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Letter to the Editor

The use of an "old-fashioned method" to assess the clinical and economic impact of a HPV vaccination program

Dear Sirs,

The appraisal of the HPV vaccination effectiveness is a very complex procedure. Many interdependent variables such as coverage rates, dynamics of viral transmission, duration of vaccine protection, and the underlying assumptions can dramatically affect the expected result. Since an assessment of two significantly different and not directly comparable vaccines (also due to widely different populations included in randomized clinical trials) was performed, the effort of Capri et al. was even harder. Naturally the higher the uncertainty the less is the Value of Information that can be provided for an effective public health decision-making process.

When an assessment of a new health technology is carried out, the identification of the proper model is needed. Actually, HPV vaccination has three potential goals: to prevent infection, to prevent disease, and to prevent transmission. Unfortunately, at present not all the sequential phases of this knotty process are perfectly known. In order to find out a useful solution, some authors used dynamic probabilistic models [1], others static ones with large reiterate computational-based sensitivity analyses such as the Monte Carlo technique [2] and finally other research groups developed a mix of both [3]. Despite these advanced methodologies, an excess of uncertainty associated with the main parameters of commonly utilized models can still be observed. The old-fashioned method adopted by Capri et al. to evaluate the cross-protection effect of vaccines seems to be excessively reductive and probably inadequate to explain the natural history of HPV-related diseases as well as the potential full clinical and economic benefits derived from HPV vaccination. Indeed, their evaluation is based on a simple multiplication of vaccine efficacy, HPV prevalence in diseases and annual number of cases, which does not reflect the multifactorial evolution of HPV and vaccines' impact over years. The herd immunity effect was not considered either. Indeed, this would generate important additional benefits when a quadrivalent HPV vaccination is implemented, especially in terms of anogenital warts avoided (in both genders). In addition, since several HPV-related events (i.e. abnormal Pap smears, CIN1, and anogenital warts) could be averted earlier right after the vaccination begins, the time horizon in the study by Capri et al. has completely neglected the early economic benefits associated with vaccination, in particular with the quadrivalent vaccine.

Using a management cost for anogenital warts of €332, as reported in an Italian study adopted as reference [4], the conclusion of the authors would have been completely reversed with an additional cost averted of 2.4 million per year generated by the quadrivalent vaccine in comparison to the bivalent vaccine. If the variation of a single parameter may completely turn over a basic finding of this study, it is likely that the so-called "straightforward model" is not suitable to assess the HPV vaccination impact.

According to the best practice in health technology assessment [5] and as mandatorily requested, in this study some sensitivity analyses were performed to test robustness of results to a variation of assumptions, costs and outcome parameters. Nevertheless, the evaluation by Capri et al. leaves some relevant issues unaddressed or biased. As a consequence, a large body of uncertainty and doubt is associated with the evidence determined in this study.

First, the underrepresented differences between vaccine efficacy and effectiveness are reasonable to be considered as an unconvincing methodological rationale which should require special attention in each study design. Moreover, accurate efficacy data or a metanalysis instead of proxies for efficacy is recommended.

Second, it would have also been relevant to perform sensitivity analyses on vaccines' cross-protection efficacy against other high-risk HPV genotypes, since this is the main driver of the authors' conclusion. Cross-protection data used for the bivalent vaccine (68.4% against CIN2+ lesions) [6] could be overestimated. Indeed, in additional analyses required by the FDA in the USA, an efficacy rate of 37% against CIN2+ lesions induced by any of 12 non-vaccine HPV genotypes was reported [7].

Third, the quality and relevance of all data sources should be critically expanded and a more balanced inclusion of different sources of data would be appropriate. Prevalence rates of HPV-16 and 18 in CIN2–3 and cervical cancer are lower than those reported in Europe [8]. As a consequence, an overestimation of the burden related to other high-risk HPV genotypes would have been determined. Moreover, HPV-6 and 11 play a significant role in the burden of HPV-related diseases whereas in the authors' reporting, the contribution of low-risk HPV genotypes resulted simply negligible. In a recent study involving 1047 ASCUS patients, it was shown that HPV-6 and 11 accounted for approximately 20% of all CIN1 lesions [9]. Similarly, in a study published in 2008 [10] it was calculated that the expected annual number of anogenital warts in the Italian female population between 14 and 64 years corresponded to 118,160 (3.9-fold greater than that reported in the study by Capri et al.). A comparable value was also recently provided by the Italian National Institute of Health (around 250,000 cases per year among male and female population) [11]. Moreover, the considered direct cost of anogenital warts management was underestimated by 2.3-fold as well [4]. Although a proportion of anogenital warts can be treated in a private setting, the source [12] and the cost they used do not properly reproduce the Italian context.

Finally, findings from previous studies suggest that cross-protection would provide minor additional benefits compared with those derived from HPV genotypes directly targeted in vaccines [13–15]. Indeed, Jit et al. showed that cross-protection benefits accounted for 13% of total costs avoided while prevention of anogenital warts represented 48% [2].

In conclusion, since the modeling method and some of the data used may have biased the results and lead to misleading deductions, the study by Capri et al. did not improve the usefulness of already existing findings about the HPV vaccination. More accurate probabilistic models such as those based on a non-frequentist approach could be taken to surely reduce the uncertainty associated with HPV vaccination.

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Conflict of interest statement
The authors declare that there are no conflicts of interest.

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