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Tetravalent Flu Vaccine in Italy: A Budget Impact Analysis (BIA)

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Abstract

Introduction: Influenza is an important problem of Public Health and source of costs: it's the main cause of school and work absences, GP (general practitioner) consultation, hospitalization for the possible implications as well as the third leading cause of death from infectious disease preceded by HIV and Tuberculosis. An Influenza Immunization Program is free and active and it is offered by the Italian Ministry of Health (MoH) for all subjects on the basis of age ≥ 65 years old and for all subjects at a higher risk despite their age or all those subjects that have pathologies that potentially increase the risk for ongoing complications of influenza. These subjects may be vaccinated by MMG (General Practitioners), PLS (family paediatrician) or USL's (Local Health Administration Unit) Vaccination Centre's. The Immunization Program takes place every year for three months, commencing from October until December with over 10 million subjects in Italy, of about 15 % of the population. From 2015 -2016, in addition to Trivalent Influenza Vaccine (TIV) Quadrivalent Influenza Vaccine (QIV) is also available. QIV protects against two lineages of virus B, solving the problem for partial and total mismatch: TIVs and QIV have a similar efficacy for what concern Virus A, and similar is their safety.

Aim of the Study: The study has been conducted in collaboration with GlaxoSmithKline, Italy's Payer and Evidence Solution Function through the use of a GSK's budget impact model. The potentially preventable influenza cases, influenza-related complications and hospitalization resulting from an incremental use of Tetravalent vaccine (QIV) in place of Trivalent (TIV) and the relative impact on budget has been analyzed.

Methods: Two scenarios were compared, a current one with data on the 2015-2016 flu immunization campaign, and a hypothetical one, which provides an increase in the market share of the QIV. The Budget Impact Analysis (BIA) considered the following input data.

- Population of the province of Viterbo.
- Distribution of 60.000 doses of vaccine between TIV and QIV
- epidemiology of influenza in Italy;

- efficacy of QIV vs TIV
- Direct influenza costs.
- Probability to require medical care for complications or hospitalization and related costs.

The analysis considered a single-year time frame due to the seasonality of the influenza immunization campaign.

Results: In the current scenario, if 35.0000 subjects are vaccinated with QIV, this will result in 1.801 cases among those vaccinated, 1.527 with complications, 176 of which will require hospitalization. In the hypothetical scenario, if 40.000 subjects were vaccinated with QIV, which is the 68 % of target population, 1.478 subjects will get sick, 1259 of which with complications and among them, 145 will be hospitalized. Therefore, the 10 % increase of QIV vaccine, would avoid 322 cases of influenza, of which 268 with complications and 31 hospitalizations. The ASL of Viterbo, thanks to a wider protection of the QIV versus TIV, would have a budget impact of -116.468 Euro. Infect, the cost sustained for the purchase of the vaccine, although increased by 2 % in comparison to the actual scenario, it is compensated by the savings originated by avoided cases of influenza, complications connected to influenza and hospitalization.

Conclusion: From the preliminary analysis of the data, concentrating on the exclusive costs of purchase of the vaccines, it is evident that the increase of QIV's quota market involves an increase of the costs, due to the greatest price of purchase, but overcoming the problematic match-mismatch of the lineage B, produces a saving of 116.468 euros. The study considered the doses of vaccine actually purchased for the influenza campaign in 2015-2016 but did not analyze age groups or administration to risk categories because the data was not available. The results obtained vary by modifying the vaccine's method of administration and the division of market shares, while maintaining the same number of doses purchased. The data can therefore be considered preliminary and to be verified on the field.

Keywords: Public Health; Influenza Research; WHO; Clinical Demonstrations

Abbreviations: GP: General Practitioner; TIV: Trivalent Influenza Vaccine; QIV: Quadrivalent Influenza Vaccine; BIA: Budget Impact Analysis; CIRI: Collaboration of the Interuniversity Centre for Influenza Research; WHO: World Health Organization.

Introduction

Influenza is problematic in Public Health and source of costs: it's the main cause of school and work absences, it is a motive for GP (general practitioner) consultation, emergency hospital admissions for possible complications and the third leading cause of death from infectious disease preceded by HIV and Tuberculosis [1].

