

The Bayesian Model on Human Papillomavirus Vaccination in Italy Lacks Transparency

To the Editor:

We refer to a recently published article¹ that shows a new Bayesian method, applied to assess a vaccination strategy preventing human papillomavirus (HPV)-related diseases. The article basically describes a model for the economic evaluation of the quadrivalent HPV vaccine in Italy, concluding that it is a cost-effective strategy. Although any model, Bayesian or Frequentist, should be “populated” with reliable data,² we felt some concern about many “inputs” regarding the Italian setting that could weaken the authors’ conclusions. We have listed some of the main ones.

- Real data on Italian vaccination coverage are referenced by an abstract,³ without specifying that this refers to a very small region in Italy (Basilicata, 0.97% of the whole Italian population). Thereafter, table 1 refers for vaccination compliance and coverage to another article, published in Italian, focussed on the efficacy of the quadrivalent vaccine.⁴
- Data on health states associated with HPV-related diseases refer to another abstract,⁵ then unspecified Italian utility weights for health states were applied, but to our knowledge, no utility tariffs have been validated so far in Italy.
- Utilities of cervical cancer, genital and cervical lesions, all refer to an article on the costs of varicella-related hospitalizations in table 1.⁶
- The vaccine price is not consistent with published data,⁷ and we could not find the figure used as a mean (€69.13, see table 1) in the references.^{8,9}

More in general, the authors state that the cost-effectiveness of the quadrivalent vaccine is proven, ignoring the other, bivalent vaccine against HPV. As 3 recent critical reviews^{10–12} on economic evaluations regarding HPV

vaccines—not cited in the article—concluded that long-term models on HPV vaccination lack transparency in key assumptions and methodological choices, we wonder whether the results of this model (producing a “virtual” follow-up of 90 y) can really be considered more reliable than the others already published.

Livio Garattini, PhD,

Katelijne van de Vooren, MSc

CESAV, Center for Health Economics
“Mario Negri” Institute for Pharmacological
Research, Ranica, Italy

The authors declare no conflict of interest.

REFERENCES

1. Favato G, Baio G, Capone A, et al. Novel health economic evaluation of a vaccination strategy to prevent HPV-related diseases: the BEST Study. *Med Care*. 2012;50:1076–1085.
2. Weinstein MC, O’Brien B, Hornberger J, et al. ISPOR Task Force on good research practices—modeling studies. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on good research practices—modeling studies. *Value Health*. 2003;6:9–17.
3. Mennini FS, Baio G, Montagano G, et al. Governance of preventive health intervention and on time verification of its efficiency in a region of southern Italy. Health Technology Assessment International (HTAi) society, 7th annual meeting, Dublin, Ireland, 6th–9th June 2010. Abstract M5-18 176–177.
4. La Torre G, Chiaradia G, de Waure C, et al. Systematic review and meta-analysis of clinical trials on the efficacy of the quadrivalent HPV vaccine. HTA reports of quadrivalent anti-HPV vaccine, Gardasil. *Ital J Public Health*. 2009;2(suppl 2):S25–S32. [Italian].
5. Mennini FS, Panatto D, Cristoforoni P, et al. The time-trade off approach to measure patients’ preferences for health states associated with HPV-related pathologies: a multi-center study performed in Italy. Health Technology Assessment International (HTAi) society, 7th annual meeting, Dublin, Ireland, 6th–9th June 2010. Abstract M5-53; p. 192.
6. Azzari C, Massai C, Poggiolesi C, et al. Cost of varicella-related hospitalizations in an Italian paediatric hospital: comparison with possible vaccination expenses. *Curr Med Res Opin*. 2007;23:2945–2954.
7. Garattini L, Van de Vooren K, Curto A. Pricing human papillomavirus vaccines: lessons from Italy. *Pharmacoeconomics*. 2012;30:213–217.
8. Mennini FS, Giorgi Rossi P, Palazzo F, et al. Health and economic impact associated with a

quadrivalent HPV vaccine in Italy. *Gynecol Oncol*. 2009;112:370–376.

9. Ferrandina G, Marcellusi A, Mennini FS, et al. Hospital costs incurred by the Italian National Health Service for invasive cervical cancer. *Gynecol Oncol*. 2010;119:243–249.
10. Koleva D, De Compadri P, Padula A, et al. Economic evaluation of human papilloma virus vaccination in the European Union: a critical review. *Intern Emerg Med*. 2011;6:163–174.
11. Newal AT, Beutels P, Wood JG, et al. Cost-effectiveness analyses of human papillomavirus vaccination. *Lancet Infect Dis*. 2007;7:289–296.
12. Puig-Junoy J, Lopez-Valcarcel BG. Economic evaluations of massive HPV vaccination: within study and between study variations in incremental cost per QALY gained. *Prev Med*. 2009;48:444–448.

