Institution: Kingston University

Unit of Assessment: 19, Business and Management Studies

Title of case study: Policy change on male HPV vaccination in Italy

1. Summary of the impact

Research by G Favato of Kingston University established that it is cost-effective to vaccinate males against the HPV virus, overturning previous studies that had suggested such vaccination was not cost-effective.

This research was presented to the Italian Agency for Drug Approval (AIFA). As a result, AIFA changed its vaccination policy for HPV, removing its previous restriction of vaccination to females only and approving vaccination also for males.

The Italian regions of Emilia-Romagna and Sicily have now begun voluntary vaccination programmes for males under 26, with economic benefits amounting to €98.9 million. In addition, Emilia-Romagna has introduced a vaccination programme for HIV-infected males under 26, providing health benefits for a high-risk sub-population.

2. Underpinning research

HPV-related genital cancers and genital warts are increasingly seen as a major public health concern, and vaccination is now available in all European countries.

The Italian Agency for Drug Approval (AIFA) first approved the HPV vaccine Gardasil in February 2008 for 9-26 year olds. Previous economic studies had suggested that vaccinating males was not incrementally cost effective, so the programme was restricted to females. This programme delivered health benefits, but population coverage could be suboptimal and it did not address HPV-related health outcomes for men.

In 2007, Giampiero Favato produced a novel multi-cohort cost-effectiveness analysis of HPV vaccination in Italy, based on a Markov simulation. (This work was produced prior to Favato joining Kingston University.)

In 2010, after he had joined Kingston University, Favato joined the BEST (Bayesian modelling assessing the Effectiveness of a vaccination Strategy To prevent HPV-related diseases) research team. The BEST study was designed to assess, using a Bayesian approach, the cost-effectiveness of a multi-cohort vaccination study. Favato's contribution to this study was to develop his earlier Markov simulation into a more sophisticated Bayesian model, that would form the core economic model of the research programme.

The BEST study concluded that a vaccination program that includes both boys and girls can be considered to be a multi-cohort strategy. In such a vaccination program, involving girls and boys aged 12 years, with reduced levels of coverage, cost-effectiveness can be improved as a result of the increased clinical benefits from herd immunity. When the combined clinical benefits for both sexes were considered, the costs per quality-adjusted life year (QALY) gained were below the established cost thresholds. Thus, in contradiction to earlier studies, the vaccination of males was shown to be cost-effective.

In particular, the research showed the following benefits of universal vaccination:

- **Health benefits of vaccination occur faster**. Less time is required to reduce HPV-related outcomes with a two-cohort vaccination than with vaccination of a single cohort of girls aged 12 years. In particular, the clinical benefits of vaccination are expected to occur 3.8 years earlier with universal vaccination [2].
- **Equality of access to healthcare is improved**. The Burden of Disease study showed that the economic burden attributable to non-cervical HPV-related diseases is higher among men than among women (60.6% vs. 39.4% of the total, respectively). The economic burden among men represented more than one third (38.8%) of the total direct costs of HPV-related diseases. [3]
- **Reduced health care costs**. The two-cohorts strategy results in a mean net reduction in cost

of €80 million to the Italian government (95% CI, h40.1–h144.7 million) due to the prevention of HPV-related diseases [1] [4]. This figure stems from the reduced cost of €12,013 per QALY gained (95% CI, €2,364 - €22,481), which is significantly below the €30,000 per QALY gained considered the threshold of good value for money. The GIOVE(Governance of preventive Health Intervention and On time Verification of its Efficiency) study [3] confirmed the allocative efficiency of the resources used for the multi-cohort vaccination programme. The two-cohort vaccination is a public health intervention that is sustainable from both an organisational and an economic point of view [2] [3].

- **Reduced uncertainty**. The Economic Value of Information (EVI) is a key parameter in decision analysis because it tests the robustness of results by taking into account several dimensions of uncertainty. The EVI indicates how much a rational decision maker should be willing to spend in order to eliminate uncertainty. The EVI presented in the research (<€13 per patient) implies that the uncertainty that is currently present in the model parameters has a very limited impact and is more robust than previous models [1]. This finding was confirmed by the real option valuation of competing HPV immunization programmes, which challenged the cost effectiveness dominance of a single cohort of 12-year old girls. The simultaneous vaccination of 2 cohorts yielded a real option value (€17,723) equivalent to that attributed to a single cohort (€17,460) [6].

Key Researcher: Giampiero Favato, Professor of Accounting and Finance, Kingston University 2010-present.

3. References to the research

[1] Mennini, F.S., Costa, S., **Favato, G**. and M. Picardo (2009) "Anti-HPV vaccination: A review of recent economic data for Italy", *Vaccine*, Vol 27, A54-61.

Journal ranking: Vaccine is the pre-eminent journal for those interested in vaccines and vaccination. 2011 Impact Factor: 3.766

[2] **Favato, G**., Baio, G., Capone, A. Marcellusi, A., Costa, S., Garganese, G., Picardo, M., Drummond, M. Jonsson, B., Scambia, G. Zweifel, P. and F. Mennini (2012) "Novel Health Economic Evaluation of a Vaccination Strategy to Prevent HPV-related Diseases: the BEST Study". *Medical Care*, Vol. 50, No 12, pg 1076-1085.

