although not yet officially published, preliminary observations of the season 2019 to 2020 vaccine coverage rates—when QIV was implemented—seem to confirm a higher vaccine coverage rate. In scenario 2, 3, and 4, the cross-protection rate between the B lineages was changed to 0%, 50%, and 90%, respectively, to account for the uncertainty in the assumption on cross-protection in the base case (70%). In scenario 5, we analyzed the cost-effectiveness of QIV compared to TIV in the predominant risk group of the older adult population (60 years and older) only; we assumed that TIV was replaced with QIV only for the population aged 60 years and older, whereas the remaining age groups belonging to the risk group continued to receive TIV. Lastly, in scenario 6, different epidemiological data, obtained from The Netherlands and England over the period 2003 until 2015, were used as input data for the probability rates for hospitalizations and deaths.<sup>5</sup> Notably, the probabilities for both parameters used in this scenario analysis were lower than the probabilities used in the base case.

## Results

### Base Case

Replacing TIV with QIV for the whole eligible at-risk population in The Netherlands for the influenza seasons 2010 to 2011 through 2017 to 2018 (assuming the actual vaccination coverage rates during the evaluated seasons) resulted in 9469 (5.5%) symptomatic influenza B cases that were averted annually. In addition, 2130 (5.6%) outpatient visits, 84 (8.3%) hospitalizations, and 38 (16.2%) deaths were averted ([Table 1](#)). The retrospective health effects of QIV on influenza illness and influenza-associated death translated into a total of 385 QALYs and 398 life-years gained. Switching from TIV to QIV could have saved an estimated total of €86 609 (8.0%) in direct costs, comprising €110 404

**Table 2.** Incremental costs and health outcomes and the related ICER of the switch from TIV to QIV in the population eligible for vaccination. Health outcomes include an annual discount rate of 1.5%.

Complete switch from TIV to QIV, difference	
<b>Incremental costs</b>	
Direct healthcare costs	€10 616 791
Direct healthcare costs + indirect costs	€7 694 230
<b>Incremental health outcomes</b>	
Life-year saved	488
Life-year saved (discounted)	398
QALY saved	465
Total QALY saved (discounted)	385
<b>ICER (€ per QALY gained)</b>	
Payer perspective	€22 845
Payer perspective (discounted)	€27 597
Societal perspective	€16 557
Societal perspective (discounted)	€20 000

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine.

in outpatient visit costs and €376 205 in hospitalization costs. From the societal perspective, an additional €2 922 561 was saved on productivity losses, which is a 7.0% reduction of the total societal costs. The incremental costs were estimated at €10 616 791 from the TPP perspective, which include the outpatient visits and hospitalizations costs, and vaccination costs of €11 103 400 due to the procurement of QIV instead of TIV (Table 2). From a societal perspective, the incremental costs were estimated at €7 694 230. The total costs and QALYs were used to calculate an incremental break-even price, assuming a threshold of €20 000 per QALY from the societal perspective. This resulted in a maximum incremental

price of QIV over TIV of €3.81 (95% CI €3.26–4.31). Ergo, prices greater than €3.81 increment are considered not cost-effective in The Netherlands. The ICER from the TPP perspective was estimated at €27 597 per QALY when the same estimated incremental price was applied. The incremental break-even price of QIV over TIV from TPP perspective was estimated at €2.81, assuming a threshold of €20 000 per QALY.