Transparency or Proper Study Valuation Procedures Missed?

OPEN

To the Editor:

We wish to thank the Editor for giving us the opportunity to think about and resolve a few potential issues with our paper. Garattini and colleagues have questioned the meaningfulness of the evidence used to inform some of the crucial parameter used in our model. This is because of a misalignment in the reference list, as a result of which, Table 1 in the paper points to the wrong references. We have fixed this and present the corrected version of Table 1 below.

Incidentally, we notice that the online appendix to the paper¹ actually has all the correct references and describes in detail all the aspects of the modeling presented in the paper. We find it slightly bizarre that Garattini and colleagues have taken such a critical stance on our work, but have failed to cross-check the most technical aspects with all the available material.

Garattini and colleagues also raise a few criticisms to our general methodology. Firstly, they question the relevance of data from the region of Basilicata on the parameter representing vaccination coverage. We would like to

TABLE 1. Distribution of Variables Used in the Model

Variable Description	Distribution	Vaccine-related Parameters		References
		Mean	95% CI	
Vaccine efficacy	Informative LogNorm	0.7830	0.6830	FUTURE II Study, FUTURE I Study and La Torre et al ^{16,17,18}
Vaccine compliance	Flat Beta	1.0000	0.9990	Mennini and colleagues, ^{13,19}
Vaccine coverage rate	Flat Beta	0.8470*	0.8340	Mennini and colleagues, ^{13,19}
Cross-protection effect	Informative LogNorm	0.0740	0.0410	Brown and colleagues, ^{20,21}
Efficacy decrease due to noncompliance	Informative Beta	0.5040	0.3110	FUTURE II Study ¹⁶
Probability of the level of compliance with vaccination programmed	Flat Dirichlet	0.0000	0.0000	Mennini and colleagues, ^{13,19}
1 dose	Flat Dirichlet	0.0000	0.0000	
2 doses	Flat Dirichlet	0.0000	0.0000	
3 doses	Flat Dirichlet	1.0000	0.9999	
Clinical Parameters				
Exposure→Infection				
12–15 y	Informative LogNorm	0.0020	0.0000	Ronco and colleagues, ^{22–26} EC
16 y	Informative LogNorm	0.0240	0.0060	
17–18 y	Informative LogNorm	0.0750	0.0620	
19–22 y	Informative LogNorm	0.1540	0.1260	
23–29 y	Informative LogNorm	0.1210	0.1030	
30–33 y	Informative LogNorm	0.0600	0.0560	
34–49 y	Informative LogNorm	0.0370	0.0350	
≥ 50 y	Informative LogNorm	0.0120	0.0120	
Infection→Exposure				
12–24 y	Informative Beta	0.7190	0.6480	Ronco and colleagues, ^{22–24,26} EC
25–29 y	Informative Beta	0.6990	0.5940	
30–39 y	Informative Beta	0.3500	0.2820	
40–49 y	Informative Beta	0.2010	0.1110	
≥ 50 y	Informative Beta	0.0990	0.0570	
Infection→CIN1	Informative Beta	0.1100	0.0660	Ronco and colleagues, ^{22–25}
Infection→CIN2	Informative Beta	0.0220	0.0140	Ronco and colleagues, ^{22,23,25,26}
Subject to coinization				
CIN1→CIN2	Informative Beta	0.1200	0.0420	Ronco and colleagues, ^{22,23,26} EC
CIN1→CIN3	Informative Beta	0.0400	0.0230	Ronco and colleagues, ^{22–27} EC
CIN2→CIN3	Informative Beta	0.1400	0.1040	Ronco and colleagues, ^{22–28} EC
CIN3→Cancer	Informative Beta	0.0150	0.0070	Ronco and colleagues, ^{22–28} EC
CIN1→Clearance	Informative Beta	0.8990	0.8350	Ronco and colleagues, ^{22–28} EC
CIN2→Clearance	Informative Beta	0.8600	0.8160	Ronco and colleagues, ^{22–28} EC
CIN3→Clearance	Informative Beta	0.8610	0.8190	Ronco and colleagues, ^{22–28} EC
Not subject to coinization				
CIN1→CIN2	Informative Beta	0.2240	0.1570	Ronco and colleagues, ^{22,23,26} EC
CIN1→CIN3	Informative Beta	0.0750	0.0570	Ronco and colleagues, ^{22–27} EC
CIN2→CIN1	Informative Beta	0.2500	0.2040	Canfell and colleagues, ^{23,25} EC
CIN2→CIN3	Informative Beta	0.3500	0.3010	Ronco and colleagues, ^{22–28} EC
CIN3→CIN1	Informative Beta	0.0200	0.0050	Ronco and colleagues, ^{22–28} EC
CIN3→CIN2	Informative Beta	0.0300	0.0070	Ronco and colleagues, ^{22–28} EC
CIN3→Cancer	Informative Beta	0.0500	0.0240	Ronco and colleagues, ^{22–28} EC
CIN1→Clearance	Informative Beta	0.710	0.6000	Ronco and colleagues, ^{22–28} EC
CIN2→Clearance	Informative Beta	0.3550	0.2040	Ronco and colleagues, ^{22–28} EC
CIN3→Clearance	Informative Beta	0.2850	0.1620	Ronco and colleagues, ^{22–28} EC
Probability of coinization in CIN1				
Immediate	Informative Beta	0.3020	0.2090	Giorgi Rossi et al ²⁷