Influenza is an extremely contagious disease, because through the mucous and droplets of saliva, the virus is easily be spread by airborne transmission (cough, sneezing, or even by talking very closely to someone) or indirectly (dispersion of droplets on surfaces and objects) [2]. The term influenza is often used improperly, attributing it to infections of the upper respiratory tract that can have both a bacterial nature and a viral nature [1].

But only after having carried out tests in the laboratory, one could speak of influence in order to verify the presence of one of the three influenza viruses recognized as etiologic agents of the disease, types A, B, C (the first two are the most responsible of disease in humans, while the C is of little relevance).

The analysis in the clinical practice test is rarely performed, so an international definition of influenza syndrome has been introduced, based on clinical demonstrations. Influenza means a clinical picture characterized by "acute respiratory disease with abrupt and sudden onset, with fever over 38 ° accompanied by at least one of the following symptoms: headache, generalized malaise, sweating, chills, asthenia and at least

one of the respiratory symptoms such as cough, pharyngodynia and nasal congestion "[1,2].

In Italy, there is an epidemiological surveillance activity called InfluNEet and serious and severe cases of active flu surveillance from 2000-2001 season [2,3]. In the 2015-2016 season, the InfluNet surveillance was coordinated by the National Health Epidemiology, Surveillance and Promotion Centre (CNPS) of the Higher Institute of Health (ISS), through the contribution of General Practitioners (MMG), Paediatricians of free Choice (PLS), hospital physicians and referents at the ASL and the Regions, as well as with the collaboration of the Interuniversity Centre for Influenza Research (CIRI) of Genoa [4]. In Italy, each year, the "Sentinel doctors" are recruited by the regions, both MMG and PLS, which are responsible for reporting each week the cases of influence observed among their patients and they collaborate to the collection of biological samples in order to identify circulating viruses [2]. During the 2015-2016 seasons the peak of influenza was reached during the eighth week of 2016 and an incidence of 6.1 cases was recorded for 1,000 people that assisted; The average age of severe cases was 57 years with a range of 0-95 and the deaths of 59 years [4].

The influenza vaccination in Italy is offered in an active form and free for people who have an age equal to or greater than 65 years and for all those individuals who belong to the so-called risk categories regardless of their age, or those who have pathologies that potentially increase the risk of ongoing complications of influenza [4]. These subjects may be vaccinated by MMG, PLS or at the ASL vaccination centers. In these cases the purchase is borne by the National Health Service (SSN), through the annual award of regional competitions. All those not included in the active and free offer can buy the vaccine at pharmacies to the public, with a doctor's prescription. The flu campaign in Italy every year involves over 10 million people in about 3 months from October to December, amounting to more than 15% of the population [5].

Not only trivalent influenza vaccines (TIV) but also tetravalent (QIV) are available from the 2015-2016 seasons [4]. TIVs contain antigens originating from 3 viral strains: A (H1N1), A (H3N2) and one of the two lineages B, between Victoria and Yamagata, according to the indications of the World Health Organization (WHO).

However, it may happen that the circulating B strain is not the one inserted in the TIVs thus providing limited protection. The 10 influenza seasons 2003-2004/2012-2013 have highlighted the variability of the circulation of virus B in Italy. The objective difficulty in choosing the circulating Lineage B, as well as the co-circulation of the two lineages B led the WHO and other scientific authorities to express in 2012 the necessity of a tetravalent vaccine, to ensure the insertion of the two lineages B in the influenza shot. The QIV completely protecting from influenza B, inherently solves the problem of the mismatch is partial, due to the co-circulation of both lineages B, both total, which is generated when there is no correspondence of the lineage B circulating with that TIV vaccine [6].

During the 2015-2016 season the InfluNet data reported that strain B circulated for 57% of cases, with 95% of lineage Victoria (Table 1) [7].

