PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Governance of Preventive Health Intervention and On Time Verification of its Efficiency: the GIOVE study
AUTHORS	F.S. Mennini, G. Baio, G. Montagano, G. Cauzillo, F. Locuratolo, G. Becce[3], L. Gitto, A. Marcellusi, P. Zweifel, A. Capone and G. Favato

VERSION 1 - REVIEW

REVIEWER	T.A. Westra PhD-student Health Economics & Modelling Department Medical Microbiology Moleular Virology section University Medical Center Groningen Groningen, the Netherlands I'm a recipient of an unristricted education grant from GlaxoSmithKline (Zeist, the Netherlands)
REVIEW RETURNED	03/02/2012

GENERAL COMMENTS	I think this is a relevant and well written paper and is acceptable for publication. However, I have some further comments/suggestion to improve the current version. - It would be of high interest if a more international perspective would be used. This is relative easy to achieve to apply different screening programs (age range of women included in the programme and screening interval). - Although this is not a finding of the authors it is of interest that the ICER of the quadrivalent vaccine is significant lower than the ICER of the bivalent vaccine. Indeed the benefits of prevention of genital warts might have a contribution to this. However, as genital warts is not a life threatening disease the ICER per LYG of the quadrivalent vaccine should be comparable to the ICER of the bivalent vaccine or even worse. How can this difference be explained? page 6 introduction - In Italia women are screened relative frequently once every 3-years. If women will be screened less frequently how does this alter the outcome? Would it be more efficient to screen women less frequently since the introduction of HPV vaccination - In other countries the bivalent vaccine has been introduced. Is the efficiency of the bivalent vaccine significant different?In other words, maybe the authors can show the efficiency of an HPV16/18 vaccine - Can the authors explain why the economic results of a multi cohort model are more favorable? Vaccination at older age seems to be

	less effective as some women will be already infected with HPV - The authors use the allocative efficiency, predicted by the bound optimization model, of 59.6% for different age groups. Is this 'threshold' not age specific as the vaccination of older girls might be less efficient. - The duration of vaccine induced protection is highly uncertain. It would be of interest if the authors could add a scenario in which vaccine induced immunity wanes after for example 20 years. - Are the costs discounted? If yes which rate was applied and to which moment? - A major limitation of the current study is that a static model is used. The benefits of herd-immunity might further improve the results. Maybe the authors should adress this in more detail in the discussion. The shortly mention herd-immunity however how does herd-immunity influence the outcome? - The relevance of the paper could be stated more clearly. Based on the results can we conclude that policy makers should aim to only vaccinate 60% of 12-year old girls?

REVIEWER	Americo Cicchetti, Professor of management, Università Cattolica del Sacro Cuore, Roma, Italy
REVIEW RETURNED	17/01/2012

THE STUDY	The abstract should be more clearly written. Methods and Results should be more detailed The english should be revised.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: T. A. Wastra

2. It would be of high interest if a more international perspective would be used. This is relative easy to achieve to apply different screening programs (age range of women included in the programme and screening interval).

3. In Italy women are screened relative frequently once every 3-years. If women will be screened less frequently how does this alter the outcome? Would it be more efficient to screen women less frequently since the introduction of HPV vaccination

4. In other countries the bivalent vaccine has been introduced. Is the efficiency of the bivalent vaccine significant different? In other words, maybe the authors can show the efficiency of an HPV16/18 vaccine

5. The duration of vaccine induced protection is highly uncertain. It would be of interest if the authors could add a scenario in which vaccine induced immunity wanes after for example 20 years.

