

ORIGINAL ARTICLE

Age- and risk-related appropriateness of the use of available influenza vaccines in the Italian elderly population is advantageous: results from a budget impact analysis

M. BARBIERI¹, S. CAPRI², C. DE WAURE³, S. BOCCALINI⁴, D. PANATTO^{5,6}

¹ Centre for Health Economics, University of York, York, UK; ² School of Economics and Management, Cattaneo University-LIUC, Castellanza, Italy; ³ Institute of Public Health, Section of Hygiene, Catholic University of the Sacred Heart, Rome, Italy; ⁴ Department of Health Sciences, University of Florence, Italy; ⁵ Department of Health Sciences, University of Genoa, Italy; ⁶ Inter-University Centre for Research on Influenza and Other Transmitted Diseases (CIRI-IT), Genoa, Italy

Keywords

Budget impact analysis • Costs • Appropriateness • Influenza • Vaccination • Elderly • Italy

Summary

Introduction. Nowadays, four different types of influenza vaccines are available in Italy: trivalent (TIV), quadrivalent (QIV), MF59-adjuvanted (aTIV) and intradermal TIV (idTIV) inactivated vaccines. Recently, a concept of the appropriateness (i.e. according to the age and risk factors) of the use of different vaccines has been established in Italy. We conducted a budget impact analysis of switching to a policy, in which the Italian elderly (who carry the major disease burden) received the available vaccines according to their age and risk profile. **Methods.** A novel budget impact model was constructed with a time horizon of one influenza season. In the reference scenario the cohort of Italian elderly individuals could receive either available vaccine according to 2017/18 season market share. The alternative scenario envisaged the administration of TIV/QIV to people aged 65-74 years and at low risk of developing influenza-

related complications, while aTIV/idTIV were allocated to high-risk 65-74-year-olds and all subjects aged ≥ 75 years.

Results. Switching to the alternative scenario would result in both significant health benefits and net budget savings. Particularly, it would be possible to prevent an additional 8201 cases of laboratory-confirmed influenza, 988 complications, 355 hospitalizations and 14 deaths. Despite the alternative strategy being associated with slightly higher vaccination costs, the total savings derived from fewer influenza events completely resets this increase with net budget savings of € 0.13 million.

Conclusions. An immunization policy in which influenza vaccines are administered according to the age and risk profile of Italian elderly individuals is advisable.

