Introduction of a quadrivalent influenza vaccine in Italy: a budget impact analysis

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Keywords

Influenza • Budget Impact Analysis • QIV

Summary

Every year in Italy, the Ministry of Health (MoH) offers influenza vaccination free of charge to all subjects at risk and to all subjects aged ≥ 65 year old. Until 2014-2015 immunization campaign against Trivalent Influenza Vaccine (TIVs) were the only vaccines used in Italy.
Traditional TIVs contain antigens from three viral strains: A(H1N1), A(H3N2), and one of the two B lineages: B(Victoria) or B(Yamagata). Each year, the World Health Organization (WHO) decides which viral strains should be included in the next seasonal influenza vaccine. However, accurately predicting which B-lineage strain will predominate in the upcoming season has proved to be a challenging task, owing to the co-circulation of both lineages.
To address the issue of B-mismatch, a new Quadrivalent Influenza Vaccine (QIV) containing both B-lineage strains has been developed, in order to achieve broader protection against influenza. The new QIV was approved in Italy in 2015 and included by the MoH in the national recommendations for the seasonal immunization campaign against influenza 2015-2016.
Recently, a Health Technology Assessment (HTA) Report has shown that, in comparison with TIVs, the new QIV is cost-effective (Incremental Cost-Effectiveness Ratio (ICER) = € 18,883/(QALY) Quality-Adjusted Life-Year) from the Italian National Health Service (NHS) perspective. The present Budget Impact Analysis (BIA) showed that the introduction of the QIV with a 9% market share in the vaccine mix for the 2015-2016 flu campaign would yield an annual saving of € 674,089, mainly owing to the broader protection offered by QIV vs TIVs with an estimated 49.12% B-mismatch.

Introduction

Every year the Italian Ministry of Health (MoH) offers an Influenza Immunization Program for all subjects at higher risk of flu complications on the basis of age (≥ 65 years old) or clinical and professional condition. Until 2014-2015 immunization campaign against influenza, Trivalent Inactivated influenza Vaccines (TIVs) were the only vaccines used in Italy.
Traditional TIVs contain antigens from three viral strains: A(H1N1), A(H3N2), and one of two B lineages: B(Victoria) or B(Yamagata). Each year, the World Health Organization (WHO) decides which viral strains should be included in the next seasonal influenza vaccine. However, accurately predicting which B-lineage strain will predominate in the upcoming season has proved to be a challenging task, resulting in frequent mismatches with the vaccine strain [1], owing to the co-circulation of both lineages or the predominant circulation of the non-vaccine B-lineage. During mismatch seasons, efficacy and effectiveness against the opposite B lineage are lower [2-8]. To address the issue of B-mismatch, a new Quadrivalent Inactivated influenza Vaccine (QIV) containing both B-lineage strains has been developed, in order to provide broader protection against influenza. The new QIV was available in Italy [9] and included by the MoH in the national recommendations for the seasonal immunization campaign against influenza 2015-2016 [10].
Recently, a Health Technology Assessment (HTA) Report has shown that, in comparison with TIVs, the new QIV is cost-effective (Incremental Cost-Effectiveness Ratio (ICER) = € 18,883/(QALY) Quality-Adjusted Life-Year) from the Italian National Health Service (NHS) perspective [11].
The objective of the present analysis was to estimate the budget impact of the new QIV after its introduction into the national flu immunization campaign in Italy.

Methods

A budget impact analysis (BIA) was made from the NHS perspective, in order to estimate the financial impact due to the introduction of the QIV into the vaccine mix included by the MoH in the influenza immunization campaign for the 2015-2016 flu season.
The BIA included the following input data:

- population eligible for influenza immunization and vaccine coverage (target population);
- epidemiology of influenza in Italy;
- efficacy of QIV *vs* TIV;
- vaccine mix and vaccine cost;
- direct influenza costs.

The analysis considered a single-year time horizon and focused on the first year of QIV introduction by the MoH in the 2015-2016 flu immunization campaign.
The results are shown as the net budget impact of the scenario of QIV in the flu vaccine mix (new scenario) versus the scenario in which only TIVs are used in the influenza immunization program (current scenario).

