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EDITORIAL

Pricing of HPV Vaccines in Europe: Back to the Future?

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1 HPV Background

Human papilloma viruses (HPV) can cause sexually transmitted infections, which in some cases persist and progress to cancer. Among the 201 HPV genotypes so far identified, more than 40 have been classified as high- and low-risk types according to their risk of progression to cancer [1].

Cervical cancer (CC) is the second most common cancer in women worldwide (about 55,000 new cases every year in Europe), and almost 100% of these are caused by HPV infection [2], which is also associated with other much less frequent cancers such as anal (around 90% of cases related to HPV in Europe), vulvar (15%), vaginal (70%), and penile (30–40%) cancers. Finally, HPV infection causes benign lesions such as genital warts (GWs) and recurrent respiratory papillomatosis (RRPs).

2 HPV Vaccination

HPV vaccination, the first available against a cancer, is now well established in most European countries [3]. Originally reimbursed only for girls in Europe, it has since been extended to boys in a few countries such as Austria and Italy. Besides protecting boys from anal cancers and lesions, male extension potentially implies 'herd immunity' for unvaccinated subjects once a high coverage rate has been achieved, as with any universal vaccination [4]. However, according to the World Health Organization, the priority of HPV immunization should still remain CC prevention through the immunization of only girls before they become sexually active [5].

The bivalent and quadrivalent vaccines have been marketed since 2007 in Europe [6]. Both protect against types 16 and 18, those most frequently associated with CC (around 70% of cases) and also provide some level of cross-protection against high-risk types 31, 33 and 45 [5], with recent evidence particularly for the bivalent vaccine [7, 8]. The quadrivalent vaccine further protects against types 6 and 11, which are responsible for around 90% of benign GWs and RRPs. Initially administered on a three-dose schedule, since 2014 both vaccines have now been reduced to two doses for adolescents [9].

The European Medicines Agency (EMA) approved the nonavalent vaccine in 2015 [2]; this includes five further high-risk oncogenic genotypes (31, 33, 45, 52, and 58) over the quadrivalent vaccine. The main advance offered by the new vaccine should be to raise the protection against CC from around 70 to 90% of cases.

3 HPV Vaccine Prices

The first HPV vaccines were by far the most expensive of all available vaccines at the time of their launch [6], with ex-factory prices around €100 per dose in most European countries. Since these unusually high prices might have been a major hurdle for vaccination programmes, many health authorities in Western European countries opted for competitive tenders including both vaccines. To account for the difference between the two vaccines in the preventions of GWs, a 'quality score' in favour of the

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quadrivalent vaccine is often added in tender clauses [9] so as not to consider only the best price offered.

The real HPV vaccine prices have fallen steeply over the last few years in many European countries, thanks to competitive tendering. For instance, the price per dose in Italy dropped under €30 in recent regional tenders [10] and even sunk under €20 in the Netherlands [11]; experts commonly felt there were similar drops in national tenders in Sweden and the UK (both countries where awarded prices are kept confidential) [12].

This experience showed that prices can drop steeply even when competition is minimal, i.e. only two manufacturers, if vaccines are judged basically equivalent by health authorities for their main health target, i.e. CC prevention in the case of HPV vaccination.

4 Policy Implications

The nonavalent vaccine is the element of novelty in HPV vaccination, and its main clinical advantage should be to increase CC prevention from around 70 to 90%. This new vaccine might also dramatically modify the 'market arena' of HPV vaccines. Being marketed by the same manufacturer as the quadrivalent vaccine, its launch was presumably planned to 'cannibalize' the latter, which is perfectly understandable from a research-oriented industry expecting high returns on investments [13]. However, particularly in this period of economic difficulties and limited public expenditure, health authorities must strive to fully exploit their purchasing power on behalf of citizens, as they have done successfully so far for HPV vaccination in many European countries.

On the basis of the existing clinical evidence [5, 7, 8], it might be hard to consider the nonavalent vaccine a true 'breakthrough' innovation. Rather, the new HPV vaccine might be considered an incremental innovation compared with the two already existing vaccines, which induce some cross-protection on three of the five extra genotypes included in the nonavalent version.