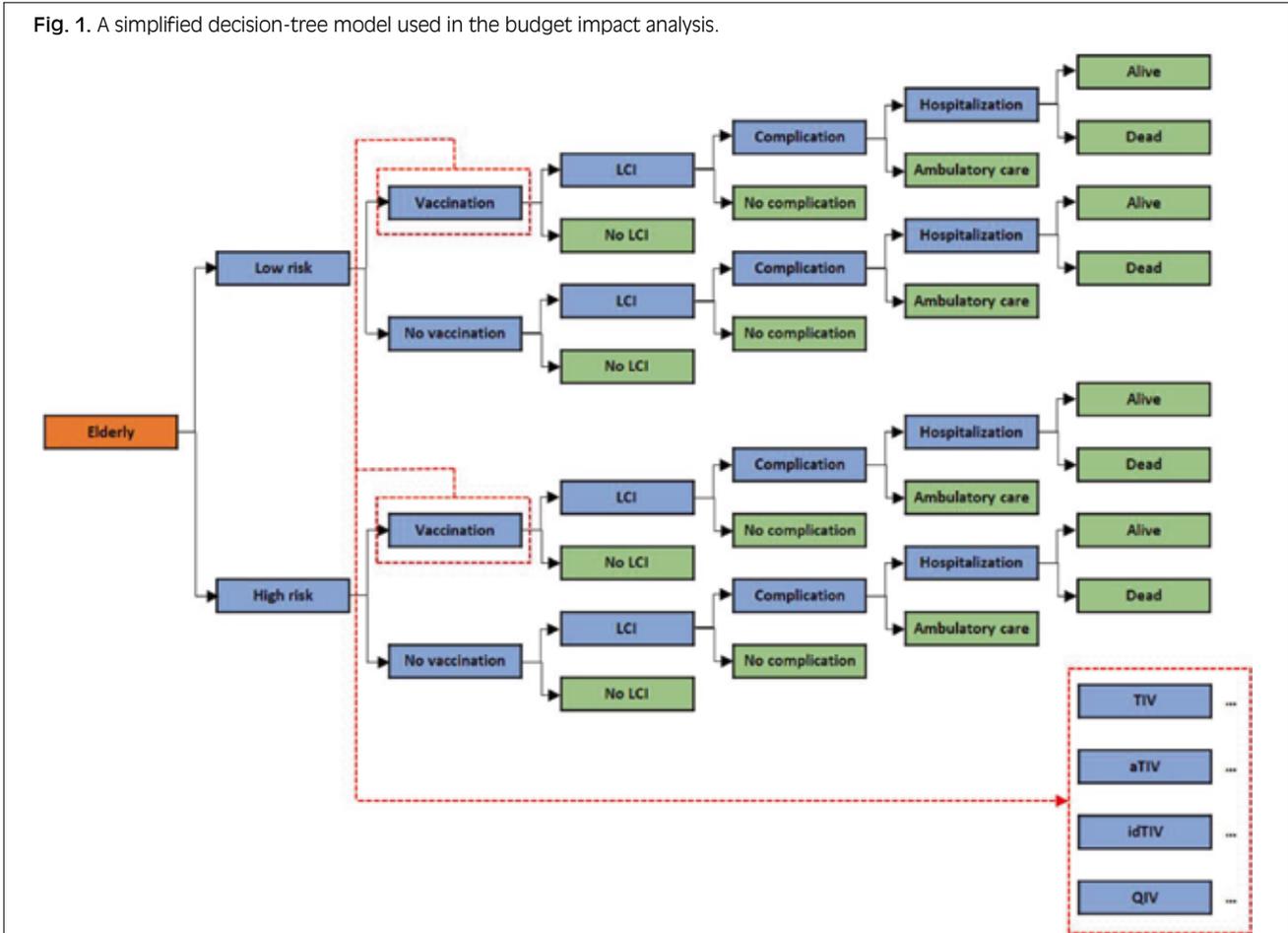
Introduction

In Italy, influenza is still the third largest cause of infectious disease-related mortality [1]; most influenza-attributable deaths occur in the elderly [2, 3]. Vaccination remains the most important and effective public health measure able to dramatically reduce the large burden of seasonal influenza [4]. Indeed, given that the elderly are the most affected population, all member states of the European Union recommend seasonal influenza immunization for this particularly vulnerable group [5]. Both National [6] and supranational [5] authorities have recognized the value of influenza immunization among seniors and demand at least a 75% vaccination coverage (VC) or better still a 95% VC.

VC rates among single Italian regions are often described as “jeopardized” [7]. This figure may be exemplified by seasonal influenza VC rates among the elderly: in 2016/17 there was a 1.7-fold difference between regions, from 37.3% in South Tyrol to 63.1% in Umbria [8]. In the context of the Italian fiscal federalism, the Ministry of Health periodically issues, following approval of the State-Regions Conference, National Immunization Pre-

vention Plans (the last edition for 2017–2019) aimed at guiding and harmonizing immunization strategies across the regions. Each Region then adopts its own immunization plan [9]. Moreover, prior to the commencement of an influenza season, the Ministry of Health issues “Prevention and Control of Influenza” recommendations for a given season [6, 10]. Each Region may then fully adopt the national recommendation or provide its own circular. Unlike vaccines against several other diseases, the market of influenza vaccines is significantly diverse. In the last 2017/18 influenza season, four different vaccine types were available for immunization of the elderly, namely, trivalent inactivated vaccines (TIVs), MF59-adjuvanted TIV (aTIV), intradermal TIV (idTIV) and quadrivalent inactivated vaccines (QIV). These four vaccine formulations have different clinically important features, including age indication, route of administration, immunogenicity, vaccine effectiveness (VE), etc. [6, 11-13]. For instance, while TIV and QIV may be administered to all principal age-classes [6], aTIV and idTIV have been specifically developed for older adults in order to overcome the suppressive phenomenon of immunosenescence [6, 14-16].

Fig. 1. A simplified decision-tree model used in the budget impact analysis.



Procurement of influenza vaccines in Italy is based on regional tenders with four separate lots for the four aforementioned vaccine types. The vaccine mix (i.e. relative procurement distribution of single vaccine types) is changing continuously and partly reflects the evolving market situation (e.g. QIV has recently entered the market). Similarly to the “jeopardized” nature of influenza VC rates, the influenza vaccine mix is highly inhomogeneous among single regions. Several factors may have contributed to this inhomogeneity. For example, in some regions the vaccine acquisition price may be crucial, with TIV (as the “oldest” of the available alternatives) being the cheapest option.

It has been recently shown [13] that all available vaccines are cost-effective in the elderly Italian population when compared with non-vaccination. However, aTIV has the most favorable economic profile, being a highly cost-effective strategy compared with TIV and the dominant (both in terms of cost-saving and effectiveness) strategy compared with idTIV and QIV. However, while the cost-effectiveness analysis allows the value comparison of different strategies, it cannot directly address the issues of the affordability and sustainability of such interventions. This is why the budget impact analysis (BIA) is increasingly required by reimbursement authorities as a part of a comprehensive economic evaluation of a technology [17]. Here we quantified the impact of a “diversified” (i.e. according to the age and risk category) seasonal influenza offer to the Italian elderly

population on the national budget with the ultimate goal of informing administrators of regional influenza vaccination programs about tender policies.

Methods

MODEL STRUCTURE AND BASIC ASSUMPTIONS

A novel budget impact model was built in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The model simulates the natural history of laboratory-confirmed influenza (LCI). Briefly, an elderly individual (defined here as subject aged ≥ 65 years) at lower or higher risk of developing an influenza-related complication (see below) may be vaccinated (according to the current VC rate) with one of the four available influenza vaccines (according to the assumed market share). The non-vaccinated sub-cohort will develop LCI according to its average natural attack rate; by contrast, the vaccinated sub-cohort will have some reduction – according to the vaccine efficacy of single vaccines – in the number of LCI and all consecutive events. People infected with virus may develop a complication that, in turn, may be treated in either outpatient or inpatient regimens. Finally, the hospitalized elderly may die or survive. A simplified version of the model is depicted in Figure 1.

TIME HORIZON AND PERSPECTIVE

Given that both consequences of seasonal influenza and associated healthcare expenditure are assessable in a short-term period and in order to facilitate the comprehension of major results by all relevant stakeholders, the time horizon was set to one year corresponding to one influenza season. As recommended [17], the analysis was conducted from the perspective of the National Healthcare Service (NHS), i.e. only direct costs were considered.