(Continued)

TABLE 1. Distribution of Variables Used in the Model (continued)

Variable Description	Distribution	Vaccine-related Parameters			References
		Mean	95% CI		
Delayed	Informative Beta	0.1700	0.1500	0.1890	EC
Probability of diagnosis without screening					
CIN2	Informative Beta	0.0250	0.0000	0.1040	EC
CIN3	Informative Beta	0.0760	0.0570	0.0960	
Anogenital warts					
Recurrence	Informative Beta	0.4250	0.2390	0.6130	French et al, ²⁹ EC
Cost parameters					
Diagnostic procedures					
Pap test [†]	Informative LogNorm	17.14	14.25	20.78	Italian Ministry of Health ³⁰
Colposcopy [‡] and biopsy	Informative LogNorm	54.23	49.00	59.41	
HPV DNA test	Informative LogNorm	78.98	77.04	81.03	Nomenclatore Tariffario ^{31,32}
Precancerous cervical lesions					
CIN1	Informative LogNorm	303.52	225.87	398.59	Giorgi Rossi and colleagues, ^{27,33}
CIN2	Informative LogNorm	1,339.36 [§]	1,021.73	1,718.62	Giorgi Rossi et al ²⁷
CIN3	Informative LogNorm	1,759.96	1,329.54	2,244.73	Giorgi Rossi et al ²⁷
External genital lesions					
Anogenital warts	Informative LogNorm	283.88	243.83	332.59	Costa and colleagues, ^{33,34}
Cervical cancer					
FIGO I	Informative LogNorm	14,430.32	2,644.27	46,689.52	Ferrandina et al ³⁵
FIGO II	Informative LogNorm	24,499.29	8,455.06	52,861.89	
FIGO III	Informative LogNorm	37,808.01	4,833.33	129,962.51	
FIGO IV	Informative LogNorm	35,350.52	2,719.00	156,840.72	
Vaccination					
Cost per dose	Informative LogNorm	69.13	60.16	79.58	
Administration cost [¶]	Informative LogNorm	6.77	5.07	8.97	Menmini and colleagues, ^{7,36}

Variable	Variable Description	Distribution	Utilities		References	
			Mean	95% CI		
u^{E^w}	External genital lesions					
	Anogenital warts	Informative Beta	0.6870	0.3530	0.9190	Menmini et al ⁴⁰
	Precancerous cervical lesions					
	CIN1	Informative Beta	0.8220	0.4360	0.9940	Menmini et al ⁴⁰
	CIN2	Informative Beta	0.8070	0.4710	0.9850	
	CIN3	Informative Beta	0.8040	0.4700	0.9820	
	Cervical cancer					
	FIGO I	Informative Beta	0.5850	0.2500	0.8800	Menmini et al ⁴⁰
	FIGO II	Informative Beta	0.5310	0.2330	0.8090	
	FIGO III	Informative Beta	0.5660	0.3780	0.7530	
	FIGO IV	Informative Beta	0.4510	0.1770	0.7500	

The notation A → B indicates the transition from state A to state B; EC, assumption based on data provided by expert clinicians; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

[†]Coverage rate extracted from the vaccination register of the Basilicata Region.^{13,19}

[‡]Approximately 75% of Pap tests are performed using conventional cytology and 25% with liquid-based cytology.