Having agreed on this preliminary assessment, we strongly recommend that health authorities rule out economic modelling as a decision support tool for pricing in the field of HPV vaccination. In fact, most of the published models have already been seen to be mere exercises in long-term forecasting [9], speculating on uncertain long-term 'trade-offs' to boost the chances of showing favourable results for vaccination [14–16]. Particularly when industry sponsored, these models may be considered exercises in marketing rather than science, mainly aimed at supporting prices held high on the basis of various heterogeneous assumptions and estimates open to the authors' discretion and manufacturers' influence [14]; these 'patchwork' analyses are eventually misleading and of scant utility for public policy purposes. The three European economic models focussed on the nonavalent vaccine to support universal coverage that we found in the literature[1] [17–19] are no exception and seem more like a further (unnecessary) confirmation of this (mal)practice. All sponsored and co-authored by at least two employees of the manufacturer, the three studies exploited the same American model and concluded that the nonavalent vaccine is cost effective at prices largely over €100 per dose in Austria, Germany and Italy, ignoring in their analyses the much lower prices awarded in domestic tenders for the two other HPV vaccines.

A sensible recommendation for European health authorities is to keep on tendering. Of course, the new tenders must be adapted to the present market situation, so a higher 'quality score' should be attributed to the nonavalent vaccine than to the quadrivalent, but real price competition is to be expected only with the bivalent vaccine because the quadrivalent and nonavalent vaccines are marketed by the same manufacturer. An alternative strategy might be to prioritize the broader protection given by the nonavalent vaccine for HPV prevention and thus try to negotiate with its manufacturer a competitive price inspired by a 'reference-based pricing' approach [20]. For instance, assuming CC prevention as the major target, a tentative price for the nonavalent vaccine in Italy could be roughly estimated at under €40 per dose through an easy calculation,[2] much less than the €63 price per dose currently offered by the manufacturer [21] and already accepted by most Italian regions. This seems too high in light of not only the negative trend of the real HPV vaccine prices but also of the indications included in the new national vaccine plan [22], which recommends male extension for adolescents (i.e. universal coverage) to all 20 Italian regions. Roughly, this would double HPV vaccination expenditure, a substantial financial increase hardly balanced by an equal health benefit.

[1] We searched the PubMed international database to select economic evaluations conducted in EU countries where the HPV nonavalent vaccine is considered for universal vaccination campaigns. We used "papillomavirus vaccine" and "HPV vaccine" and "costs and cost analysis" as search terms. From the 149 articles published in English and initially identified from January 2015 until December 2017, 145 were discarded as studies conducted outside Europe and/or focused on HPV bivalent or quadrivalent vaccines (78); reviews (29); clinical and biological studies (25); or editorials, letters and surveys (13). We finally identified four articles conducted on the nonavalent vaccine in Europe and further excluded one study not considering the male extension of HPV vaccination.

[2] Since the expected increase of CC prevention thanks to the nonavalent vaccine is 20%, and the awarded prices in the last regional tenders went under €30 per dose, a reasonable price could be €38 per dose (€29 × 0.9/0.7).

5 Comment

Vaccination is often perceived as a cost-effective health intervention. However, in this apparently never-ending period of economic difficulties and limited public expenditure, the sky-high prices of new vaccines are a major concern in Western European countries. Although it is the purview of public health experts to advise decision makers on what new vaccinations to adopt and whether to do so, health economists should provide information on the potential choices of public health sustainable in practice by promoting strategies to enhance competitive prices whenever possible. To guarantee the economic sustainability of vaccinations for society in the long run, this might imply not always maximizing individual protection with the newest vaccine in the short term. Since any 'competitor' is (obviously) expected to be against price competition [13], striving more to stress any 'plus' of its product, the main issue is where to 'draw the line' of substantial equivalence between similar products.

To cope with this issue for HPV vaccines, here we offer tentative proposals open to debate.

Compliance with Ethical Standards

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Conflict of interest Anna Padula and Livio Garattini have no conflicts of interest that are directly relevant to the content of this article.

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