	41	42	43	44	45	46	47	48	49	50	51	52	53	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	TOT
FLU A	1	2	0	0	0	0	0	1	2	3	6	10	11	11	27	30	78	95	119	107	123	105	82	77	51	42	32	24	7	1.046
A									1				1	2	5	1	9	7	5	5	6	11	6	4	5	14	7	1	3	93
A(H3N2)		1	1					1	1	2	2	3	6	6	7	13	40	49	74	73	81	54	59	47	26	15	11	17	3	592
A(H1N1)pdm2009		1								1	4	7	4	3	15	16	29	39	40	29	36	40	17	26	20	13	14	6	1	361
FLU B	0	1	0	0	1	0	0	0	2	0	1	0	0	3	19	34	102	133	137	154	197	152	110	116	86	71	35	31	19	1.404
TOT POSITIVE	1	3	0	0	1	0	0	1	3	4	7	10	11	14	46	64	180	228	256	261	320	257	192	193	137	113	67	55	26	2.450*

Table 1: Results of the typing/subtyping of influenza viruses circulating in Italy (starting from week 41/2015), InfluNet source.

For the 2016-2017 seasons the WHO indicated the following composition of the vaccine for the Northern hemisphere:

Antigen similar to the A/California/7/2009 (H1N1) strain pdm09; A/Hong Kong/4801/2014 strain antigen (H3N2); b/Brisbane/60/2008 Strain antigen (b/Victoria) [4].

The most effective and efficient strategy to prevent the serious and complicated forms of influenza is vaccination, which makes it possible to reduce premature mortality in groups with increased risk of serious illness. A meta-analysis review carried out in 2015 by Cadeddu and Raponi [8] on the TIV in which the authors considered as outcome the cases confirmed influenza by laboratory

(LCC) and those clinically confirmed (CCC), it has emerged that the efficacy is between 59 and 67%. Moreover, with regard to safety, the authors declare that the reactions to influenza vaccines are constantly of a mild and transient nature, therefore of little clinical relevance. The age class with the highest number of reports was the one of the over sixty-five, i.e. that class where you have the highest levels of vaccination coverage. The reported adverse events are predominantly fever, headache, erythema, urticaria, local reactions: all reactions reported in the summary of the product characteristics of influenza vaccines. 55.8% of the reports concern skin and subcutaneous tissue diseases [8].

From a literature review carried out in 2015 by Tosatto, et al. [6] the tetravalent vaccine showed that the QIV against TIV protects against both lineages of virus B by resolving the mismatch problem both partial and total. With regard to the virus A the QIV has a super comparable efficacy compared to TIV, therefore the QIV does not cause further issues.

Materials and Methods

The objective of the study, which was carried out in collaboration with the function of Payers and Evidence Solution by GlaxoSmithKline Italia through the use of a model of impact on the Budget owned by GSK, was to analyze in the ASL of Viterbo the potentially avoidable cases of:

1. Influenza
2. Influenza related complications
3. Hospitalization resulting from an incremental use of tetravalent vaccination (QIV) in place of the trivalent (TIV) and its impact on the Budget.

The time horizon of the budget impact analysis was 1 year, considering the seasonality of the influenza vaccination.

Two scenarios were compared, a current one with data on the 2015-2016 influenza campaign, and a hypothetical one, which predicted an increase in the market share of the QIV as in table 2.

The Budget Impact Analysis (BIA) includes the following input data:

Scenario	Current scenario				Hypothetical scenario			
	Split	Flu adjuvanted	Intradermal 15 µg	QIV	Split	Flu adjuvanted	Intradermal 15 µg	QIV
Market share	17%	25%	0%	58%	16%	16%	0%	68%
Doses	10	15	0	35	10	10	0	40
Price	€ 2,10	€ 5,25	€ 5,29	€ 5,90	€ 2,10	€ 5,25	€ 5,29	€ 5,90

Table 2: Current scenario versus hypothetical – market share.