TARGET POPULATION

The latest Italian National Vaccine Prevention Plan [18] recommends a universal seasonal influenza vaccination for people aged ≥ 65 years. As of 2017, a total of 13,528,550 Italian people were aged 65 years or more [19]. The whole elderly cohort is not homogeneous with regard to different features; it, for example, is comprised of people with and without serious chronic conditions. The presence of at least one underlying serious disease significantly increases the likelihood of developing an influenza-related complication [20, 21]. According to the National Institute of Statistics [22], 44.1% of Italian ≥ 65 -year-olds have at least one serious chronicity. The assumed parameter is very close to that used in a previous Italian economic evaluation [23]. Moreover, compared with elderly individuals aged 65-74 years, those aged ≥ 75 years (51.2% of the elderly [19]) have significantly more pronounced features of immunosenescence [24], which results in suboptimal immune responses to traditional influenza vaccines [14-16].

IMMUNIZATION RATE, CURRENT VACCINE MIX AND HYPOTHETICAL VACCINE MIX WITH RATIONALE

The probability of receiving vaccination was set to 52.0%, which reflects the last available (season 2016/17) official VC data among the Italian elderly [8], and is independent of vaccine type.

As mentioned above, four different vaccine types (with four different lots in public tenders) are currently commercially available in Italy. The current (season 2017/18) market share was quantified through analysis of allotments requested by single Italian regions. However, these estimates do not exactly reflect the vaccine mix among the elderly since (i) no elderly-specific number of doses of single vaccines requested were known, (ii) all four types of vaccine are routinely administered to the elderly, (iii) and idTIV and aTIV may be administered only to older adults. To establish an elderly-specific market share we proceeded as follows. Given that, the Italian Ministry of Health provides data [8] on VC relative only to the elderly and general populations (15.1%), we first calculated a VC among people aged < 65 years (4.5%). We then assumed (following a consultation with external experts) that the off-label administration of idTIV and aTIV can be neglected; therefore, non-elderly people may receive TIV or QIV only. To figure out the elderly-specific market share, we adjusted the parameter of interest by subtracting the

quota of TIV and QIV allocated to non-elderly individuals.

To establish a hypothetical market share, we both consulted experts and analyzed the available regional policies regarding seasonal influenza immunization among the elderly. We found annual recommendations issued by the Region of Emilia-Romagna [25, 26] very comprehensive and in line with a recently published paper by Bonanni et al. [27] on the appropriateness of the use of different influenza vaccines available in Italy. In particular, in the latest Emilia-Romagna circular [26] it is stated that subunit TIVs are the only available alternative for young children aged 6-35 months, and may be eventually administered to healthy people aged up to 65 years. QIVs should be given to people aged 3-65 years with chronic underlying conditions, healthcare professionals, and it is also possible to administer these vaccines to people aged 65-74 years without immunosuppressive pathologies. aTIV is recommended for people aged ≥ 65 years especially if affected by underlying conditions leading to immunosuppression and all elderly individuals aged > 75 years. idTIV, which is indicated for those ≥ 60 years old, may be also used – specifically due to the intradermal route of administration – in people with coagulopathies (that easily encounter hemorrhage or hematomas following an intramuscular injection) and those being immunized at home [26].

The imputation process of a hypothetical vaccine mix considered both the abovementioned statements from the latest Emilia-Romagna circular [26] and the fact that the elderly in low- and high-risk groups have different patterns of vaccination and clinical outcomes (see below). Thus, at the first step we established a vaccine mix for the elderly at high-risk of LCI-related complications. Considering the Emilia-Romagna circular [26], it was assumed that only aTIV and idTIV should be administered to this subpopulation in a ratio of 5.6, which reflects the latest tender allotment in Emilia-Romagna. To establish a vaccine mix for the low-risk elderly group (again, in order to reflect the Emilia-Romagna circular [26]), these were divided into two sub-cohorts, namely 65-74 year-olds and ≥ 75 year-olds. The first sub-cohort could receive either TIV or QIV according to their current countrywide elderly-specific market share ratio of 0.79, while the second sub-cohort may be immunized only with aTIV and idTIV in the above-described ratio of 5.6. The current and hypothetical vaccine mixes are summarized in Table I.

Tab. I. Current and hypothetical vaccine mixes, by vaccine type.

Vaccine	Current elderly-specific vaccine mix (low risk and high risk), %	Alternative elderly-specific vaccine mix (low risk/high risk), %
TIV	20	26/0
aTIV	40	37/85
idTIV	15	6/15
QIV	25	31/0

Tab. II. Input parameters used to populate the model (base case), by risk group.

Parameter		Low-risk elderly	High-risk elderly	Reference
Epidemiological and clinical, %	Vaccination	47.8	57.3	8, 28
	LCI	5.4	5.4	29, 30
	Outpatient visit LCI	38.6	38.6	32
	P Bronchitis LCI	2.69	3.46	21
	P Pneumonia LCI	1.04	1.31	21
	P URTI LCI	4.50	4.67	21
	P CV complication LCI	0.09	0.80	21
	P CNS complication LCI	0.21	0.31	21
	P Renal complication LCI	0.05	0.16	21
	P Otitis media LCI	0.21	0.15	21
	P GI bleeding LCI	0.66	0.66	21
	P Hospitalization complication	26.4	34.3	33–35
	P Death complication	3.6	3.8	21, 37
	VE, %	TIV	58.0	
rVE (vs TIV) of aTIV		25.0		39
rVE (vs TIV) of idTIV		16.5		40
rVE (vs TIV) of QIV		6.6		23, 41, 42
Costs, €	TIV price	2.11		Weighted average (regional allotments)
	aTIV price	5.28		Weighted average (regional allotments)
	idTIV price	5.37		Weighted average (regional allotments)
	QIV price	5.80		Weighted average (regional allotments)
	Vaccine administration	6.16		44
	GP visit	20.66		43
	Outpatient treatment of complications (except for otitis media)	80.0		45
	Outpatient treatment of otitis media	50.0		45
	Bronchitis (DRG 097)	1,832		23, 46
	Pneumonia (DRG 090)	2,291		23, 46
	URTI (DRG 080)	4,422		23, 46
	Cardiovascular complications (weighted mean DRGs)	3,544		29
	Renal complications (DRG 316)	3,734		23, 46
	CNS complications (weighted mean DRGs)	3,507		29
	Otitis media (DRG 069)	1,247		23, 46
GI bleeding (DRG 175)	2,091		23, 46	