### Sensitivity Analysis

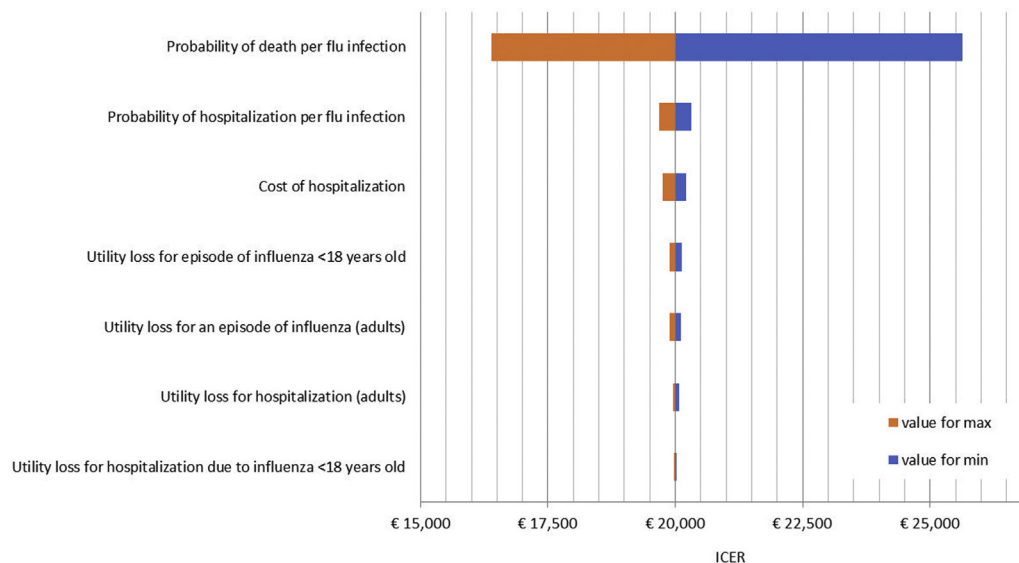
Outcomes of the deterministic sensitivity analysis are displayed in a tornado diagram (Fig. 2). The ICER was most sensitive to changes in the probability of death per symptomatic influenza case. Two other parameters with a medium impact on the ICER were the probability of hospitalization per influenza case and the costs of hospitalization. Utility losses for influenza infection and hospitalization (for all ages) had a very small impact on the ICER.

Results of the PSA are presented in a cost-effectiveness acceptability curve and a cost-effectiveness plane (Fig. 3). The cost-effectiveness plane shows robustly scattered results of the PSA. Results of the acceptability curve reveal that the probability that QIV is cost-effective is 44.8% at a willingness to pay (WTP) of €20 000 per QALY. Moreover, the PSA demonstrated that 100% of the simulations were cost-effective from the societal perspective using a WTP of €26 750 per QALY.

### Scenario Analysis

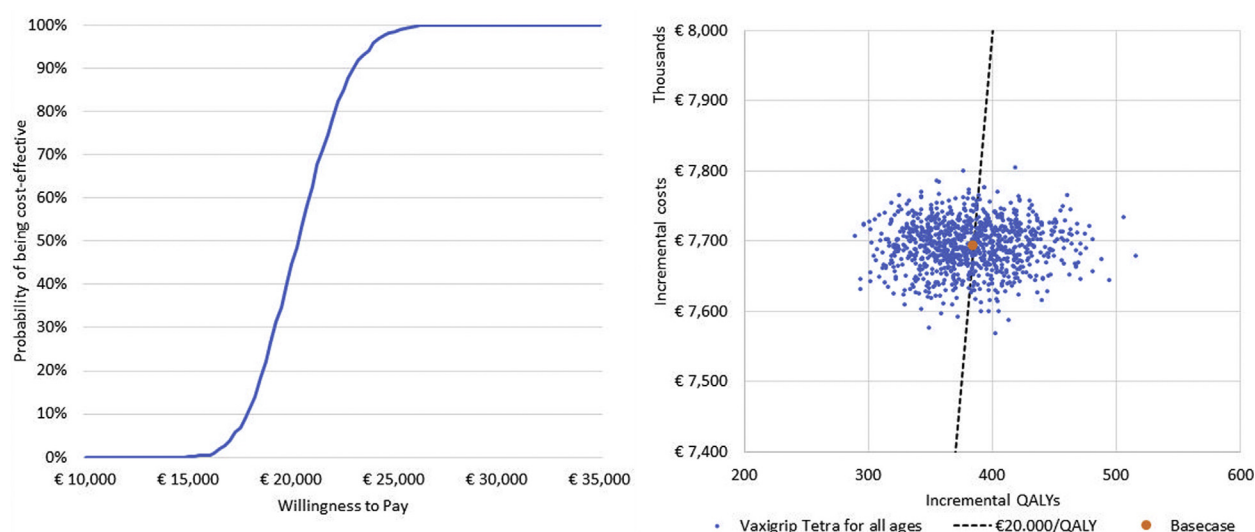
Results of the scenario analysis are shown in Table 3. Scenario analyses showed a 68% decrease in the ICER when it was assumed that the 2010 (high) coverage rates were used for all seasons (see Supplemental Materials found at <https://doi.org/10.1016/j.jval.2020.11.002>). Adjustments of the cross-protection rate have a major impact on the ICER; changing the 70% base-case cross-protection rate to 0% or 50% decreased the ICER 98% and 58%, respectively, and a rate of 90% increased the ICER significantly (318% increase). A 28% increase of the ICER was observed when only the population aged 60 years and older was switched from TIV to QIV, instead of the total at risk population. For scenario 6, in which

**Figure 2.** Tornado diagram of the univariate sensitivity analysis.



Flu indicates influenza; ICER, incremental cost-effectiveness ratio.