1. ISTAT population relative to the residents of the province of Viterbo updated to January 1, 2015 [9].
2. Distribution of 60,000 doses of vaccine divided into split, adjuvant and QIV as reported by the requirements expressed in the public bid of the Lazio Region for the ASL of Viterbo in relation to the year 2015 [10]. The division of market shares between the vaccines for the 2015-2016 seasons was provided by the E. Procurement of the ASL of Viterbo, which has the task of managing the purchases of the company and has relations with the Lazio region to indicate the requirements of Medicines and medical devices to be included in regional competitions [11].
3. Epidemiology of influenza in Italy, as reported by the Ministerial Circular "Influenza prevention and control: Recommendations for the 2016-2017 season" [4].
4. Effectiveness of the QIV versus TIV. Specifically, the data on the efficacy of TIV versus type A influenza were obtained from 3 meta-analyses of Jefferson, et al. [12,14] and the same values have been assimilated for the QIV. The efficacy of the TIV vaccine against influenza B was obtained from a meta-analysis of Tricco, et al. [15] which included 4 controlled and randomized trials. The efficacy against type B influenza of the QIV vaccine was equal to that of the trivalent vaccine in the case of matching. The overall efficacy of TIVs versus type B influenza was derived by pondering the data of Tricco, et al. For the circulation of the two lineages of virus B, applying the following formula: TIVs versus the influence of type B = (effectiveness of the TIV in the situation of match * B-matching) + (efficacy of TIV in mismatch situation * B-mismatching)
5. Costs of vaccines as reported by the award of the regional tender influenza vaccines of the Lazio region of 2015 [10].
6. Likelihood of medical care, complications and hospitalizations and related costs.

The data on the probability of requesting medical assistance from MMG and PLS following influenza was obtained from an article by Sessa, et al. [16] in which the authors in an observational study estimated that about 60%

of the subjects resort to such assistance. The risk of complications, hospitalization and death for each complication has been extrapolated from a study by Tappenden, et al. [17] stating that respiratory complications amounted to 90.77%, while the remaining 9.23% are cardiac, renal, acute otitis media, central nervous system and gastrointestinal related. By separating the various data reported in the article by Sessa, et al. [16] The specific complication rates for groups of patients defined by the age and the status of a person at risk have been obtained. It was assumed that the distribution by type of complication is uniform for groups of healthy-young, healthy-old, and risk-young, risk-old. Specifically, age-related RR and risk factors for the four groups were calculated as shown in table 3. The age distribution of vaccines delivered was considered in the 2015-2016 influenza campaign.

	RR age	RR risk	RR tot	Probability of complication
Healty and youth	1	1	1	26,27 %
Healty and old	1,789,474	1	1,789,474	47,00 %
Risk and youth	1	203,691,275	2,04	53,5 %
Risk ad old	1,789,474	203,691,275	3,645,002	95,7%
Average				35,1 %

Table 3: Age and complication RR calculations.

The costs of visits, antiviral and antibiotic therapies, and possible hospitalizations with related sources are given in tables 4 & 5. The above costs were discounted within the model per year 2013 [18-25]. The time taken to complete the analysis was one year, due to the seasonality of the influenza vaccination.

Cost categories	Cost (C)	Source
MMG (General Practitioners) or PLS (family paediatrician) visits	€20,66	Outpatient Performance Tariff 2013, Ministry of Health
Antiviral Therapy BB	€ 17,30	Unit cost: IMS sata, Dosing, from electronic Medicines Compendium (eMC) 2014.
Antiviral Therapy AA	€ 38,50	Unit cost: IMS sata, Dosing, from electronic Medicines Compendium (eMC) 2014.
Antibiotic therapy BB	€ 3,70	Esposito et al (2011)
Antibiotic therapy AA	€ 3,21	Iannazzo et al (2011)

Table 4: Visits and therapies costs, its source.

Complications	Cost (c)	Source
Ambulatory treatment Complications (execpt OM)	90,32 €	Marchetti (2007). Value of 80 Euro revalued at 2013. Monetary revaluation coefficient, 1.129.
Outpatient Treatment Otitis Media	56,45 €	Marchetti (2007). Value of 50 Euro revalued at 2013. Monetary revaluation coefficient, 1.129.
Bronchitis (hospitalization) < 18 years old	1.54 €	DRG 98 Bronchitis and Asthma < 18 age (2013)
Bronchitis (hospitalization) > 18 years old	1.83 €	DRG 98 Bronchitis and Asthma > 17 age (2013) without CC (2013)
Pneumonia (hospitalization) < 18 years old	1.95 €	DRG Simple Pneumonia and pleurised, < 18 years old
Pneumonia (hospitalization) > 18 years old	2.29 €	DRG simple Pneuminia and pleurised, > 17 years old wihout CC (2013)
URTI < 18 years old	5.77 €	DRG Infections and respiratory inflammations <18 years old (2013)
URTI > 18 years old	4.42 €	DRG Infections and respiratory inflammations > 17 years old without CC (2013)
Otitis media < 18 years old	662 €	DRG 69 Otitis media and upper respiratory tract infection > 17 years old

		without CC (2013)
Otitis media > 18 years old	1.25 €	DRG 91 Simple Pneumonia and pleurised, <18 years old (2013)
Gastrointestinal hemorrhage	2.09 €	DRG 175 Gastrointestinal hemorrhage without CC (2013)

Table 5: Outpatient treatment costs and hospitalization, relative source.

