

Evaluation of the economic impact produced by the prevention of events induced by the HPV 6-11 virus types contained in the quadrivalent vaccine.

Dr. Silvano Costa¹ and Dr. Giampiero Favato²

¹ Department of Obstetrics and Gynaecology, S. Orsola-Malpighi Hospital, Bologna, Italy

² School of Projects, Processes and Systems, Henley Management College, Henley, UK

Abstract

Although the integration of the fragmentary data concerning the total expenses borne for the early diagnosis and the treatment of HPV-induced pathologies is problematic, it is possible to break down the total burden of HPV-induced events into the leading determinants of cost. By entering the results obtained from several published studies into a model specifically designed to evaluate the economic effectiveness of the implementation of a multi-cohort vaccination strategy in Italy, it is possible to estimate the effect of the quadrivalent vaccine in terms of number of prevented events and the potential cost reduction. The quadrivalent vaccine should determine a significant cost-saving of 68.6%, corresponding to approximately 70 million euros.

Introduction

The exponential growth of healthcare demand urges that medical decisional processes are based on the comparison of alternative options that compete within an economical context characterized by limited resources. The same applies to those events which require a considerable fund allocation, like the prevention of the cervical cancer and of the main HPV-induced pathologies.

Although the integration of the fragmentary data concerning the total expenses borne for the early diagnosis and the treatment of HPV-induced pathologies is problematic, it is still possible to estimate a sufficiently reliable range of absorbed economical resources. In Italy, it has been estimated that every year the total cost of the HPV-related pathologies ranges between 200 and 250 million euros ^[1]. A significant portion of these costs, in excess of 210 million euros ^[2], is absorbed by the prevention and treatment of pre-cancerous lesions and invasive cervical cancer. This expense level, weighted by demographic dimensions and/or by macro-economic indicators (GDP, medical expenses in relation to the GDP) is however lower than the costs estimated for the U.S. (~1.7 billion dollars) and the Great Britain (~300 million euros) ^[3, 4].

Determinant of costs of HPV-induced events

On the ground of the most conservative data ^[1], it is possible to break down the total burden of HPV-induced events into the leading determinants of cost, according to what indicated in Table I.

Table I - Economic impact of the HPV-induced pathologies

Process	Estimated number of cases ^[3, 5-19]	Average cost (€)	Expense interval (€ in Ml)
Pap tests ^(a)	4,000,000 - 4,600,000	15	60.0 - 69.0
Abnormal Pap tests	315,000 - 415,000	15	4.7 - 6.2
Colposcopies	107,000 - 116,000	250 ^(c)	26.8 - 29.0
LSIL & ASCUS ^(d)	78,000 - 91,000	400	31.2 - 36.4
HSIL ^(e)	11,700 - 13,700	900	10.5 - 12.3
Cervix-carcinoma	3,500 - 4,000	16.700	58.5 - 66.8
Genital warts ^(f)	104,000 - 125,000	240	25.0 - 30.0
TOTAL COSTS			216.7 - 249.7

(a) = value calculated conservatively on the total female population deemed eligible for the screening (25-64 year old)

(b) = including a percentage of unsuitable samples

(c) = including pap test and colposcopy repetitions in the follow-up period

(d) = ASCUS (atypical squamous cells of undetermined significance); LSIL (Low grade Squamous Intraepithelial Lesions)

(e) = HSIL (High grade Squamous Intraepithelial Lesions)

(f) = unpublished data of the Henley Centre for Value Improvement, Henley Management College, Oxford, UK

Reduction of low-grade lesions and relative costs

By entering the results obtained from several published studies ^[20-24] into a model specifically designed to evaluate the economic effectiveness of the implementation of a multi-cohort vaccination strategy in Italy, it is possible to estimate the effect of the quadrivalent vaccine in terms of number of prevented events and the potential cost reduction. In particular, Table II indicates the number of the currently observed events and the expected maximum reductions of abnormal Pap tests, colposcopies, low-grade lesions and ASCUS, while Table III includes the valorisation of the cost reductions.