MODEL INPUT PARAMETERS AND SOURCES

Most input parameters relative to epidemiology, clinical outcomes of LCI, and costs were adapted from our recent CEA [13]; these are summarized in Table II. Some parameters were extracted as shown in Table II, some were averaged in order to reflect different seasons, while some were interpolated to reflect the Italian reality. Italy-based parameters were comprehensively searched and preferred providing that these were robust and nationally representative. For a detailed description of all model parameters, their strengths and shortcomings, readers are invited to assess a report by Di Pietro et al. [13]. Briefly, considering that the official VC data do not distinguish between low- and high-risk elderly, risk-specific VCs were imputed. It has been established [28] that compared to the Italian elderly at low risk of developing influenza-related complications those at high risk have a relative risk of being immunized of approximately 1.2. To establish a risk-category-specific VC we formulated the follow-

ing equation: $(0.559 \times VC_{\text{low risk}}) + (0.441 \times VC_{\text{high risk}}) = 52.0\%$, i.e. $(0.559 \times VC_{\text{low risk}}) + (0.441 \times 1.2 \times VC_{\text{low risk}}) = 52.0\%$. This equation allowed us to assume VC rates of 47.8% and 57.3% for the elderly at low and high risk, respectively.

The natural attack rate of influenza was set to 5.4%. This came from an imputation approach: a baseline meta-analytically obtained influenza-like illness (ILI) attack rate among the Italian elderly (16.8%) [29] was weighted by an average Italy-specific influenza virus isolation rate (32%) [30]. The assumed parameter resulted congruent with an estimate (5.7%) from a pooled analysis of placebo arms in elderly-specific randomized controlled trials [31]. It was next assumed that approximately a third (38.6%) of the elderly with LCI will seek care from their general practitioners (GPs). This estimate is an elderly-specific average and came from a web-based Italian participatory surveillance system for influenza [32].

Tab. III. Comparison of the current and alternative scenarios in terms of laboratory-confirmed influenza and following events (base-case results).

Parameter	Current scenario	Alternative scenario	Difference
LCI	479,149	470,948	-8,201
Complicated LCI	49,419	48,431	-988
Hospitalizations	14,867	14,512	-355
Deaths	551	537	-14

Given the unavailability of large-scale elderly-specific Italian data on the consequences of LCI, these were established by experts from the international literature. A large-scale UK study by Meier et al. [21] was used to quantify influenza-related complications among the elderly belonging to low- and high-risk categories. The probability of hospitalization following a LCI-related complication was interpolated from the United States surveillance system FluSurv-NET (elderly-specific averaged data) [33] to the Italian elderly population. The estimated figure was then adjusted to the sensitivity of the polymerase chain reaction (PCR) influenza test that is relatively low in the elderly [34, 35]. By performing calculations, a total of 23,539 expected hospitalizations were established. It was assumed that, like in the case of LCI-related complications, the elderly at high risk had a greater probability of being hospitalized (relative risk vs elderly at low risk of 1.3 [21]). The resulting probabilities were 26.4% and 34.3% for the elderly at low and high risk, respectively.

Considering the mortality following LCI, it was decided not to use the statistically imputed excess mortality estimates since it is based on a statistical imputation. Indeed, a recent meta-regression analysis [36] highlighted that the statistical model selected has a significant impact on the estimate and that “no average estimate of excess mortality could reliably be made”. Instead, we identified a study by Arriola et al. [37] that reported LCI-related mortality among non-vaccinated elderly being 3.8%. Given that almost all elderly in that subsample had at least one underlying health condition, we attributed this proportion to the at risk elderly. To figure out the mortality rate among the elderly at low risk, we deflated the estimate by Arriola et al. [37] by applying a correction factor derived from a ratio of the probability of death among low- and high-risk elderly reported by Meier et al. [21]. However, it should be considered that the number of deaths was considered only in the comparison between alternative scenarios from the point of view of Public Health impact and not budgetary impact (i.e. the cost of death was not quantified).

A meta-analytically obtained TIV VE of 58.0% [38] was used. The relative (i.e. vs TIV) VE (rVE) of aTIV, idTIV and QIV was assumed to be 25.0%, 16.5% and 6.6%, respectively. While the rVE of aTIV and idTIV were adopted from a large-scale multi-season observational study [39] and robust regression modeling [40], respectively, that of QIV was imputed, given the unavailability of VE data in the elderly. The additional benefit of the second B lineage strain was imputed, using a methodology similar to previous research on the topic [23], by

weighting the relative frequency of B virus type in the elderly (17.9%), average level of B lineage mismatch (60.1%) [23] and rVE of QIV vs TIV against the mismatched B lineage (35%) [41, 42].