Results

As shown in table 2, 2 scenarios were compared, which differ in the market share of QIV versus TIV: specifically, the market share of split has shifted from 17% to 16%, that of the influenza adjuvant from 25% to 16% (both of these vaccines are trivalent), while there was an increase in the QIV of ten percentage points, from 58% of the current scenario to 68% of the hypothetical scenario. Both scenarios include 60,000 vaccinated subjects, with a vaccine coverage below that indicated by the Ministry of Health, whereas in the province of Viterbo are 321,955 residential inhabitants and without explaining the subdivision for Age groups or by mentioning the categories at risk [4,9].

The decision to increase the market share of QIV completely at the expense of the adjuvant was acquired within the Company Committee for General Medicine of the ASL of Viterbo, which in April 2015 agreed for the influenza campaign 2015-2016, together with MMG to reduce the amount of adjuvant vaccine and to introduce the tetravalent vaccine.

In the current scenario, vaccinating 35,000 subjects with QIV have 1,801 cases of influenza among the vaccinated, of which 1,527 will have complications, of which 176 will be hospitalized; in the hypothetical scenario, vaccinating 40,000 subjects with QIV, or 68% of the target population, those who fall ill are 1,478, of which 1,259 with complications, between these 145 hospitalized. Thus the increase of ten percentage points of the QIV vaccine would avoid 322 cases of influenza, of which 268 with complications and 31 hospitalizations (Table 6). The results of table 6 consider the efficacy data of vaccines, both in case of match and mismatch.

Scenario	Actual scenario QIV (58 %)	Hypotetical Scenario QIV (68 %)	Δ
Vaccinated subjects	60.000 of which 35.000 with QIV	60.000 of which 35.000 with QIV	_
Flu cases	1.801	1.478	-322
of which with complications	1.527	1.259	-268
of which hospitalizations	176	145	-31

Table 6: Cases of influenza, complications and hospitalization.

The ASL of Viterbo, thanks to the broader protection conferred by the QIV compared to the TIVS and the increase in the market share of the QIV, could achieve an impact on the budget of-116,468 euro. In fact, the cost incurred for the purchase of vaccines, although increased by 2% compared to the current scenario, is offset by the savings resulting from avoided cases of influenza, complications and admissions (Table 7).

Scenario	Actual scenario QIV (58 %)	Hypotetical Scenario QIV (68 %)	Δ
Vaccination	€ 307.23	€ 313.32	€ 6.09
Treatment of flu cases	€ 25.06	€ 20.57	-€ 4.48
Complications	€ 671.99	€ 553.92	-€ 118.07
of which hospitalizations	€ 551.35	€ 454.46	-€ 96.88
Total	€ 1.004.279	887.811	**€ - 116.468**
Incremental spending over the previous year 2%			

Table 7: Analysis of Budget impact.

Discussion and conclusions

From the preliminary analysis of the data, focusing on the exclusive costs of purchase of the vaccines, it is noted that the increase of the market share of the QIV entails an increase of the costs, because of the higher purchase price (Table 2) but the overcoming of the problematic Match

mismatch of lineage B, generates altogether a saving of 116,468 euro (Table 7).

The results obtained vary by modifying the vaccine administration logic and the division of market shares, while maintaining the same number of doses purchased. The data can therefore be considered preliminary and to be verified on the field. The WHO and the National Vaccine Prevention Plan 2017-2019 indicate as targets for influenza vaccination, in the over-sixty-five age group and risk groups including 75% as a viable minimum target and 95% as a target optimal.