Target Population

The population targeted by the national Influenza Immunization Program was calculated on the basis of the Italian population in 2014 [12].
Every year in Italy, the MoH offers free influenza vaccination to all subjects at risk (for clinical/professional reasons) and to all subjects aged ≥ 65 year old, regardless of other risk factors.
The prevalence of at-risk subjects eligible for influenza vaccination was calculated from the data collected in 25 EU countries (including Italy) by Ryan et al. [13]. The influenza vaccine coverage data in 2014 were then applied to the Italian general population, in order to estimate the annual number of subjects undergoing influenza vaccination within the national Immunization Program [14, 15].
The target population included in the BIA is summarized in Table I.

Epidemiology of influenza in Italy

The probability of contracting influenza in an unvaccinated population was derived from the study by Turner et al. and is reported in Table II [16].
The prevalence of A and B influenza viruses circulating during a season was estimated as the average data (A virus = 74.12% and B virus = 25.88%) from ECDC Surveillance Reports from 2003 to 2012 (excluding the 2009-2010 pandemic season) [11].
The prevalence of B-lineage strains circulating during a season was estimated as the average data from ECDC Surveillance Reports from 2003 to 2012 (B-Yamagata = 50.88% and B-Victoria = 49.12%) [11].

Tab. I. Target population included in the BIA.

Age-range	Population	Overall Vaccine Coverage (%)	Population at risk (%)	Population at risk vaccinated (%)
< 5	2,724.106	2.04	15.10	9.66
5-17	7,433.899	2.30	15.18	10.86
18-49	25,543.294	3.87	16.52	17.24
50-59	8,435.388	9.50	45.36	19.30
60-64	3,361.039	9.50	45.36	19.30
65-69	3,447.791	55.40	45.63	55.40
70-74	3,044.129	55.40	46.15	55.40
75-79	2,645.596	55.40	47.31	55.40
80-84	2,013.904	55.40	50.05	55.40
≥ 85	1,863.522	55.40	57.44	55.40
Total	60,782,688	16.33	28.66	31.02

Tab. II. Probability of contracting influenza in the population broken down age-range.

Age-range	Probability (%)
< 5	19.21
5-17	19.21
18-49	6.55
50-59	6.55
60-64	6.55
65-69	6.17
70-74	6.17
75-79	6.17
80-84	6.17
≥ 85	6.17
Average	8.58

Efficacy of QIV vs TIV

In the present BIA, we assumed that:

- the efficacy of QIV *vs* TIVs in preventing influenza A viruses was the same; age-specific QIV and TIV efficacy versus influenza A viruses is reported in Table III [17-19];
- the efficacy of QIV *vs* TIVs in preventing influenza B virus was the same for the vaccine B-strain (matching) in TIVs but higher for the B-strain not

Tab. III. Efficacy of QIV *vs* TIVs in preventing influenza viruses.

	Influenza A virus		Influenza B virus			
Age-range	QIV efficacy	TIV efficacy	QIV efficacy	TIV efficacy in match	TIV in mismatch	**Overall TIV efficacy *vs* B virus**
< 5	59%	59%	66%	66%	44%	55%
5-17	59%	59%	77%	77%	52%	64%
18-49	61%	61%	77%	77%	52%	64%
50-59	61%	61%	73%	73%	49%	61%
60-64	61%	61%	73%	73%	49%	61%
65-69	58%	58%	69%	69%	47%	58%
70-74	58%	58%	69%	69%	47%	58%
75-79	58%	58%	66%	66%	44%	55%
80-84	58%	58%	66%	66%	44%	55%
≥ 85	58%	58%	66%	66%	44%	55%
Total	59%	59%	66%	66%	44%	55%

Tab. IV. Unit prices and market shares of the vaccines in the BIA.

Vaccine	Current scenario		New scenario	
	Market share (MS)	Unit price	Market share (MS)	Unit price
Split	49%	2.55 €	52%	2.55 €
Intradermal	26%	5.36 €	25%	5.36 €
Adjuvanted	25%	5.33 €	14%	5.33 €
QIV	0	0	9%	6.00 €
Total	100%		100%	

Tab. V. Cost of influenza: direct costs included in the BIA and probabilities that patients with influenza will generate these costs.