Vaccine acquisition price is a weighted average of awarded prices at regional tenders. Costs relative to vaccine administration and general GP visits derived from official documents [43, 44], while the ambulatory treatment of LCI-related complications were adapted from Marchetti et al. [45]. Diagnosis-related groups (DRGs) reimbursement tariffs were used to establish the costs of inpatient treatment of complications. Most DRGs (097, 090, 080, 316, 069 and 175) were taken directly from the current official reimbursement documents [46]. By contrast, given that cardiovascular and central nervous system complications are associated with several DRGs, we used a weighted average tariff estimated by Iannazzo [29].

SCENARIO ANALYSIS

In order to address the uncertainty, two scenario analyses were conducted by changing the vaccine mix and/or vaccine price. In particular, in the first analysis QIV took the whole quatum of TIV among low-risk people aged 65-74 years. The second scenario considered the same vaccine mix as the first, but with a decrease in QIV price by 20% (€ 4.64). Both scenarios were compared with the base case.

Results

Table III reports results of the base-case analysis relative to the most important clinical events. Over a single average influenza season, switching to the alternative scenario would, approximately, prevent an additional 8,201 cases of LCI, one thousand complications, 350 hospitalizations, and 14 LCI-related deaths.

From the point of view of budget implication, the alternative strategy would be associated with a slightly higher total investment (€ 1.1 million). On the other hand, the total savings derived from fewer influenza-related events completely reset (€ 1.3 million) the increase in vaccination campaign costs. Indeed, the alternative strategy would allow a saving of approximately 0.13 million (Tab. IV). In summary, the base-case results suggested that implementation of the alternative strategy would allow not only for significantly fewer number of LCI and LCI-related events, but also significant financial savings. If the market share of TIVs is completely absorbed by QIV in the low-risk 65-74 year-olds (scenario analysis 1), some health-related savings would be observed

Tab. IV. Comparison of the current and alternative scenarios in terms of direct costs (base-case results).

Parameter	Current scenario	Alternative scenario	Difference
Total vaccination costs, €	77,012,493	78,131,409	+1,118,916
Total event costs, €	15,079,950	13,828,051	-1,251,899
Overall costs, €	92,092,443	91,959,460	-132,983

(Tab V). From the economic perspective (Tab. VI), a slight increase (3.6% or €0.24 per person) in overall costs would be seen. If, on the other hand, QIV price is reduced by 20% (scenario 2) the overall incremental cost goes up by only 1% corresponding to € 0.07 per person.

Discussion

The findings reported here suggest that a shift to the alternative scenario would be associated with both significant health gains and net financial saving. The alternative scenario tried to incorporate the issue on equity considering that the pool of elderly Italians is highly inhomogeneous in terms of both immune response following immunization and risk of developing LCI-related complications. Such a “diversified” influenza vaccination offer finds its grounds in epidemiological and immunological aspects of ageing. Thus, the prevalence of underlying chronicities increases sharply with age. If, for example, the prevalence of at least one serious chronic condition among elderly Italians aged 65-69 years is 31.7%, it grows by 21% and 68% among people aged 70-74 and ≥ 75 years, respectively [22]. In turn, several chronic conditions increase risk of immunosuppression [47-49]. Furthermore, it has been demonstrated that compared with subjects aged 60-75 years, in those aged > 75 years the number of lymphocytes falls below a critical threshold and the T cell receptor repertoire diminishes abruptly [24]. This is why the immune response to vaccination is less efficacious the most senior individuals and the elderly with underlying conditions [24, 50]; these subjects are therefore in need of enhanced influenza vaccines like aTIV, idTIV, or high-dose TIV (which is currently unavailable in Italy).

We also showed that a complete switch from TIV to QIV in the low risk elderly aged 65–74 years would be associated with substantial health benefits and a low budget impact of € 0.24 per person. If, however, the price of QIV drops, which is highly probable, the net impact would be of only € 0.07 per person. This strategy should therefore be considered in regions with a more flexible budget. This scenario would also be similar to the recently published paper by Bonanni et al. [27] on the appropriateness of the use of influenza vaccines in Italy; this paper states that subunit TIVs should be administered to children aged 0.5-3 years, split QIVs to subjects aged 3-70 years at high risk (except for people aged ≥ 60 and ≥ 65 years who due to health conditions need idTIV or aTIV, respectively) and aTIV/idTIV for all elderly individuals aged > 70 years [27].

More generally, our results confirm that the influenza immunization policy adopted by Emilia-Romagna [25, 26] is sound also from both public health and economic impact points of view. Emilia-Romagna may be considered as a benchmark Region in terms of both healthcare performance and immunization policies. The most recent *Meridiano Sanità* regional index [51] put Emilia Romagna at second place in the area “Effectiveness, efficiency and appropriateness of healthcare provision”. In 2016, the Region was the first to introduce a mandatory character for some vaccines in order to access educational services for young children [52]. The seasonal influenza coverage rate in Emilia-Romagna is also higher than the national average [8].

Our discussion should include the comparison of our findings with previous research. However, only a few BIAs on this topic have been conducted so far. The early BIA by Iannazzo [29] compared the budget impact of a complete switch from TIV to aTIV; the budget impact of the use of either vaccine was also compared with non-

Tab. V. Scenario analysis: comparison of the base-case and scenarios 1 and 2 in terms of laboratory-confirmed influenza and following events.