**Figure 3.** Cost-effectiveness acceptability curve (CEAC) (left) and cost-effectiveness plane (right) for the switch from the trivalent influenza vaccine (TIV) to the quadrivalent influenza vaccine (QIV) in the Dutch National Influenza Immunization Program.



QALY indicates quality-adjusted life-years.

different probabilities for hospitalization and deaths were used,<sup>5</sup> the ICER increased by 12%.

## Discussion

Our analysis indicates that vaccination with QIV instead of TIV between 2010 and 2018 would have reduced the health burden of influenza during that period, with an estimated average of 9500 averted symptomatic influenza cases. In addition, 2130 outpatient visits, 84 hospitalizations, and 38 deaths could have been averted per year. Furthermore, assuming a WTP of €20 000 per QALY, the switch to QIV in The Netherlands would have been cost-effective from the societal perspective, with an incremental QIV price of

€3.81 (95% CI €3.26–4.31) per dose versus the cost price of TIV. The 9500 annually averted symptomatic influenza cases translate into 385 QALYs gained. Additionally, on average, €2.8 million in societal costs would have been saved each year. The ICER was most sensitive to the probability of death after an influenza infection. The PSA indicates that our outcomes are robust and showed that 44.8% of the simulations were below the threshold of €20 000 per QALY. However, at a threshold of €26 750 per QALY, all the simulations were cost-effective.

In our scenario analysis, we applied the relatively high 2010 vaccine coverage rates for QIV during all the seasons in the 8-year time horizon, as we might have seen no decrease in vaccine coverage rate, as was seen for TIV, would QIV have been implemented in 2010. The Ministry of Health also suggested that the

**Table 3.** Scenario analyses with: (1) high vaccine coverage for quadrivalent influenza vaccine (QIV); (2) no cross-protection between B-lineages; (3) low cross-protection between B-lineages; (4) high cross-protection between B-lineages; (5) trivalent influenza vaccine (TIV) replaced with QIV only for the population aged 60 years and over, while the remaining age groups belonging to the at-risk population continued to receive TIV, and (6) different input data for the probability rates for hospitalizations and deaths.

	Incremental costs	Incremental health effects (QALYs)	ICER (€ per QALY gained)
Base case	€7 694 230	385	€20 000
Scenario			
1. High vaccine coverage for QIV	€9 609 636	1500	€6406
2. No cross-protection between B lineages	€483 882	1524	€317
3. Low cross-protection between B lineages (50% of matched efficacy against the mismatched lineage)	€5 708 444	684	€8347
4. High cross-protection between B lineages (90% of matched efficacy against the mismatched lineage)	€9 339 233	147	€63 666
5. Only switching to QIV in older adults (60+)	€7 241 455	283	€25 622
6. Probabilities by Backer et al 2019 <sup>5</sup>	€7 764 014	346	€22 408

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QIV, quadrivalent influenza vaccine.

better vaccine efficacy of QIV compared to TIV in itself could already contribute to an increase of the vaccine coverage rates, considering that decreased confidence in the vaccine's efficacy was identified to be the foremost reason for individuals to refuse an influenza vaccination.<sup>25,26</sup> The ICER decreased significantly when higher coverage rates for QIV only were included. Another scenario analysis assumed offering QIV to those 60 years and older only, while maintaining the group below 60 years on TIV, to analyze whether such an approach to reduce budget impact would influence the cost-effectiveness. We found that a complete switch is more cost-effective because the ICER increased with 28% compared to the base case in which the whole eligible population is vaccinated. Probably, there is still a considerable disease burden in the at-risk population below 60 years and a positive effect on herd immunity when the at-risk group younger than 60 years are also vaccinated.