Table II - Yearly maximum theoretical projection of events that can be prevented with the quadrivalent vaccination compared to the HPV event cumulative incidence

Process	Initial events	HPV 6-11 Prevented events	HPV 16-18 Prevented events	HPV 6-11 effect (%)	HPV 16-18 effect (%)	Net total
Anomalous Pap tests	415,000	47,643	190,573	11.5%	45.9%	57.4%
Colposcopies	116,000	10,433	59,121	8.9%	51.0%	59.9%
LSIL & ASCUS	91,000	8,354	46,246	9.2%	50.8%	60.0%
Genital warts	125,000	112,500	--	90.0%	--	90.0%

The projection's results are consistent with the outcomes of a recently published case-control study on the prevalence of carcinogenic low risk HPV viruses (types 6 and 11) and high risk ones (types 16, 18, 31 and 33) [25]. On a total amount of 1,636 women with an abnormal Pap test, the HPV viruses, types 6 and 11, were the most frequently types recorded in the ASCUS category, (60.8% on the whole). In particular, in the 24.2% of the cases, it was HPV type 6 and in the 36.6% of the cases, it was HPV type 11.

The same frequency was observed in LSIL, where HPV 6 and 11 were the most frequently found types, with percentages of 12% and 23% respectively. These evidences confirm the previous observations on the high frequency of HPV 6 and 11 in women with a borderline cytology (percentages exceeding the 35% for ASCUS and the 42% for LSIL) [26, 27].

From the analysis of table III, it can be observed that the decrease of abnormal pap tests, colposcopies, pre-cancerous low-grade lesions and ASCUS induced by HPV 6-11, can determine cost reductions of 6.6 million Euros. If we add, to this value, the percentage of expenses that are allocated to the treatment of genital warts, which burden directly on the National Health Service at the rate of a minimum proportion of about 35% of the total, the cost reduction determined by the quadrivalent vaccine is bigger than 16 million euros.

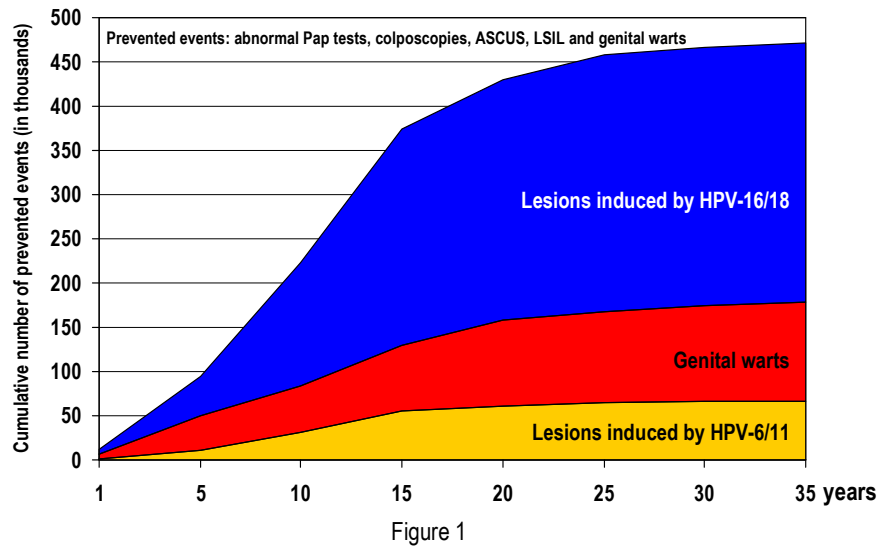
Table III - Yearly cost abatement achievable by the maximum theoretical reduction of low-grade preventable events

Process	HPV 6-11 Prevented events	Cost reduction (€ in Ml)	HPV 16-18 Prevented events	Cost reduction (€ in Ml)	Total reduction (€ in Ml)
Anomalous Pap tests	47,643	0.71	190,573	2.86	3.57
Colposcopies	10,433	2.6	59,121	14.8	17.4
LSIL & ASCUS	8,354	3.3	46,246	18.5	21.8
Total	66,430	6.6	295,940	36.2	42.8
Genital warts	112,500	27.0	--	--	27.0
TOTAL	178,930	33.61	292,117	36.2	69.8

Effects in time of the quadrivalent vaccination on the low-grade lesions and on the genital warts