Health resource	Probability of generating the cost for patients with influenza (%)	Cost	Source
GP consultation	60%	20.66 €	[21]
Antibiotic therapy	47.3%	3.53 € (< 18 years)/ 3.06 € (≥ 18years)	Final cost on multiplying the initial cost by the likelihood of receiving antibiotics [22, 23]
Antiviral therapy	0.17%	17.3 € (< 5years) / 38.5 € (≥ 5years)	[24, 25]

included in TIVs, (mismatching); these are reported in Table III. In both cases, the efficacy of QIV *vs* TIVs was derived from the meta-analysis by Tricco et al. [20];
- the B-mismatch value considered in order to estimate the overall efficacy of TIVs *vs* influenza B was 49.12%.

The overall efficacy of TIVs *vs* influenza B virus in the present analysis was derived by applying the following formula:

TIVs Overall efficacy *vs* influenza B-virus = (TIV efficacy in match*B-matching) + (TIV efficacy in mismatch*B-mismatching)

For example, if, in subjects aged 5-17 years, the efficacy of TIVs *vs* B is 77% in the scenario of matching and 52% in the scenario of mismatching, on considering an average TIV B-match of 49.12%, the overall efficacy of TIVs *vs* influenza B in that age-group is:

TIV Overall Efficacy *vs* influenza B virus = (77%*100%-49.12%)+(52%*49.12%) = 64%

Vaccine mix and vaccine cost

The BIA was conducted by comparing two scenarios:
Current scenario: this scenario included only TIVs in the vaccination strategy, and the vaccine mix was based on the TIV doses included in the allotments requested by the 20 Italian Regions for the 2014-2015 flu season (when QIV was not yet available on the market); specifically, the vaccine mix in the analysis included:
- inactivated trivalent split influenza virus vaccine (Split);
- intradermal influenza vaccine (Intradermal);
- adjuvanted influenza vaccine (Adjuvanted).

New scenario: this scenario included the QIV as an alternative to TIVs and the vaccine mix was based on QIV and TIV doses included in the allotments requested by the 20 Italian Regions for the 2015-2016 flu season; specifically, the vaccine mix in the analysis included:
- inactivated trivalent split influenza virus vaccine (Split);
- intradermal influenza vaccine (Intradermal);
- adjuvanted influenza vaccine (Adjuvanted);
- inactivated tetravalent split influenza virus vaccine (QIV).

It was assumed that in both scenarios the B-strain included in TIVs was Yamagata, in accordance with TIV antigen composition in the 2014-2015 and 2015-2016 flu seasons.
Vaccine prices in the analysis were based on the average regional tender price in the 2015-2016 flu season.
The vaccine mix and vaccine prices in both scenarios are summarized in Table IV.

Direct influenza cost

The analysis estimated one-year health resource consumption related to influenza, with or without the introduction of QIV into the National Influenza Immunization program.
Table V reports the direct costs included in the analysis and the probabilities that patients with influenza will generate these costs.
The analysis also took into account the frequency and the cost of influenza patients with complications:
- the frequency of complications in patients with influenza, regardless of age, was 29.46%; this was estimated from the data reported by Sessa et al. [21];
- the frequency of complications requiring hospitalization was 11.56% for subjects at risk and 7.15% for subjects not at risk [26];
- in the analysis, it was assumed that 90.77% of these complications requiring hospitalization were respiratory, and that 9.23% were other complications unrelated to the respiratory tract.

Tab. VI. Costs of influenza complications: inpatient and outpatient settings.

Respiratory complications	Inpatient cost < 18 years	Inpatient cost ≥ 18 years	Outpatient
Bronchitis	1,538 €	1,832 €	90 €
Pneumonia	1,948 €	2,291 €	90 €
Upper Respiratory Tract Infections (URTI)	5,768 €	€4,422	€90
Other complications not related to respiratory tract	2,777 €	2,900 €	83 €

Table VI reports the costs of complications in inpatient (hospitalization) and outpatient settings, based on DRG tariffs.