Although all the above questions are relevant and insightful, the Authors felt that their discussion would fall beyond the objectives and the scope of the research, aimed to estimate the efficient allocation of resources between two anti-HPV prevention programmes given a number of constraints established ex-ante. Actually, frequency and coverage of screening, choice of the anti-HPV vaccine, multi-cohort immunisation strategy and maximum allowable budget were already set since the beginning of the vaccination programme in Basilicata. The research question was aimed to set the most efficient coverage rate, given the constraints and the uncertainty (including the length of

immunity) and to monitor its implementation after 12 months. We took the opportunity to clarify this point by adding the given sets of constraints on page 7, by clarifying the boundaries of the research objectives on page 8 and 9 and by adding a sensitivity analysis to the key parameters of the bound optimisation model on page 14 and 15 (paragraphs highlighted in yellow). A Figure was also added (now Figure 1 on page 23). The sensitivity analysis is intended to give a feel of the elasticity of the optimal vaccination coverage to the main inputs of the model, therefore providing an indirect answer to most of the points raised above.

6. Are the costs discounted? If yes which rate was applied and to which moment?

As the analysis refers to an actual 12-month time period, both cost and budget values have not been discounted. This comment was added on page 11 (paragraph highlighted in yellow).

7. A major limitation of the current study is that a static model is used. The benefits of herd-immunity might further improve the results. Maybe the authors should address this in more detail in the discussion. The shortly mention herd-immunity however how does herd-immunity influence the outcome?

This point was already addressed on page 16 (paragraph highlighted in green) and further discussed on page 16 and 17 (paragraph highlighted in yellow)

8. The relevance of the paper could be stated more clearly. Based on the results can we conclude that policy makers should aim to only vaccinate 60% of 12-year old girls?

The Authors are reluctant to reach this conclusion. A four-cohort vaccination programme was one of the ex-ante constraints. Based on the outcome of the bound optimisation model, the only acceptable conclusion is that, given the ex-ante constraints (including the multi-cohort immunisation) the optimal coverage rate of vaccination was 59.6% at a vaccine price of €100 per vial and 69.5% at €85 per vial. The actual vaccination rate achieved after 12 months was 72.8%, reasonably close to the most effective allocation of resources.

9. Although this is not a finding of the authors it is of interest that the ICER of the quadrivalent vaccine is significant lower than the ICER of the bivalent vaccine. Indeed the benefits of prevention of genital warts might have a contribution to this. However, as genital warts is not a life threatening disease the ICER per LYG of the quadrivalent vaccine should be comparable to the ICER of the bivalent vaccine or even worse. How can this difference be explained? page 6 introduction

Fair point. The following statement was added on page 6 (paragraph highlighted in yellow): “The difference in the economic evaluation of the two anti-HPV vaccines were mostly determined by the quadrivalent’s efficacy in preventing anogenital warts, a non-life threatening HPV-induced disease.”

10. Can the authors explain why the economic results of a multi cohort model are more favourable? Vaccination at older age seems to be less effective as some women will be already infected with HPV

This point is clearly addressed on page 6 (paragraph highlighted in green), then on page 16 (mid page, paragraph highlighted in green), then in the Figure 3 (on page 25) and in the reference 19. As the multi-cohort vaccination was one of the ex-ante constraints anyway, the Authors felt to have given adequate space to its discussion.

11. The authors use the allocative efficiency, predicted by the bound optimization model, of 59.6% for different age groups. Is this ‘threshold’ not age specific as the vaccination of older girls might be less efficient.

The relative efficiency of the cohorts was not one of the parameters included in the model since the choice to vaccinate four cohorts was made ex-ante. The four-cohort model does take into consideration the relative efficiency of the cohorts, reaching the conclusion that a multi-cohort approach is cost effective when compared to a single cohort of 12 year old girls. Actual data on the vaccination rate by cohort are reported on page 14 (paragraph highlighted in green).

Reviewer 2: Prof. Americo Cicchetti
12. The abstract should be more clearly written. Methods and Results should be more detailed

The abstract was fully revised and the Methods and Results section completely re-written.

13. The English should be revised.

The Authors reviewed the English to the best of their ability. The manuscript could be reviewed by a professional English editing service, if the Editor of BMJ Open believes it is necessary. The turnaround would require at least a couple of extra weeks.

Kind regards,

Prof. Francesco Saverio Mennini.