[§]A gynecologic office visit (at a fee of 20.66 Euro) is included.³⁰

^{||}Calculated considering that CIN2 account for 45% of all high-grade cervical lesions (CIN2, CIN3, and adenocarcinoma in situ—AIS).²⁷

[¶]The price range is based on Regional tenders that occurred during 2008 and 2009 in Italy.

^{**}Included in this value are costs generated by additional medical consultations induced by mild adverse effects of vaccination. We assumed that approximately 1.8% of vaccinees require an additional visit to a general practitioner.

point out that, although not covering a very large area, Basilicata was the only Italian region to implement a multicohort vaccination program, including 4 cohorts of girls aged 12, 15, 18, and 25 years. The empirical evidence derived by the Basilicata vaccination register has been published in a full paper (the GIOVE study²). In addition, this information is not used at face value, but the uncertainty underlying the estimation is fully acknowledged and propagated through the entire Bayesian model. The prior distribution of parameters that play a relevant role in the cost-effectiveness of vaccination, such as coverage rates in 4 cohorts, were drawn directly from the real-world data (information uniquely registered in the Basilicata Region) rather than from assumptions. The rates of coverage are particularly important when levels $\leq 50\%$ are achieved in a single cohort of girls; and in this situation, a vaccination including a cohort of both boys and girls can improve the cost-effectiveness as a result of the increased clinical benefits determined by herd immunity. Actually, we must be wondering whether the most economic and clinically effective decision is provided by the immunization of both sexes or by an increase in the coverage rate in a single cohort of females. Probably, the latter might be more complicated and less effective than expected. Increasing the coverage rate may require complex interventions, a long period of time, and a significant incremental cost that could determine a diseconomy of scale. Truly, a scarce result when compared with the huge investment that is needed to increase the baseline rate value by 1 percentage point. Our study reported some indirect and preliminary indication; however, a specific Bayesian dynamic model addressing the cost-effectiveness of a vaccination program that includes a cohort of boys and girls has already been designed and results will be assessed and published shortly.

As for patients' health-state preferences, we agree with Garattini and colleagues that they represent a highly sensitive variable for the economic evaluations. In this case, we developed an algorithm for the fully computerized administration of a Time Trade-Off questionnaire; this was validated and published in 2011.³ In that publication,

the standardized elicitation of utilities was focused on cervical intraepithelial neoplasia (grades 2 and 3), anogenital warts, and cervical cancer exclusively.³ Thus, to include a broader range of human papillomavirus (HPV)-induced pathologies (which were indeed considered in the model developed in the BEST study) and a larger sample size, we used data from an ongoing study that involved >450 patients. Preliminary results from this large study have been communicated or presented in several congresses (including HTAi⁴) and the overall evaluation will be published as soon as it is completed. We believe that it is noteworthy that the elicitation of each utility used to inform our model relied on a solid and well-acknowledged procedure.^{3,5,6} Similarly to the point we have made earlier, by using a fully Bayesian model, we incorporated the uncertainty in the estimated values of utilities.

Another issue is about the vaccine price. We modeled this parameter using a probability distribution eliciting the information about the mean unit price of €69.13 and encoding the assumption that 95% of the most plausible values were included in the interval between €60.16 and €79.58. This was based on Regional tenders that occurred in 2008 and 2009 in Italy. Although in a commentary published in early 2012,⁷ neither an accurate mean price nor a SD were specifically reported for HPV vaccines, a mean price per quadrivalent vial seems to be very close to the range of values we used to inform our model. Although an effective public health intervention is not exclusively a matter of price,⁸ any value below the lower limit of the range adopted in our study would have had a favorable effect on the cost-effectiveness of the vaccination strategy that we evaluated using a Bayesian framework.

Finally, Garattini and colleagues wonder about the reliability of the results of our model. We are seeking to produce a structured research program, building on the findings of the GIOVE study, which was related to the effectiveness of a multicohort quadrivalent-based vaccination program. Consequently, the BEST study was specifically designed to assess the cost-effectiveness of this predefined vaccination strategy. Although a potential direct comparison evaluating the

most cost-effective option between the 2 available vaccines might be interesting, this is an objective that was not consistent with the aim of the BEST study.

Although some biological characteristics of HPV are uncertain, the value of information derived from current clinical trials is improved and the accuracy is increased by the incorporation of prior information in a Bayesian modeling. Further, prior distribution of parameters significantly influencing the impact of vaccination (ie, coverage rates and risk factors having an effect on the dynamic transmission of HPV infection) were directly drawn from the health programs already implemented in Italy and not from assumptions. Although financing and sustaining immunization programs are health governance challenges that public health authorities have to deal with, an assessment of a multicohort or both sexes vaccination strategy with a Bayesian model can inform decision-makers with more reliable data about both the cost-effectiveness of interventions as well as its budgetary implications. In conclusion, Bayesian analytic models have a wide range of uses and can be deemed as important and powerful tool for economic evaluations in health care.⁹

Especially when associated with the expected value of information, Bayesian models can provide with an accurate valuation of any future implementation of a quadrivalent-based HPV vaccination program.