Results

The objective of this analysis was to estimate the budget impact of the new QIV after its introduction into the National Immunization campaign in Italy.
In the base-case scenario, we assumed that, in the 2015-2016 flu season:

- the TIVs used contained the Yamagata B-strain;
- the prevalence of A and B viruses circulating during the 2015-2016 flu season was 74.12% and 25.88%, respectively, and that of the Yamagata and Victoria B-strains circulating during the same year was 50.88% and 49.12%, respectively;
- the QIV was used in 9% of the population eligible for the National Influenza Immunization campaign in Italy;
- the price of a single dose of QIV was 6.00 €.

The results of the base-case scenario are shown in Tables VII and VIII. The base-case scenario simulated the impact of QIV introduction on the basis of the real volumes of influenza vaccines requested by the Italian Regions for the 2015-2016 flu season, in comparison with the vaccine mix without QIV and based on the TIV volume requested by the Italian Regions for the 2014-2015 flu season (when QIV was not yet on the market).
Comparison of the two scenarios (new versus current) revealed that, according to the estimates in the present analysis (49.12% B-mismatch), the introduction of QIV would prevent 1,601 influenza events (including 1,031 with complications), as a consequence of the broader protection of QIV against B-strain virus.
This broader protection of QIV *vs* TIVs in the new scenario resulted in a saving of € 419,389 in the annual influenza treatment costs borne by the NHS. Although the cost of introducing QIV at 9% (858,538 units) was € 5,151.230 (due to the higher purchase cost of QIVs *vs* TIVs), it was fully offset by the 3% increase in the MS of the split vaccines and the 12% decrease in the MS of the intradermal vaccine and adjuvanted vaccine, which yielded a saving of € 5,405.930. Thus, the net result of introducing QIV on the cost of vaccination was a saving of € 254,700.
The estimated net budget impact of the introduction of QIV into the National Influenza Immunization program in the flu season 2015-2016 was a saving of € 674,089 *vs* the scenario with no QIV.

Tab. VII. Impact of the introduction of a QIV in Italy on influenza cases: base-case results.

	Current scenario	New or alternative scenario	Δ (avoided cases with new scenario)
Subjects covered by vaccination	9,539.315	9,539.315	
With TIVs	9,539.315	8,680.777	
With QIV	0	858,538	
Influenza events without complications in immunized subjects	255,703	254,102	-1,601
Influenza events with complications in immunized subjects	166,596	165,565	-1,031
Bronchitis in immunized subjects	69,924	69,491	-433
Pneumonia in immunized subjects	6,351	6,312	-39
Upper respiratory tract infections (URTI) in immunized subjects	74,944	74,481	-464
Other complications not related to respiratory tract in immunized subjects	15,377	15,282	-95
Hospitalization in immunized subjects	16,073	15,973	-100

The BIA considered two alternative scenarios in addition to that of the base-case:
no B-mismatch:

- prevalence of A and B influenza virus circulating during a season: A virus = 74.12% and B virus = 25.88%;
- prevalence of B-lineage strains circulating: B-Yamagata = 100% and B-Victoria = 0%;
- the QIV was used in 9% of the population eligible for the National Influenza Immunization campaign in Italy;
- the price of a single dose of QIV was € 6.00;
- TIVs contained the Yamagata B-strain.

Tab. VIII. Impact of the introduction of a QIV in Italy on direct influenza costs: base-case results.

	Current scenario (€)	New Scenario (€)	Δ (€)
Vaccination cost	37,924.500	37,669.800	-254,700
TIVs	37,924.500	32,518.570	
QIV	0	5,151.230	
Cost of influenza	3,559.199	3,536.906	-22,293
GP consultation	3,169.698	3,149.846	-19,852
Antibiotic therapy	372,881	370,543	-2,337
Antiviral therapy	16,620	16,516	-104
Cost of influenza with complications	63,844.008	63,446.912	-397,096
Inpatient cost	50,394.190	50,080.269	-313,920
Outpatient cost	13,449.818	13,366.643	-83,176
Total	105,327.707	104,653.618	-674,089

full B-mismatch:

- prevalence of A and B influenza virus circulating during a season: A virus = 74.12% and B virus = 25.88%;
- prevalence of B-lineage strains circulating: B-Yamagata = 0% and B-Victoria = 100%;
- the QIV was used in 9% of the population eligible for the National Influenza Immunization campaign in Italy;
- the price of a single dose of QIV was € 6.00;
- TIVs contained the Yamagata B-strain.