A similar economic analysis, assessing the switch from TIV to QIV, has been performed by the RIVM for the purpose of vaccination policy decision making.<sup>12</sup> Although the outcomes of this recent study have been made publicly available, the model specifics and input data have not been published and thus have not been peer reviewed. However, it is documented that a static cost-effectiveness model was adopted in their study. The study conducted by the RIVM estimated that 4562 symptomatic influenza cases were averted, which is 48% lower than the cases averted in our estimation. Additionally, it was estimated that 348 hospitalizations and 84 deaths were averted, which is, respectively, 24% and 45% higher when compared to our study. The significantly higher hospitalization and mortality reduction among older adults from the RIVM's static economic model analysis mainly contributed to a more favorable ICER compared to our analysis (€12 500/QALY versus €20 000/QALY), as more QALYs were averted (631 versus 385) in the RIVM's study. However, the increase in overall vaccination costs due to switching from TIV to QIV for the whole population eligible for vaccination was comparable (€9.8 million in RIVM analysis versus €10.6 million in our analysis), and thus both analyses estimated a comparable increase in the QIV price. The societal costs saved (before the inclusion of the vaccination costs incurred) were lower in the static model (€1.8 million versus €2.8 million), which can be attributable to multiple factors (eg, lower hospitalization costs, fewer GP visits). Even though 1 specific scenario analysis was conducted with parameters from the study conducted by the RIVM (scenario 6),<sup>5</sup> the ICER and/or the number of averted hospitalizations and deaths of our scenario were not comparable to the previously mentioned RIVM analysis for the switch from TIV to QIV.<sup>12</sup> Our scenario and the RIVM's static analysis yielded results of 65 versus 348 hospitalizations and 34 versus 84 deaths, respectively. The difference in results can be attributed to several reasons, such as the use of a dynamic model instead of a static model that applies, for example, natural and vaccine immunity. In addition, the difference in the results indicates the sensitivity of the outcomes to the influenza seasons included in the analysis, as the impact of influenza varies each year depending on the severity of the epidemic and whether there was a B strain mismatch. Also, the decreasing trend in vaccination coverage since 2009 has negatively affected the cost-effectiveness in our base case, as illustrated by our scenario analysis, in which we assumed that the vaccine coverage rate remained constant at the level of 2010. This specific scenario shows that using higher coverage rates for QIV would have resulted in a more favorable cost-effectiveness at €6406/QALY than we found in the base case.

Our methodology can be applied to other countries, obviously using different input parameters for key factors that reflect countries' specific policies, cost-effectiveness thresholds, requirements for cost-effectiveness analyses, targeted populations

for influenza vaccination, influenza seasons, and so on. Although the study results cannot straightforwardly be transferred to other countries, our analysis provides a valuable addition to those that have been made in other Northern European countries,<sup>27–29</sup> confirming the potential for favorable cost-effectiveness of switching from TIV to QIV.

Our study has several limitations. First, the data used may be biased by underreporting. Limited numbers of recorded patients only as well as unspecific influenza-like illness symptoms suggest that reliable estimates of influenza incidence, GP visits, hospitalizations, and deaths due to influenza are difficult to obtain.<sup>30,31</sup> As a result, we may have underestimated the influenza burden in our base case. Our scenario and sensitivity analyses indicate that lower or higher probabilities of hospitalizations and, in particular, mortality have a considerable impact on the ICER, particularly resulting in a potential overestimate. Ergo, assuming hospitalization and death probabilities as used in a previous static analysis<sup>12</sup>—which are higher than the probabilities used in our base case—we found higher incremental break-even prices of QIV versus TIV. Second, the probability of symptomatic influenza cases, GP visits, and hospitalizations used are based on pre-2010 studies.<sup>32–34</sup> Obviously, these probabilities may have changed over the years due to the decrease in vaccination coverage and changes in the targeted populations—for example, considering the switch from 65 to 60 years and older in 2012. Third, the modeled number of symptomatic cases cannot be calibrated or validated with the observed number of cases by age group, reducing some of the implied advantages of the age-structured element in our model. Fourth, we assumed that the QALY loss of an influenza hospitalization and the days of productivity loss are equal to that of pneumococcal infection. Even though these are well-substantiated assumptions, influenza-specific parameters should be gathered to improve future analyses. Lastly, our retrospective approach presents a specific limitation as these results may have restricted predictive power, depending on the similarity of upcoming influenza seasons compared to the time period included in the analysis. This similarity may be likely, given the 8-year horizon we used, but it is obviously uncertain.