Parameter	Base-case	Scenarios 1/2	Difference
LCI, N	470,948	469,019	-1,929
Complicated LCI, N	48,431	48,249	-182
Hospitalizations, N	14,512	14,464	-48
Deaths, N	537	536	-1

Tab. VI. Scenario analysis: comparison of the base-case and scenarios 1 and 2 in terms of direct costs

Parameter	Base-case	Scenario 1	Difference*	Scenario 2	Difference*
Total vaccination costs, €	78,131,409	81,599,501	+3,468,092	79,209,359	+1,077,950
Total event costs, €	13,828,051	13,644,505	-183,546	13,644,505	-183,546
Overall costs, €	91,959,460	95,244,006	+3,284,546	92,853,864	+894,404

*Difference between the base-case and a given scenario.

vaccination. In particular, the author established that the use of either vaccine would be associated with significant reduction in the number of cases of ILI and following events. However, compared with non-vaccination, the use of TIV would have produced a 4.6% increase (€ 50.2 million) in overall costs; while the universal use of aTIV among the elderly would have yielded a net saving of € 74 million. The results by Iannazzo [29] cannot be directly compared with our findings due to differences in model structures and several assumptions. First, given that, in the time frame only two alternatives were available, Iannazzo [29] compared the budgetary impact of only TIV, aTIV and no vaccination, assuming their universal use and therefore without establishing a vaccine mix. Second, the attack rate of ILI and not LCI were used, overestimating the economic output. Third, a significantly higher proportion of the elderly at high risk of developing complications was exploited. Fourth, the TIV acquisition price was much higher (€ 3.81 vs € 2.25), while the relative (vs aTIV) increase in price was much lower (+46% vs +150%) [29].

The second more recent BIA [53] investigated the introduction of QIV; the model was not elderly-specific, i.e. the entire Italian population was included. The introduction of QIV with a market share of 9% was associated with both health benefits and some net savings (€ 674,089; € 0.01/person). However, the increase in QIV market share (from 0% to 9%) was mostly determined by reduction in the market share of aTIV (from 25% to 14%). Moreover, in that model the market share of TIV had a slight increase (from 49% to 52%) [54]. In real life, however, the increase in QIV was mostly driven by a progressive reduction in the quatum of TIV, while aTIV market share saw some increase.

Although all costs used in our model are specific to the Italian healthcare system, some input parameters relative to the disease natural history came from non-Italian sources. Indeed, it was sometimes not possible to identify robust, population-based representative and elderly-specific data from Italian literature. It is likely that some crucial model parameters were underestimated. For instance, the hospitalization rate was not adjusted by the likelihood of influenza testing that is relatively low among seniors. In this regard, Reed et al. [35] have estimated that the number of observed influenza-related hospitalizations in over-65-year-olds should be inflated by a factor of 5.2. Given that hospitalization is a major driver of LCI-related costs, our estimates are conservative. Moreover, the assumed rVE (25%) of aTIV vs TIV may be underestimated: it has been shown [54] that aTIV is more effective than TIV in preventing LCI among the Canadian elderly by 63%.

In conclusion, a seasonal influenza immunization policy targeting the elderly Italian population, in which enhanced vaccines (aTIV and idTIV) are administered to high-risk elderly individuals aged 65-74 years and all those \geq 75 years old, while TIV/QIV are administered to the low-risk elderly individuals aged 65-4 years, would be associated with both substantial health benefits and net financial savings. Moreover, this strategy is more equitable and

therefore decision-makers and other relevant stakeholders should consider the implementation of such age- and risk-tailored influenza vaccination policies in their regions.

Acknowledgements

The study was supported by Seqirus srl. The sponsor had no role in any aspect of the project apart from providing financial support.

Authors' contributions

MB and SC conceived, designed and conducted the study, collected data on costs and wrote the manuscript; CdW, PB and DP collected epidemiological data. All authors approved the final manuscript.

References

- [1] Brussaferro S, Chitarro M, De Carli G, Raffaele B, Puro V. *Italian hospital policies for the prevention of influenza in health care workers*. J Prev Med Hyg 2004;45:9-11.
- [2] Rizzo C, Bella A, Viboud C, Simonsen L, Miller MA, Rota MC, Salmaso S, Ciofi degli Atti ML. *Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969-2001*. Emerg Infect Dis 2007;13:694-9.
- [3] Gasparini R, Amicizia D, Lai PL, Panatto D. *Clinical and socio-economic impact of seasonal and pandemic influenza in adults and the elderly*. Hum Vaccin Immunother 2012;8:21-8.
- [4] Nagata JM, Hernández-Ramos I, Kurup AS, Albrecht D, Vivas-Torrealba C, Franco-Paredes C. *Social determinants of health and seasonal influenza vaccination in adults \geq 65 years: a systematic review of qualitative and quantitative data*. BMC Public Health 2013;13:388.
- [5] European Centre for Disease Prevention and Control. *Seasonal influenza vaccination and antiviral use in Europe – Overview of vaccination recommendations and coverage rates in the EU Member States for the 2013-14 and 2014-15 influenza seasons*. Stockholm: ECDC; 2016. Available at: <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Seasonal-influenza-vaccination-antiviral-use-europe.pdf>. [Accessed 23/11/17].
- [6] Italian Ministry of Health. *Prevention and control of influenza: recommendation for season 2017-2018*. Available at: http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?jsessionid=JCEbZYZ6VGHbhyATrnouzg__.sgc4-prd-sal?anno=2017&codLeg=60180&parte=1%20&serie=null. [Accessed 23/11/17].
- [7] Fortunato F, Tafuri S, Cozza V, Martinelli D, Prato R. *Low vaccination coverage among Italian healthcare workers in 2013*. Hum Vaccin Immunother 2015;11:133-9.
- [8] Italian Ministry of Health. *Influenza vaccine coverage rate*. Available at: http://www.salute.gov.it/imgs/C_17_tavole_19_allegati_iitemAllegati_0_fileAllegati_itemFile_3_file.pdf. [Accessed 23/11/17].
- [9] Bonanni P, Ferro A, Guerra R, Iannazzo S, Odone A, Pompa MG, Rizzuto E, Signorelli C. *Vaccine coverage in Italy and assessment of the 2012-2014 National Immunization Prevention Plan*. Epidemiol Prev 2015;39(4 Suppl 1):146-58.
- [10] Italian Ministry of Health. *Prevention and control of influenza: recommendation for season 2016-2017*. Available at: <http://www.trovanorme.salute.gov.it/norme/renderNormsanPd f?anno=2016&codLeg=55586&parte=1%20&serie=null>. [Accessed 23/11/17].