At the moment we are very far from the above percentages, as confirmed by the survey "indicators-steps 2012-2015", where it is reported in the 18-64 year old patients with at least a chronic pathology at the national level a coverage equal to 21.4%, while in Lazio it even drops to 19.8% [26]. It would be interesting to hypothesize an increase in vaccination coverage by focusing attention on the categories at risk, i.e. all those subjects that have pathologies that potentially increase the risk of ongoing complications of influenza, so to be able to control the infectious disease better. The goal during the next influenza campaign will be to increase the vaccination needs, certainly focusing on the over 65, but concentrating equally on the categories at risk for which you are so far from the minimum coverage that should be pursued.

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References

1. Ministero della Salute.
2. Boccalini S, Pellegrino E, Bonanni P (2015) Epidemiologia dell'Influenza, Italian Journal of Public Health 4(5).
3. Istituto Superiore di Sanità.
4. Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2016-2017. Ministero della Salute.
5. General Directorate of Health Prevention. CCM Ufficio V ex DGPREV-Malattie Infettive e Profilassi Internazionale.
6. Marinello G, Tosatto R, Silvestri R (2015) La vaccinazione antinfluenzale in Italia: organizzazione e vaccini disponibili, Italian Journal of Public Health 4(5).
7. Tosatto R, Castagna S, Lapinet JA (2015) Il vaccino antinfluenzale quadrivalente Flu-QIV, Italian Journal of Public Health 4(5).
8. Higher Institute of Health, Virological surveillance of influenza.
9. Cadeddu C, Raponi M (2015) Efficacia e sicurezza del vaccine antinfluenzale trivalente inattivato (TIV). Italian Journal of Public Health 4(5)
10. Geo demo ISTAT. Demografia in cifre. Disponibile su.
11. Stazione Appaltante Centrale Acquisti Regione Lazio, Determinazione G10615 del 07/09/2015. Procedura aperta per l'aggiudicazione dell'Appalto Specifico per la fornitura di vaccini antinfluenzali (campagna antinfluenzale 2015/16). Approvazione graduatoria definitiva condizionata alla verifica del possesso dei requisiti di partecipazione.
12. Dari S, Verginelli F, Aquilani S (2014) Aspetti di farmacoeconomia collegati al vaccino antipneumococcico coniugato 13-valente nella ASL di Viterbo: analisi preliminare, Farmeconomia. Health economics and therapeutic pathways 15(4).
13. Jefferson T, Rivetti A, Harnden A, Di Pietrantonj C, Demicheli V (2008) Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2: CD004879.
14. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E (2018) Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2: CD001269.
15. Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer GA, Al-Ansary LA, et al. (2014) Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 3: CD001269.
16. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, et al. (2013) Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med 11: 153.
17. Sessa A, Costa B, Bamfi F, Bettoncelli G, D'Ambrosio G (2001) The incidence, natural history and associated

outcomes of influenza like illness and clinical influenza in Italy. Fam Pract 18(6): 629-634.

18. Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, et al. (2009) Amantadine, oseltamvir and zanamavirfor the prophylaxis of influenza (including a review of existing guidance no. 67): A systematic review and economic evaluation. HTA 3(11): 1-246.

19. Rate of outpatient specialist assistance services, Annex 3 to the Decree of the Ministry of Health.

20. 2014 Unit cost: IMS data, Dosing, from the electronic Medicines Compendium (eMC). Oseltamivir.

21. 2014 Unit cost: IMS data, Dosing, from the electronic Medicines Compendium (eMC). Zanamivir. Disponibile.

22. Esposito S, Cantarutti L, Molteni CG, Daleno C, Scala A, et al. (2011) Clinical manifestations and socio-economic impact of influenza among healthy children in the community. J Infect 62(5): 379-387.

23. Iannazzo S (2011) Pharmacoeconomic evaluation of the MF59 adjuvanted influenza vaccine in the elderly population in Italy. J Prev Med Hyg 52(1): 1-8.

24. Marchetti M, Ursula M Kuehnel, Giorgio L Colombo, Susanna Esposito, Nicola Principi (2007) Cost-Effectiveness of Adjuvanted Influenza Vaccination of Healthy Children 6 to 60 Months of Age. Human Vaccines 3(1): 14-22.

25. General series of the Ministry of Health, Rate of outpatient specialist assistance, Annex 3 to the Decree of 18/10/2012. Official Journal S23.

26. Indicators Steps 2012-2015.