Our model included the evolution of the 2 B strains over an 8-year (2010–2018) time horizon. This strengthened the robustness of our model because this time horizon captures the interseasonal variability of the B strains and the actual vaccination coverage rates. Obviously, an approach using only a single influenza season could over- or underestimate the influenza burden in other years. A further strength of the analysis concerns the use of a dynamic epidemiological modeling approach capable of reproducing the direct effects on those who actually receive the vaccination in addition to the indirect effects, such as averted secondary infections. Dynamic modeling explicitly incorporates that the probability of infection exposure is variable over time and can be affected by the intervention, in this case vaccination with QIV. In contrast, static modeling as was used in the RIVM analysis<sup>12</sup> assumes a constant disease exposure over time and shows only the impact of vaccination at the start of an influenza season.

In the base case we used a cross-protection rate of 70%. This is based on a meta-analysis of controlled trials with TIV<sup>35</sup> and is in line with rates used in other cost-effectiveness studies on the switch from TIV to QIV.<sup>21,27–29,36–43</sup> Nevertheless—given the generally acknowledged decrease in cross-reactivity observed in more recent cost-effectiveness studies on QIV<sup>43</sup> and the reduction in cross-protection rates over time due to antigenic drift of both B strains<sup>8–10</sup>—70% may be considered a conservative estimate. However, it is not well known what the actual cross-protection rates are because a naturally acquired immunity in older adults

by previous exposure may also affect the vaccine effectiveness.<sup>44</sup> Therefore, in our analysis we assumed a conservative and relatively high cross-protection rate between the B lineages of the vaccine, with an additional scenario analysis in which cross-protection rates where varied by using 0%, 50%, and 90%. The outcomes of this scenario analysis suggest that if the reduction in cross-protection over the years is taken into account, the ICER will decrease and vaccination with QIV instead of TIV will become even more cost-effective.

Various routes for future research that are worth exploring can be inferred from our approach. In addition to our retrospective approach, a prospective approach could also be taken by forecasting the model inputs, in particular vaccines coverage rates that are expected to increase owing to improved vaccine efficacy of QIV, for the upcoming influenza seasons and analyzing prospective ICERs. Also, with better vaccine effectiveness it would be worthwhile to study whether a further expansion of the target population for QIV by lowering the age limit could be a cost-effective use of resources from a public health point of view.

## Conclusion

With our cost-effectiveness analysis, we have demonstrated that if a switch from TIV to QIV had occurred in the Dutch National Influenza Immunization Program as of 2010 until 2018, the number of influenza B cases could have been reduced annually by 9500 cases. Moreover, 2130 outpatient visits, 84 hospitalizations, and 38 deaths could have been avoided. From a societal perspective, the analysis showed that the switch to QIV would have been cost-effective in The Netherlands at an incremental break-even price of maximally €3.81 (95% CI €3.64–4.31) per dose, when applying a cost-effectiveness threshold of €20 000/QALY. Sensitivity analysis showed consistent findings on the break-even incremental price in the same ballpark range.

## Supplemental Materials

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2020.11.002>.