Figures 1 and 2 summarize the results from these two additional scenarios versus the base-case.

In the No B-mismatch scenario, there was no impact of QIV introduction in preventing influenza cases versus TIVs, owing to the complete match between the B-strain circulating and the B-strain contained in the TIVs. Nevertheless, the net budget impact in this scenario was favourable, because the incremental cost due to QIV introduction was fully offset by increased use of split vaccine (Market Share (MS) +3%) and the decreased use of intradermal vaccine and adjuvanted vaccine (MS -12%), produced a net saving of € 254,700 in a year.

In the Full B-mismatch scenario, the influenza cases avoided through the introduction of QIV was 3,120. In this scenario, the broader protection offered by QIV *vs* TIVs was maximized by the 100% mismatch between the B-strain circulating and the B-strain contained in the TIVs. The net budget impact in this scenario was highly in favour of the introduction of QIV, with € 1,087.382 saved in one year. The majority of this saving came from the reduction in influenza treatment costs produced by QIV versus TIVs, owing to the full B-mismatch (-€ 832,692).

Discussion

The WHO and European Health Authorities encouraged the development of QIV in order to achieve broader protection against influenza by reducing the impact of

Fig. 1. Number of avoided cases of influenza due to QIV introduction in the 3 scenarios included in the BIA.

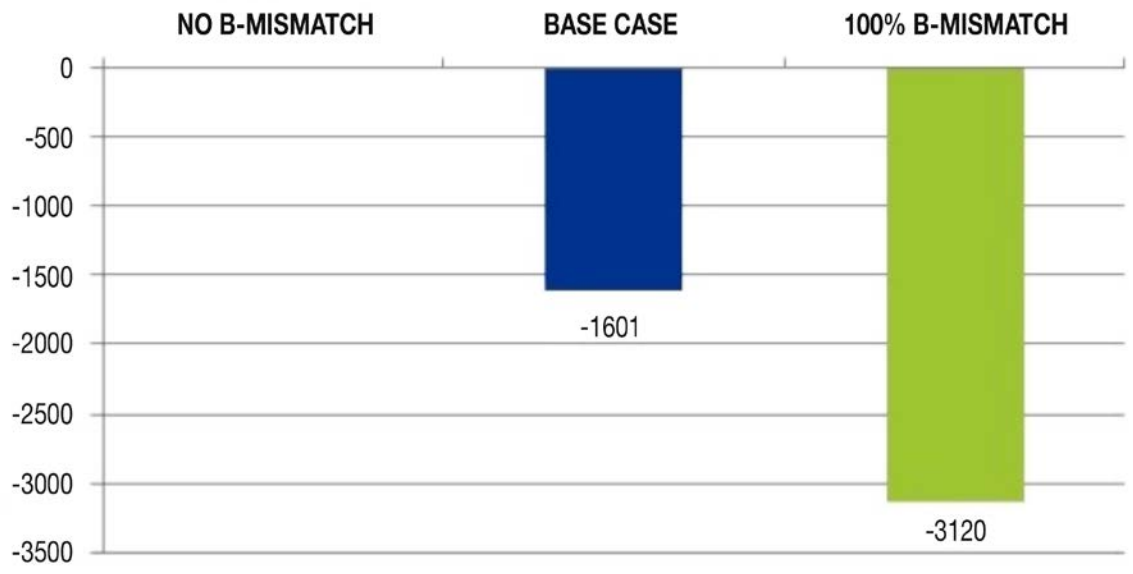
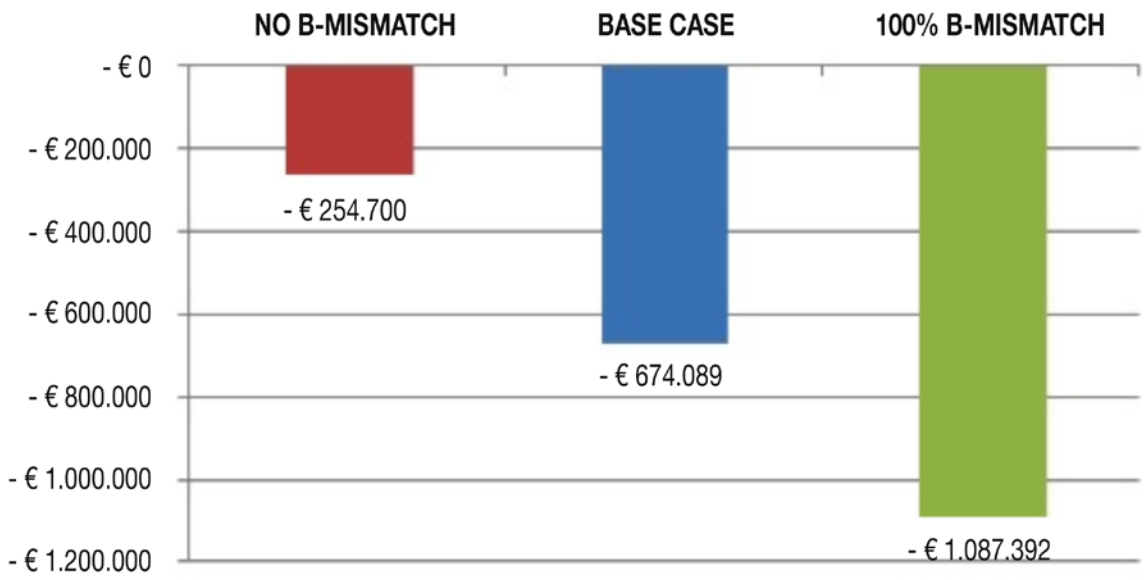