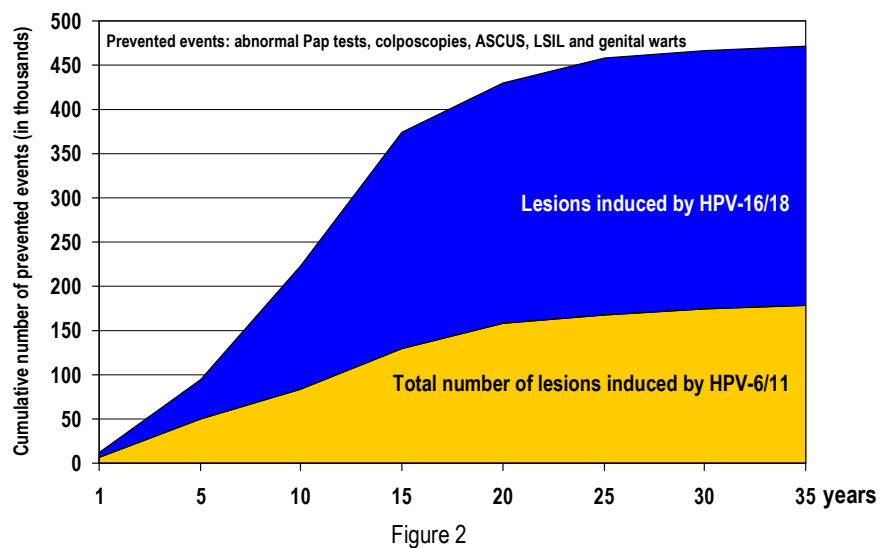
The model evaluating the overall effectiveness of the multi-cohort vaccination strategy, provides also the possibility to identify other clinical indicators (i.e. prevented events) and economic indicators (i.e. break-even point and vaccination convenience) which are useful to establish the investment level compatible with the available resources in order to ensure equitable access and offer parity to the female population deemed eligible to vaccination. As a result, the 3-cohort vaccination strategy is the most cost-effective option. Taking into account the above mentioned considerations, it is possible to make a projection of the low-grade lesions over time (Figure 1).

Longitudinal projection of the reduction of low-grade lesions



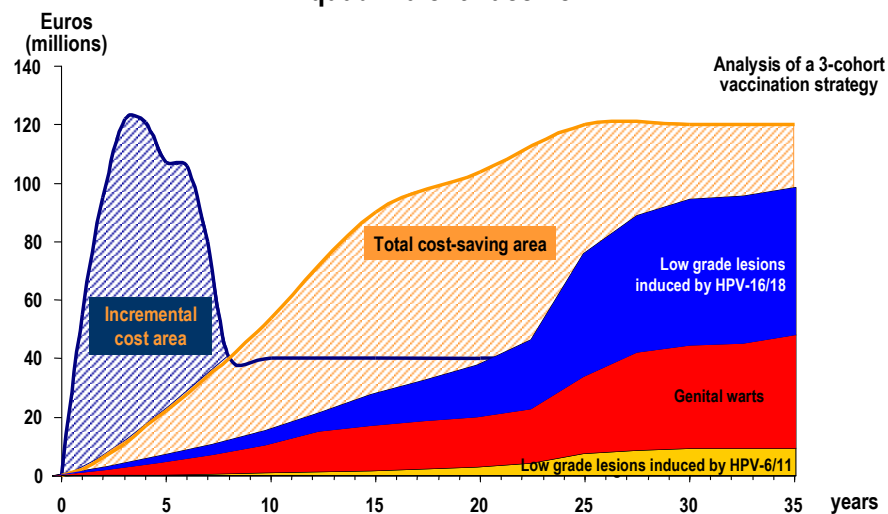
Genital warts excluded, the HPV 6 and 11 contained in the quadrivalent vaccine are responsible for the decrease of the low-grade lesions in the $18.4\% \pm 0.2\%$ of the total cases (range: 18.2% - 18.6%). Taking into account the genital warts, the contribution of HPV 6 and 11 is even more evident (Figure 2). In this case, the percentage rises to $43.2\% \pm 6.5\%$ (range: 34.8% - 53.1%).