- [11] Barberis I, Martini M, Iavarone F, Orsi A. *Available influenza vaccines: immunization strategies, history and new tools for fighting the disease*. J Prev Med Hyg 2016;57:E41-6.
- [12] Treanor JJ. *Clinical practice. Influenza vaccination*. N Engl J Med 2016;375:1261-8.
- [13] Di Pietro ML, Poscia A, Specchia ML, de Waure C, Zaccaro D, Gasparini, et al. *Health Technology Assessment (HTA) of the adjuvanted influenza vaccine in the elderly Italian population*. QJPH 2017;6.
- [14] O'Hagan DT, Ott GS, Nest GV, Rappuoli R, Giudice GD. *The history of MF59(®) adjuvant: a phoenix that arose from the ashes*. Expert Rev Vaccines 2013;12:13-30.
- [15] Podda A. *The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine*. Vaccine 2001;19:2673-80.
- [16] Holland D, Booy R, De Looze F, Eizenberg P, McDonald J, Karrasch J, McKeirnan M, Salem H, Mills G, Reid J, Weber F, Saville M. *Intradermal influenza vaccine administered using a new microinjection system produces superior immunogenicity in elderly adults: a randomized controlled trial*. J Infect Dis 2008;198:650-8.
- [17] Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, Orlewska E, Penna P, Rodriguez Barrios JM, Shau WY. *Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force*. Value Health 2014;17:5-14.
- [18] Italian Ministry of Health. *National Vaccine Prevention Plan 2017-2019*. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf. Accessed 23/11/2017.
- [19] National Institute of Statistics (ISTAT). *Population on Jan 1, 2017*. Available at: <http://demo.istat.it/pop2017/index.html>. [Accessed 23/11/17].
- [20] Nichol KL, Wuorenma J, von Sternberg T. *Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens*. Arch Intern Med 1998;158:1769-76.
- [21] Meier CR, Napalkov PN, Wegmüller Y, Jefferson T, Jick H. *Population-based study on incidence, risk factors, clinical complications and drug utilisation associated with influenza in the United Kingdom*. Eur J Clin Microbiol Infect Dis 2000;19:834-42.
- [22] National Institute of Statistics (ISTAT). *2014 annual report. Situation of the country*. Available at: <http://www.istat.it/files/2014/05/Rapporto-annuale-2014.pdf>. [Accessed 23/11/17].
- [23] Kheiraoui F, Cadeddu C, Quaranta G, Poscia A, Raponi M, de Waure C, et al. *Health technology assessment of the quadrivalent influenza vaccine Flu-QIV (Fluarix Tetra)*. QJPH 2015;4.
- [24] Goronzy JJ, Weyand CM. *Understanding immunosenescence to improve responses to vaccines*. Nat Immunol 2013;14:428-36.
- [25] Emilia-Romagna Region. *Prevention and control of influenza. Recommendations for season 2016-2017*. Available at: <https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=0ahUKEwi99Yvcz8XXAhWIIZAKHW0uDAkQFggsMAE&url=http%3A%2F%2Fsalute.regione.emilia-romagna.it%2Fdocumentazione%2Fleggi%2Fregionali%2Fcircolari1%2Fcircolare-n-16-2016-prevenzione-e-controllo-dell2019influenza-raccomandazioni-per-la-stagione-2016-17201d%2Fdownload%2Ffile%2FCircolare%2520n.16-%2520Prevenzione%2520e%2520controllo%2520influenza%25202016-17%2520e%2520allegati.pdf&usg=AOvVaw0ps7xHKq9EGOR6EZCDxkH->. [Accessed 23/11/17].
- [26] Emilia-Romagna Region. *Prevention and control of influenza. Recommendations for season 2017-2018*. Available at: <https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&cad=rja&uact=8&ved=0ahUKEwiLoOKm0MXXAhVMipAKHYBOBbgQFggsMAI&url=http%3A%2F%2Fsalute.regione.emilia-romagna.it%2Fdocumentazione%2Fleggi%2Fregionali%2Fcircolari1%2Fcircolare-8-2017-influenza%2Fdownload%2Ffile%2FCircolare-8-2017-influenza.pdf&usg=AOvVaw0NvMwK8RaNaWxiRT4fT8u>. [Accessed 23/11/17].
- [27] Bonanni P, Boccalini S, Zanolini P, Dakka N, Lorini C, Santomauro F, Bechini A. *The appropriateness of the use of influenza vaccines: Recommendations from the latest seasons in Italy*. Hum Vaccin Immunother 2017 (In press).
- [28] National Institute of Health (ISS). *Reports ISTISAN 13/9*. Available at: http://www.iss.it/binary/publ/cont/13_9_web.pdf. [Accessed 23/11/17].
- [29] Iannazzo S. *Pharmacoeconomic evaluation of the MF59-adjuvanted influenza vaccine in the elderly population in Italy*. J Prev Med Hyg 2011;52:1-8.
- [30] Influnet. *Virological surveillance*. Available at: <http://www.iss.it/fluv/index.php?lang=1&anno=2017&tipo=13>. [Accessed 23/11/17].
- [31] Chit A, Roiz J, Briquet B, Greenberg DP. *Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors*. Vaccine 2015;33:734-41.
- [32] Perrotta D, Bella A, Rizzo C, Paolotti D. *Participatory online surveillance as a supplementary tool to sentinel doctors for influenza-like illness surveillance in Italy*. PLoS One 2017;12:e0169801.
- [33] Centers for Disease Control and Prevention (CDC). *Laboratory-confirmed influenza hospitalizations*. Available at: <https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html>. [Accessed 23/11/17].
- [34] Millman AJ, Reed C, Kirley PD, Aragon D, Meek J, Farley MM, et al. *Improving accuracy of influenza-associated hospitalization rate estimates*. Emerg Infect Dis 2015;21:1595-601.
- [35] Reed C, Chaves SS, Daily Kirley P, Emerson R, Aragon D, Hancock EB, et al. *Estimating influenza disease burden from population-based surveillance data in the United States*. PLoS One 2015;10:e0118369.
- [36] Li L, Wong JY, Wu P, Bond HS, Lau EHY, Sullivan SG, Cowling BJ. *Heterogeneity in estimates of the impact of influenza on population mortality: a systematic review*. Am J Epidemiol 2017 Jun 30. doi: 10.1093/aje/kwx270.
- [37] Arriola CS, Anderson EJ, Baumbach J, Bennett N, Bohm S, Hill M, et al. *Does influenza vaccination modify influenza severity? Data on older adults hospitalized with influenza during the 2012-2013 season in the United States*. J Infect Dis 2015;212:1200-8.
- [38] Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thoring S, Thomas RE. *Vaccines for preventing influenza in the elderly*. Cochrane Database Syst Rev 2010;CD004876.
- [39] Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. *Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy*. Am J Epidemiol 2012;176:527-33.
- [40] Coudeville L, Andre P, Bailleux F, Weber F, Plotkin S. *A new approach to estimate vaccine efficacy based on immunogenicity data applied to influenza vaccines administered by the intradermal or intramuscular routes*. Hum Vaccin 2010;6:841-8.
- [41] DiazGranados CA, Denis M, Plotkin S. *Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials*. Vaccine 2012;31:49-57.
- [42] Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, Tashkandi M, Bauch CT, Loeb M. *Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis*. BMC Med 2013;11:153.
- [43] Gazzetta Ufficiale della Repubblica Italiana. *Remunerazione delle prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale*. 28 Gennaio, 2013.
- [44] Nomenclatore tariffario delle prestazioni aggiuntive, Accordo Collettivo Nazionale medici generici, 23 marzo 2005. Available at: http://www.sisac.info/aree/www.sisac.info/resources/MEDICINA_GENERALE/ACN_testo_integrato.pdf.
- [45] Marchetti M, Kühnel UM, Colombo GL, Esposito S, Principi N. *Cost-effectiveness of adjuvanted influenza vaccination of healthy children 6 to 60 months of age*. Hum Vaccin 2007;3:14-22.