Journal ranking: Public, Environmental, and Occupational Health 18/157; Health Care Sciences and Services 7/76; 2011 Impact Factor: 3.411

Note: In early 2013, this paper was reviewed by the National Institute for Health Research Centre for Reviews and Dissemination (CRD), with the research selected for publication in the NHS Economic Evaluation Database. The CRD database provides the NHS with information on the effectiveness and cost-effectiveness of treatments, and the delivery and organisation of health care.

[3] Mennini, F., Baio, G., Montagano, G., Causzillo, G. Locuratolo, F. Becce, G., Gitto, L, Marcellusi, A., Zweifel, P. Capone, A. and **G. Favato**. (2012) "Governance of preventive Health Intervention and On time Verification of its Efficiency: the GIOVE Study", BMJ Open vol 2 no 2 doi:10.1136/bmjopen-2011-000736

Journal ranking: Peer-reviewed, open access journal of BMJ. 2012 Impact Factor: 1.583.

[4] Baio, G., Capone, A., Marcellusi, A., Mennini, FS. and **G. Favato**. (2012) "Economic Burden of Human Papillomavirus-Related Diseases in Italy" *PLoS ONE* 7(11):e49699. doi:10.1371/journal.pone.0049699

Journal ranking: open access peer-reviewed scientific journal published by the Public Library of Science. 2011 Impact Factor: 4.092

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Research Centres funding scheme.

[5] Mennini, F.S., Marcellusi, A., Baio, G., Haeussler, K., **Favato, G**. and A. Capone, PRM142 "Loss of health utilities due to hpv-induced diseases in men and women: A multicenter italian study", *Value in Health*, Volume 16, Issue 3, May 2013, Page A38, ISSN 1098-3015, 10.1016/j.jval.2013.03.219.

(http://www.sciencedirect.com/science/article/pii/S1098301513002908)

Note: *Value in Health* is the official journal of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). This multidisciplinary publication has an impact factor of 3.433 offers an outlet for discussion and debate about the principles and substance of pharmacoeconomics and outcomes research.

[6] **Favato, G**.., Baio, G., Capone, A. , Macellusi, A. and F.S. Mennini "A Novel Method to Value Real Options In Health Care: The Case of a Multicohort Human Papillomavirus Vaccination Strategy", *Clinical Therapeutics*, Volume 35, Number 7, 2013, pg. 904-914.

Journal ranking: this journal has a 5 year impact factor of 2.746.

4. Details of the impact

The research produced health-economic Italian evidence which demonstrated that HPV vaccination in males is cost-effective. These research outcomes were incorporated into a reimbursement dossier produced by Sanofi Pasteur Merck [1], prior to their publication in the open literature.

The company submitted this dossier to AIFA in December 2011 to obtain reimbursement for Gardasil HPV vaccination to males. On 18 September 2012, on the basis of the submitted dossier, AIFA approved Gardasil for HPV vaccination to males, changing its indications as follows: "Gardasil is a vaccine indicated from 9 year of age….." [2].

Any reference to gender is now removed, thus approving and reimbursing Gardasil for use in both males and females after 9 years of age.

The funding of the anti-HPV immunisation was limited to a national school programme targeting 12 year old girls by the 2012-2014 National Plan of Preventive Vaccination (PNPV, approved earlier on March 2012) [3]. Individual regions had only two options to extend the vaccination coverage to boys:

1. Immunising individuals at risk (HIV infected boys, already included in the PNPV funding);
2. Voluntary vaccination of boys with the HPV vaccine charged at regional tender cost at no incremental cost to the regions.

In November 2012, two regions (Emilia-Romagna and Sicily) took one or both options [4].

Both of these regions have undertaken voluntary vaccination of 11-26 year old males. With an effective coverage of 80%, the total savings accruing from this vaccination programme are €98.9 million

In addition, Emilia-Romagna undertook the immunisation of HIV-infected males up to 26 years old resident in the region. This programme provides immunisation benefits to a high-risk sub-population at a relatively modest total cost of €40,273

The economic benefits of this policy change were estimated in collaboration with the Italian Agency for Drug Approval (AIFA) [5].

The medical benefits of the anti-HPV immunisation of a cohort of males also include:

1. Overall health benefits of a universal vaccination
2. Improved health outcomes for men, who represent more than one-third total direct costs of HPV related disease
3. Improved 'herd immunity' resulting from vaccinating a larger percentage of the population.

5. Sources to corroborate the impact

[1] Sanofi Pasteur Merck reimbursement dossier to AIFA called “GARDASIL suspension for injection”. The main contribution of Kingston economic research to the lengthy dossier is covered on pages 27-35 in the section titled: “Cost –effectiveness of the Quadrivalent Vaccine in Men” (annotated copy available – translated from Italian)

[2] New approval (18 September 2012) by AIFA for vaccine Gardasil for boys and girls from 9 years of age. (Annotated copy available – translated from Italian)

[3] 2012-2014 National Plan of Preventive Vaccination (PNPV) in Supplemento ordinario n. 47 of the Gazzetta Ufficiale n. 60 (General Series), 12 March 2012. Available online at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1721_allegato.pdf

[4] Istituto Superiore Sanita’ (ISS). Stato di avanzamento della campagna vaccinale per l’HPV: dati di copertura vaccinale 31/12/2012. Rapporto Semestrale. Available online at: http://www.epicentro.iss.it/problemi/hpv/pdf/Aggiornamento_HPV_31122012.pdf

[5] Director of Italian Agency for Drug Approval (AIFA). Economic impact of Gardasil vaccination. 19th September 2013. (Corroborating Statement Identifier: 1)