Giampiero Favato, PhD*

Gianluca Baio, PhD††

Alessandro Capone, MD*

Andrea Marcellusi, MSc§

Silvano Costa, MD||

Giorgia Garganese, MD¶

Mauro Picardo, MD#

Mike Drummond, PhD**

Bengt Jonsson, PhD††

Giovanni Scambia, MD¶

Peter Zweifel, PhD††

Francesco S. Mennini, MSc§

*Institute of Leadership and Management in Health, Kingston University

†Department of Statistical Science

University College London, London, UK

‡Department of Statistics, Biostatistics Unit, University of Milano-Bicocca, Milan

§Centre for Health Economics and Management, Faculty of Economics

University of Tor Vergata, Rome

||Department of Gynecology and Obstetrics
S. Orsola-Malpighi Hospital
University of Bologna, Bologna
¶Department of Obstetrics and Gynecology
Catholic University of the Sacred Heart
#Laboratory of Cutaneous Pathophysiology
San Gallicano Dermatological
Institute (IRCCS), Rome, Italy
**Centre for Health Economics Alcuin
A Block, University of York, Heslington, UK
††Stockholm School of
Economics, Stockholm, Sweden
‡‡Socioeconomic Institute, University of
Zurich, Zurich, Switzerland

The authors declare no conflict of interest.

This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

REFERENCES

1. Favato G, Baio G, Capone A, et al. Novel health economic evaluation of a vaccination strategy to prevent HPV-related diseases. The BEST Study. *Med Care*. 2012;50:1076–1085. The full text of the Supplementary Appendix is available for download from the following Web site: <http://links.lww.com/MLR/A330>.
2. Mennini F, Baio G, Montagnano G, et al. Governance of preventive health intervention and on time verification of its efficiency: the GIOVE study. *BMJ Open*. 2012;2:e000736. doi:10.1136/bmjopen-2011-000736.
3. Mennini FS, Panatto D, Marcellusi A, et al. Time Trade-Off procedure for measuring health utilities loss with Human papillomavirus-induced diseases: a multicenter, retrospective, observational pilot study in Italy. *Clin Ther*. 2011;33:1084–1095.
4. Mennini FS, Panatto D, Cristoforoni P, et al. The time-trade off approach to measure patients' preferences for health states associated with HPV-related pathologies: a multicenter study performed in Italy. Health Technology Assessment International (HTAi) Society 7th Annual Meeting. Dublin, Ireland, June 6-9, 2010. Abstract M5-53; p. 192.
5. Torrance GW, Tomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res*. 1972;7:118–133.
6. Furlong W, Feeny D, Torrance GW, et al. Guide to design and development of health-state utility instrumentation. Full text available for download from the following website: <http://www.chepa.org/Files/Working%20Papers/WP%2090-9.pdf>. Originally accessed on September 2009 and controlled on January 2013.
7. Garattini L, van de Vooren K, Curto A. Pricing human papillomavirus vaccines: lessons from Italy. *Pharmacoeconomics*. 2012;30:213–217.
8. Capone A, Favato G. Human papillomavirus vaccination is not exclusively a matter of price. *Pharmacoeconomics*. 2012;30:443–444.
9. Baio G. Bayesian Methods in Health Economics. Boca Raton FL: CRC Press; 2012.

Erratum

To the Editors:

The letter by Garattini et al (The Bayesian Model on HPV Vaccination in Italy Lacks Transparency) being published in this issue of *Medical Care* gave us the opportunity to reread our entire paper (Favato G, Baio G, Capone A, et al. Novel Health Economic Evaluation of a Vaccination Strategy to Prevent HPV-related Diseases: The BEST Study. *Med Care*. 2012;50:1076–1085) and check every reference reported in the study. Unfortunately, we discovered that, due to our error, some of the references listed in Table 1 were misaligned in the published paper. The corrected table can be found in this issue in our response to the letter by Garattini et al (Transparency or Proper Study Valuation Procedures Missed?).

We regret the error and appreciate the opportunity to correct it.

Dr Gianluca Baio
Department of Statistical Science, University College London
Gower Street
London WC1E 6BT
UK
E-mail: gianluca@stats.ucl.ac.uk