## Article and Author Information

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## REFERENCES

- Lier A van, McDonald SA, Bouwknegt M, et al. Disease burden of 32 infectious diseases in The Netherlands, 2007–2011. *PLoS One*. 2016;11(4):e015106.
- Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD). Types of influenza viruses: seasonal influenza (flu). <https://www.cdc.gov/flu/about/viruses/types.htm>. Accessed September 6, 2018.
- Teirlinck AC, Van Asten L, Brandsema PS, et al. *Annual report - Surveillance of influenza and other respiratory infections in the Netherlands: winter 2016/2017*. Bilthoven: RIVM; 2017.
- Reukers DFM, Van Asten L, Brandsema PS, et al. *Annual report - Surveillance of influenza and other respiratory infections in the Netherlands: winter 2017/2018*. Bilthoven: RIVM; 2018.
- Backer JA, Wallinga J, Meijer A, Donker GA, Hoek W van der, Boven M van. The impact of influenza vaccination on infection, hospitalisation, and mortality in The Netherlands between 2003 and 2015. *Epidemics*. 2018;26:77–85.
- Heins M, Hooiveld M, Davids R, Korevaar J. Monitor Vaccinatiegraad Nationaal Programma Grieppreventie 2016. <http://www.nivel.nl>. Accessed March 12, 2020.
- Heins M, Hooiveld M, Korevaar J. Monitor vaccinatiegraad Nationaal Programma Grieppreventie 2017. <http://www.nivel.nl>. Accessed November 30, 2018.
- Bedford T, Suchard MA, Lemey P, et al. Integrating influenza antigenic dynamics with molecular evolution. *Elife*. 2014;3:e01914.
- Tewawong N, Suntronwong N, Korkong S, Theamboonlers A, Vongpunswad S, Poovorawan Y. Evidence for influenza B virus lineage shifts and reassortants circulating in Thailand in 2014–2016. *Infect Genet Evol*. 2017;47:35–40.
- Vijaykrishna D, Holmes EC, Joseph U, et al. The contrasting phylogenetics of human influenza B viruses. *Elife*. 2015;4:e05055.
- Rijksinstituut voor Volksgezondheid en Milieu. *Maatregelen griep seizoen 2019–2020 ministerie VWS | RIVM*. RIVM; 2018. <https://www.rivm.nl/griep/informatie-voor-professionals/maatregelen-griep-2019-2020-ministerie-vws>. Accessed January 20, 2019.
- van Dissel JT. Advies aan BAO n.a.v. 55e OMT: Influenza d.d. 4 september 2018 [Dutch] Brief | Rijksoverheid.nl. <https://www.rijksoverheid.nl/documenten/brieven/2018/10/14/advies-aan-bao-n.a.v.-55e-omt-influenza-d.d.-4-september-2018>. Accessed November 1, 2018.
- Heins M, Hooiveld M, Korevaar J. Monitor vaccinatiegraad Nationaal Programma Grieppreventie 2017. <http://www.nivel.nl>. Accessed November 30, 2018.
- Hakkaart-van Roijen L, Linden N van der, Bouwmans C, Kanters T, Swan Tan S. *Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg*. Zorginstituut Ned. 2016:1–120.
- Houweling H, Verweij M, Ruitenbergh EJ. Criteria for inclusion of vaccinations in public programmes. *Vaccine*. 2010;28(17):2924–2931.