Longitudinal projection of the reduction of low-grade lesions



By repeating the same process, with cost variables only, it is possible to obtain a projection of cost-savings connected with the prevention of low-grade lesions, as a result of the use of the quadrivalent vaccine. Figure 3 shows both the curve related to the resources necessary for the implementation of the multi-cohort vaccination program (incremental costs), and the total savings limiting curve. By adding the cost-savings of the low-grade lesions induced by HPV 6-11 to those of the averted genital warts, the value of potential reduction of the costs for the quadrivalent vaccine is of about 34 million euros (Figure 4).

Projection of total costs and savings connected to the use of the quadrivalent vaccine



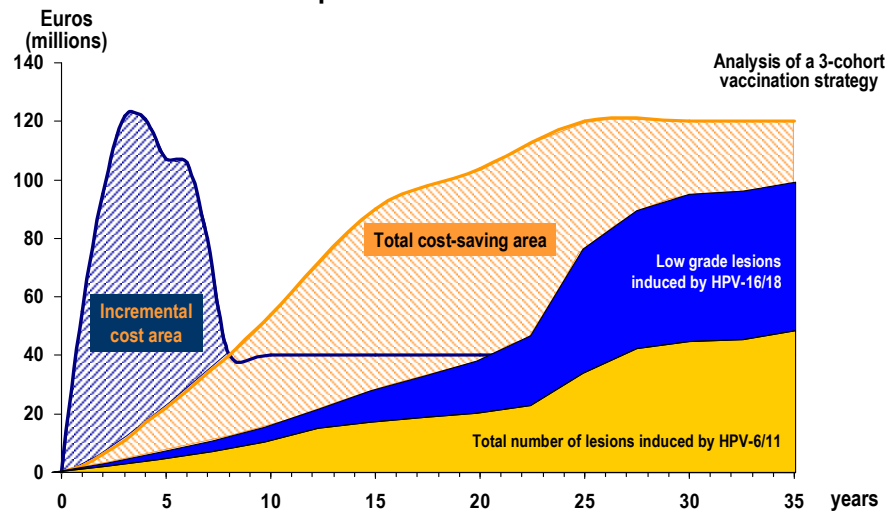
Modified by Favato G. et al. [1]

Figure 3

In conclusion, comparing the total reduction of costs for the low-grade lesions and genital warts with the expenses currently borne to manage these pathologies (corresponding to approximately 102 million euros), the quadrivalent vaccine should determine a considerable cost-saving of 68.6% (equivalent to approximately 70 million euros).

The solution to the problem of the effectiveness of resource allocation in the health sector cannot merely be based on the persistent search for the lowest price for required goods or services. An objective «spending review» that allows qualifying the costs and make economical and profitable strategic choices cannot be disregarded to provide diagnostic instruments, drugs and vaccines that are innovative and characterized by a high technological content. For vaccines, these considerations take an even more relevant importance. In fact, as also suggested by the World Health Organization, making public health choices exclusively on the ground of prices can be chancy and anti-economic [28].

Projection of total costs and savings connected to the use of the quadrivalent vaccine



Modified by Favato G. et al. [1]