Fig. 2. Number of avoided costs due to QIV introduction in the 3 scenarios included in the BIA.



B-Mismatch. Until 2014-2015 immunization campaign against influenza, only TIVs were available for the National Influenza Immunization campaign in Italy. Traditional TIVs contain antigens from three viral strains: A (H1N1), A (H3N2), and one of two co-circulating B lineages: B(Victoria) or B(Yamagata). Each year, the WHO decides which viral strains should be included in the next seasonal influenza vaccine.

However, accurately predicting which B-lineage strain will predominate in the upcoming season has proved to be a challenging task, resulting in frequent mismatches with the vaccine strain. During mismatch seasons, efficacy and effectiveness against the opposite B lineage are lower because of the lack of cross-protection of the B-strain contained in the TIVs *vs* the circulating B-strain, when they differ.

In 2015, the first QIV was approved by the Italian Drug Agency (AIFA), and was included in the National Influenza Immunization campaign by the MoH for the 2015/2016 flu season.

An HTA Report showed that this new QIV was more cost-effective than TIVs (ICER = € 18,883/QALY) from the Italian NHS perspective.

In the present analysis, we estimated the BIA after the introduction of QIV as an alternative to TIVs. The BIA showed that, with a 9% MS in the vaccine mix for the 2015-2016 flu campaign, the introduction of the QIV yielded an annual saving of € 674,089, mainly due to the broader protection offered by QIV *vs* TIVs with an estimated 49.12% B-mismatch.

QIV is an effective and safe alternative to TIVs, offering broader protection when B-mismatch occurs in the flu season. From the NHS perspective, QIV is cost-effective in Italy; our budget impact analysis estimated that the introduction of QIV into the influenza immunization campaign in 2015/2016 would produce a net annual saving ranging from € 254,700 (0% B-mismatch, Incremental cost of QIV fully offset by the saving due to the increased MS of split vaccines and the decreased MS of intradermal and adjuvanted vaccines) to € 1,087,392 (100% B-mismatch).

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