16. Crépey P, Boer PT de, Postma MJ, Pitman R. Retrospective public health impact of a quadrivalent influenza vaccine in the United States. *Influenza Other Respi Viruses*. 2015;9(Suppl 1):39–46.
17. World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. [https://www.who.int/immunization/documents/who\\_ivb\\_19.10/en/](https://www.who.int/immunization/documents/who_ivb_19.10/en/). Accessed January 12, 2020.
18. Pitman R, Fisman D, Zanic GS, et al. Dynamic transmission modeling: A report of the ISPOR-SMDM modeling good research practices task force working group-5. SAGE Publications; Sage CA: Los Angeles, CA *Med Decis Mak*. 2012;32(5):712–721.
19. Willem L, Verelst F, Bilcke J, Hens N, Beutels P. Lessons from a decade of individual-based models for infectious disease transmission: A systematic review (2006–2015). *BMC Infect Dis*. BioMed Central Ltd. 2017;17(1):1–16.
20. Miksch F, Jahn B, Espinosa KJ, Chhatwal J, Siebert U, Popper N. Why should we apply ABM for decision analysis for infectious diseases? An example for dengue interventions. *PLoS One*. 2019;14(8):e0221564.
21. Boer PT de, Crépey P, Pitman RJ, Macabeo B, Chit A, Postma MJ. Cost-effectiveness of quadrivalent versus trivalent influenza vaccine in the United States. *Value Health*. 2016;19(8):964–975.
22. Baguelin M, Camacho A, Flasche S, Edmunds WJ. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: a cost-effectiveness study. *BMC Med*. 2015;13(1):1–13.
23. Boersma C, Broere A, Postma MJ. Quantification of the potential impact of cost-effectiveness thresholds on Dutch drug expenditures using retrospective analysis. *Value Health*. 2010;13(6):853–856.
24. Heins M. NIVEL: Monitor vaccinatiegraad Nationaal Programma Grieppreventie 2018. <http://www.nivel.nl>. Accessed January 10, 2020.
25. Blokhuis. Kamerbrief Verder met vaccineren | Kamerstuk | Rijksoverheid.nl. <https://www.rijksoverheid.nl/documenten/kamerstukken/2018/11/19/kamerbrief-verder-met-vaccineren>. Accessed March 4, 2019.
26. Schmid P, Rauber D, Betsch C, Lidolt G, Denker M-L. Barriers of influenza vaccination intention and behavior: a systematic review of influenza vaccine hesitancy, 2005–2016. *PLoS One*. 2017;12(1):e0170550.
27. Dolc C, Eichner M, Welte R, et al. Cost-utility of quadrivalent versus trivalent influenza vaccine in Germany, using an individual-based dynamic transmission model. *Pharmacoeconomics*. 2016;34(12):1299–1308.
28. Meier G, Gregg M, Poulsen Nautrup B. Cost-effectiveness analysis of quadrivalent influenza vaccination in at-risk adults and the elderly: an updated analysis in the UK. *J Med Econ*. 2015;18(9):746–761.
29. Uhart M, Bricout H, Clay E, LARGERON N. Public health and economic impact of seasonal influenza vaccination with quadrivalent influenza vaccines compared to trivalent influenza vaccines in Europe. *Hum Vaccin Immunother*. 2016;12(9):2259–2268.
30. Gezondheidsraad. *Griepvaccinatie: herziening van de indicatiestelling*. 118. 2007.
31. Dutch Health Council (Gezondheidsraad). *Grip op griep*. 2014.
32. Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol*. 2008;167(7):775–785.
33. Friesema IHM, Koppeschaar CE, Donker GA, et al. Internet-based monitoring of influenza-like illness in the general population: experience of five influenza seasons in The Netherlands. *Vaccine*. 2009;27(45):6353–6357.
34. Wijngaard CC van den, Asten L van, Meijer A, et al. Detection of excess influenza severity: associating respiratory hospitalization and mortality data with reports of influenza-like illness by primary care physicians. *Am J Public Health*. 2010;100(11):2248–2254.
35. Yang MC, Tan ECH, Su JJ. Cost-effectiveness analysis of quadrivalent versus trivalent influenza vaccine in Taiwan: a lifetime multi-cohort model. *Hum Vaccines Immunother*. 2017;13(1):81–89.
36. Chit A, Roiz J, Aballea S. An assessment of the expected cost-effectiveness of quadrivalent influenza vaccines in Ontario, Canada using a static model. *PLoS One*. 2015;10(7):e0133606.
37. Chit A, Roiz J, Briquet B, Greenberg DP. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. *Vaccine*. 2015;33(5):734–741.
38. Bellinghen L-A Van, Meier G, Vlaenderen I Van. The potential cost-effectiveness of quadrivalent versus trivalent influenza vaccine in elderly people and clinical risk groups in the UK: a lifetime multi-cohort model. *PLoS One*. 2014;9(6):e98437.
39. You JHS, Ming W, Chan PKS. Cost-effectiveness analysis of quadrivalent influenza vaccine versus trivalent influenza vaccine for elderly in Hong Kong. *BMC Infect Dis*. 2014;14(1):618.
40. Clements KM, Meier G, McGarry LJ, Pruttivarasin N, Misurski DA. Cost-effectiveness analysis of universal influenza vaccination with quadrivalent inactivated vaccine in the United States. *Hum Vaccin Immunother*. 2014;10(5):1171–1180.
41. Tsuzuki S, Schwehm M, Eichner M. Simulation studies to assess the long-term effects of Japan's change from trivalent to quadrivalent influenza vaccination. *Vaccine*. 2018;36(5):624–630.
42. García A, Ortiz de Lejarazu R, Reina J, Callejo D, Cuervo J, Morano Larragueta R. Cost-effectiveness analysis of quadrivalent influenza vaccine in Spain. *Hum Vaccin Immunother*. 2016;12(9):2269–2277.
43. Thommes EW, Ismaila A, Chit A, Meier G, Bauch CT. Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: a dynamic modeling study of Canada and the United Kingdom. *BMC Infect Dis*. 2015;15(1):465.
44. Henry C, Palm A-KE, Krammer F, Wilson PC. From original antigenic sin to the universal influenza virus vaccine. *Trends Immunol*. 2018;39(1):70–79.