Figure 4

References

1. Favato G, Pieri V, and Mills RW. Cost-effective analysis of anti-HPV vaccination programme in Italy: a multi-cohort Markov model. **Henley Discussion Paper Series**, February 2007 no. 13. **Henley Centre for Value Improvement**, Henley Management College, Henley on Thames, UK
2. Giorgi Rossi P, et al. The burden of cervical diseases caused by human papillomavirus in Italy. 5th **International Conference on Cervical Cancer (ICCC)**. Venice, Italy, April 13th - 15th, 2007. **ICCC 2007**
3. Brown, RE Costs of detection and treatment of cervical cancer, cervical dysplasia and genital warts in the UK. **Current Medical Research and Opinion** 2006; Vol 22 (4): 663-670
4. Brown M.L. et al. Estimate health care costs related to cancer treatment from SEER-Medicare data. **Medical Care** 2002; 40 (suppl. 8): IV-104-117
5. Franceschi S. HPV e prevenzione. **GISCI (Gruppo Italiano Screening del Cervicocarcinoma) National Congress; Rome, April 20-21 2006**. <http://www.gisci.it/aggiornamento/Relazioni/Roma2006/franceschi/index.htm> (last accessed on September 2006)
6. Ferlay J, et al. GLOBOCAN 2002: cancer incidence, mortality, and prevalence worldwide. **International Agency for Research in Cancer** 2004. Cancer Base n. 5
7. Karnon J. et al. Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. **Health Technology Assessment** 2004; Vol. 8 (20): 1-90
8. **Ministero della Salute**. Dati SDO 1999-2003. (http://www.ministerosalute.it/programmazione/sdo/ric_informazioni/default.jsp)
9. **Istituto Superiore di Sanità**. La mortalità per causa in Italia: 1980-2002. (<http://www.iss.it/site/mortalita/Scripts/Uscita.asp>)
10. Cancer Incidence, Mortality and Prevalence Worldwide - GLOBOCAN 2002. Descriptive Epidemiology Group of International Agency for Research on Cancer (**IARC**). <http://www-dep.iarc.fr>
11. Leyden WA. et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. **Journal of the National Cancer Institute** 2005; 97: 675-683
12. Del Turco M, Zappa M. et al. **Osservatorio Nazionale Screening - Quarto Rapporto**, 2005
13. Holowaty P. et al. Natural history of dysplasia of the uterine cervix. **Journal of the National Cancer Institute** 1999; 91: 252-258
14. Östör AG. Natural history of cervical intraepithelial neoplasia: a critical review. **International Journal of Gynaecological Pathology** 1993; 12: 186-192

15. Syrjänen KJ. Spontaneous evolution of intraepithelial lesions according to the grade and type of the implicated human papillomavirus (HPV). **European Journal of Obstetrics & Gynaecology and Reproductive Biology** 1996; 65: 45-53
16. Ho GY et al. Natural history of cervicovaginal papillomavirus infection in young women. **The New England Journal of Medicine** 1998; 338:423-428
17. Gonzalez DI. et al. Recurrence of dysplasia after loop electrosurgical excision procedures with long-term follow-up. **American Journal of Obstetrics and Gynaecology** 2001; 184: 315-321
18. Kim JJ. et al. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. **Journal of the National Cancer Institute** 2005; 97: 888-895
19. Clifford GM, Rana RK, Franceschi S, et al. Human papillomavirus genotype distribution in low grade cervical lesions: comparison by geographic lesions and with cervical cancer. **Cancer Epidemiol Biomarkers Prev** 2005; 14: 1157-64
20. The FUTURE II Study Group. Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions. **The New England Journal of Medicine** 2007; 356: 1915-1927
21. The FUTURE I Study Group. Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases **The New England Journal of Medicine** 2007;356:1928-1943
22. The FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. **The Lancet** 2007; Vol 369: 1861-1868
23. BROWN D. The Future Study Group. HPV type 6/11/16/18 vaccine: first analysis of cross-protection against persistent infection, cervical intraepithelial neoplasia (CIN), and adenocarcinoma in situ (AIS) caused by oncogenic HPV types in addition to 16/18. 47th **Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)**. Chicago, U.S.A., September 17-20, 2007. ICAAC 2007. Abstract G-1720b
24. Villa L. for the FUTURE I and II Study Group. Quadrivalent human papillomavirus (hvp) type 6/11/16/18 l1 virus-like particle vaccine: first analysis of cross-protection against cervical intraepithelial neoplasia (cin) and adenocarcinoma in situ (ais) caused by oncogenic hvp types in addition to 16/18. **EUROGIN 2007**; Monaco October 4-6. Abstract SS2-2
25. Panotopoulou E, Tserkezoglou A, Kouvousi M, et al. Prevalence of human papillomavirus types 6, 11, 16, 18, 31, and 33 in a cohort of Greek women. **J Med Virol** 2007; 79: 1898-1905
26. Myers ER, McCrory DC, Nanda K, et al. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. **Am J Epidemiol** 2000; 151: 1158-1171

27. Evans MF, Adamson CS, Papillo JL, et al. Distribution of human papillomavirus types in ThinPrep Papanicolaou tests classified according to the Bethesda 2001 terminology and correlations with patient age and biopsy outcomes. *Cancer* 2006; 106: 1054-1064
28. **World Health Organization.** Immunization financing, supply and procurement. Posted by: WHO, Geneva, Switzerland, 3 February 2006. http://www.who.int/immunization_supply/en/ (last accessed on December 2007)