- [46] New DRG tariffs 2015. Available at: https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=0ahUKEwj41djStr3WAhUL4mMKHdAnDDEQFggsMAE&url=http%3A%2F%2Fnormativaservizirl.it%2Fport%2FGetNormativaFile%3FfileName%3D5641_DGR2014_2989_AllB3_TariffeDRG2015.xls&usq=AFQjCNF9tYVqpNvA297MD61vHMNRajjSs. [Accessed 12/10/17].
- [47] Heise ER. *Diseases associated with immunosuppression*. Environ Health Perspect 1982;43:9-19.
- [48] Bhat TA, Panzica L, Kalathil SG, Thanavala Y. *Immune dysfunction in patients with chronic obstructive pulmonary disease*. Ann Am Thorac Soc 2015;(12 Suppl 2):S169-75.
- [49] McElhaney JE, Herre JM, Lawson ML, et al. *Effect of congestive heart failure on humoral and ex vivo cellular immune responses to influenza vaccination in older adults*. Vaccine 2004;22:681-8.
- [50] Weinberger B, Herndler-Brandstetter D, Schwanninger A, Weiskopf D, Grubeck-Loebenstein B. *Biology of immune responses to vaccines in elderly persons*. Clin Infect Dis 2008;46:1078-84.
- [51] The European House Ambrosetti. Meridiano Sanità. *Le coordinate della salute. Rapporto 2017*. Available at: https://www.ambrosetti.eu/wp-content/uploads/Rapporto_MS2017.pdf. [Accessed 23/11/17].
- [52] Regione Emilia-Romagna. Legge Regionale 25 novembre 2016, n. 19. Available at: <http://www.regione.emilia-romagna.it/notizie/2016/novembre/adesso-e-legge-in-emilia-romagna-obbligatorio-vaccinare-i-bambini-per-iscriverli-al-nido/legge-regionale-19-del-25-novembre-2016>. [Accessed 23/11/17].
- [53] Pitrelli A. *Introduction of a quadrivalent influenza vaccine in Italy: a budget impact analysis*. J Prev Med Hyg 2016;57:E34-40.
- [54] Van Buynder PG, Konrad S, Van Buynder JL, Brodtkin E, Krajdén M, Ramler G, Bigham M. *The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly*. Vaccine 2013;31:6122-8.

■ Received on September 27, 2017. Accepted on November 27, 2017.

■ Correspondence: Marco Barbieri, via Cracovia 23, 40139 Bologna, Italy - E-mail: mc.barbier@libero.it