

INTRODUCING HUMAN PAPILLOMAVIRUS (HPV) VACCINATION - A CHALLENGE FOR EUROPEAN VACCINE ADVISORY COMMITTEES AND PUBLIC HEALTH SERVICES

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The development of efficient human papillomavirus (HPV) vaccines has required long lasting and tremendous research and development efforts by both academia and industry. However, their availability now turns out to be a major challenge for the public health services of many member states within the European Union (EU) and beyond. Shortly after the two HPV vaccines, Gardasil from Sanofi Pasteur MSD and Cervarix from GSK, were found acceptable for the EU market by the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) based in London, and were subsequently granted a community marketing authorization by the European Commission, the public perception was entirely focussed on the surprisingly high efficacy against cervical cancer caused by HPV high risk types 16 and 18 in a population that was not previously exposed to HPV types contained in these vaccines.

Both vaccines contain particulate recombinant L1 structural protein of HPV types 6, 11, 16 and 18 (Gardasil) or 16 and 18 only (Cervarix). The manufacturing processes as well as formulation and composition of both vaccines differ, however, markedly [1,2].

Protection from persistent HPV infection (virological endpoint) in parallel to prevention of CIN 2+ (histopathological endpoint) were chosen as surrogate parameters for efficacy. It is accepted within the scientific and regulatory community that compliance during clinical studies with predefined criteria regarding these two endpoints will correlate with prevention of and protection from cervical cancer caused by the vaccine specific high risk HPV types, thus supporting licensure of a given HPV vaccine.

This novel option, preventing cervical cancer by prophylactic vaccination has put enormous pressure on those institutions within the individual EU member states which are responsible for vaccination recommendations and also on those in charge of designing and financing vaccination strategies and campaigns. In some countries public demand was so explicitly expressed that neither vaccination advisory committees nor health insurance companies had options other than rapidly fulfilling these demands in a most generous manner. Other countries were following with their recommendations with some delay and a considerable number of member states has meanwhile chosen a more cautious position and continue to explore how HPV vaccines can be optimally used [3].

However, over the months following the initial licensure of HPV vaccines a number of issues have drastically modified the early

enthusiastic views on HPV vaccination into apparently much more critical considerations. These issues evolved from the immediate widespread use of HPV vaccines in the countries that first introduced HPV vaccination and were faced with a phenomenon that is routinely observed upon introduction of new vaccines into a given population, i.e. side effects following vaccination not known from clinical studies. Adverse events ranging from mild to very severe conditions including autoimmune disease and some cases of death were reported in close temporal relationship to HPV vaccination [4]. Applying contemporary pharmacovigilance principles causality between vaccination and side effects can often be proven or disproven, nevertheless, public perception was distracted from the overwhelming efficacy of HPV vaccines and attention was focused on diffused and largely unfounded safety concerns. These public concerns were again and again taken up by virtually all media resulting in a massive confusion about the true value of HPV vaccines not only among those for whom these vaccines were officially recommended but also among health care providers and authorities. In many cases planned vaccinations were cancelled or missing remaining vaccinations rejected. Regulatory professionals have met such situations very frequently in the past and learned that explanatory efforts from agencies and official bodies aimed at adding science to what is communicated by headlines is hardly accepted or understood by the public either because the scientific or medical background is too complicated or the risk communication principles are not applied efficiently enough by the authorities.

For these reasons the integrated approach employed in the framework of the VENICE project aimed to facilitate the introduction of HPV vaccines in Europe (described in the article by King et al.) is of particular value and importance. Availability of a common platform for sharing scientific considerations which are based on hard data but also on modelling systems will become increasingly essential in the future when new vaccines and other novel medicinal products targeted at a significant proportion of the member states' population will be introduced in the EU. Strategies commonly acceptable to many if not all member states will put public health agencies in a much stronger position to justify and convincingly communicate the reasons why for a new prophylactic or therapeutic approach the apparent benefits are considered to outweigh by far known and presumed risks. Closely linked to these questions is to an increasing extent the cost-effectiveness ratio of new therapeutic or prophylactic options. These economical aspects rapidly move into the foreground and are particularly applicable to HPV vaccination

since HPV vaccines are the most expensive vaccines available on the common market and the size of target groups is especially large. The immediate and long term benefits of HPV vaccines for health care systems are, however, not instantly recognizable. For example, compared to the incidence of breast cancer, rates of cervical cancer are relatively low in the EU and mortality due to it is even lower [5]. In addition there are reliable screening measures in place in all member states that are generally considered to be suitable and sufficient to prevent cervical cancer although not all eligible women will participate in screening programs and efficiency of screening programs might be overestimated when not sufficiently quality controlled [6]. Nevertheless their existence raises the question why widespread application of HPV vaccines should be financed in addition to screening programs by health care insurers or public health services without having clear evidence about the economical impact. Concerns have also been raised that HPV vaccination may induce false understanding of protection from disease prompting vaccinated women to deviate from or skip regular cervical screening. However, this kind of argumentation is always brought up following the development of new prophylactic or therapeutic antiviral solutions. Seriously following this line of argumentation would, however, ultimately block any progress in this field.

At the same time, public health services might ask themselves the question whether this money could be better invested in medical interventions where economic benefits are apparent or at least detectable easier and earlier. To answer this type of questions the VENICE platform might also be helpful since it may enable us to ask precise questions and get the most conclusive answers based on specific investigations or previous experience made in individual member states. Relevant questions to determine the cost-effectiveness of HPV vaccination may include:

- To what extent will HPV vaccination help to further reduce surgical intervention?
- Will this reduction outweigh the cost for HPV vaccination programs?
- Which population should be vaccinated to achieve optimal individual, population and economical effects?

It is very important to keep in mind in this context that we are at present just collecting first experience with the first generation of HPV vaccines. Extensions of indications of first generation HPV vaccines based on new data coming in from ongoing and additional studies are very likely and second generation HPV vaccines will follow providing options to also protect from other high risk HPV types. These vaccines will address concerns related to potential strain replacement probably triggered by the current HPV vaccines but may also allow to speculate about the elimination of cervical cancer if future HPV vaccines will contain all the high risk HPV types that are causative agents for virtually all cervical cancers diagnosed in the EU. This rather futuristic outlook should emphasize that integrated EU approaches to measure the value of new prophylactic and therapeutic options will follow a dynamic rather than a static principle meaning that what might not appear cost effective today might turn into an effective tool tomorrow reducing or abolishing significant health burdens to the EU population and financial burdens to national health systems in parallel.

Hopefully VENICE turns out to be an effective tool to reach that goal.

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