# Cervical cancer and vaccination – an overview

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Currently, there are two prophylactic vaccines against cervical cancer and its precursors available: The quadrivalent HPV 6, 11, 16, 18 vaccine (Gardasil®, Sanofi Pasteur MSD, Lyon, France) and the bivalent HPV 16/18 vaccine (Cervarix®, Glaxo Smith Kline, Rixensart, Belgium). Both vaccines are based on recombinant L1 proteins; 360 of these L1 proteins build a virus like particle (VLP) which mimics an empty virus shell and does not contain viral DNA – therefore, the vaccines are not infectious. The quadrivalent uses an established aluminium hydroxyphosphate-sulphate as an adjuvant while the bivalent HPV vaccine utilises a new adjuvant system (AS04).

Both vaccines demonstrated excellent efficacy in the per protocol analyses against cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma *in situ* (AIS), caused by HPV 16 and 18, the most common oncogenic types causing 70% of all cervical cancers. A 99% (95% confidence interval [CI] 93–100) efficacy of the quadrivalent vaccine was demonstrated [1]. Vaccine efficacy of the bivalent vaccine was 92.9% (96.1% CI 79.9–98.3) in the primary analysis and 98.1% (88.4–100) in an analysis related to HPV-type causality [2].

In addition to the effect on the cervix, a 100% efficacy against vulval and vaginal intraepithelial neoplasias (VIN and VaIN 2/3), caused by HPV16 and 18 (in women negative to the relevant types), could also be demonstrated with the quadrivalent vaccine [3]. A 100% (95% CI 94–100) efficacy was also seen with the quadrivalent vaccine against genital warts, 86% of which are caused by HPV 6 and 11 [4].

These studies have provided the basis of the EMEA approval; meanwhile, many results have been presented at various conferences. At the International Papillomavirus Conference (IPC 2007, Beijing), a 90% protection against disease in women aged up to 45 years and negative to HPV 6/11/16/18 was demonstrated by Luna and colleagues; an extension of the license up to this age can be expected.

Men have a key role in transmitting HPV and they also have a substantial burden of HPV related disease. Males are even more affected by genital warts than women (>10% lifetime risk); they also suffer from HPV related cancers of the oropharynx, the anus and the penis. In an ongoing trial in 2800 men, the prophylactic efficacy against condyloma and penile intraepithelial neoplasia was 90.4% (95% CI 69–98) for the quadrivalent vaccine; the efficacy against persistent infection with HPV 6/11/16/18 was 85.6% (97.5% CI 73–93) (Giuliano A and Palefsky J, IPC 2009, Malmö).

Both vaccines also demonstrated an effect against oncogenic HPV types other than the standard vaccine types. The bivalent vaccine showed excellent efficacy against HPV 45 and 31 (Skinner R, IPC 2009, Malmö); the quadrivalent vaccine demonstrated cross-protection against HPV 31. In total, for 5 oncogenic non vaccine types, the reduction was 29% (95% CI 8–45) in a 14 type HPV negative population [5].

The duration of protection is of crucial importance to vaccination programmes and their cost effectiveness. In a 9.5 year follow up of 290 subjects of a phase II clinical trial with a monovalent HPV 16 vaccine, the efficacy against HPV 16 related disease remained 100% (Rowhani-Rahbar A, IPC 2009, Malmö). The bivalent vaccine has demonstrated high antibody levels against HPV 16/18 over a period of up to 7.3 years (De Carvalho N, IPC 2009, Malmö). The efficacy against disease caused by the relevant types was 100% (95% CI 12–100) for the quadrivalent vaccine after 5 years of a phase II trial [6]; end of study data (4 years phase III, >17,000 subjects) also reported 97–100% efficacy against high grade CIN and AIS for the quadrivalent vaccine (Joura E, International Conference for Anticancer Treatment, ICACT, 2008, Paris). The demonstration of an immune memory for a HPV vaccine is very promising for long-lasting and sustained protection [7]. Even in the case of waning antibodies, no breakthrough disease has been observed [8]. To date, no antibody correlate of protection has been established; the clinical effect appears

to be independent of the antibody concentration as measured by current methods.

There is an ongoing safety discussion in the media and over the internet regarding these vaccines; however, the study data of 50,000 study participants and the post marketing surveillance after the distribution of more than 44 million doses did not identify any safety issues, as stated by the Center for Disease Control (CDC, USA) and the EMEA on a regular basis.

These studies provide promising results but the hallmark of effectiveness is the reduction of disease in real life in the general population. A reduction of pre-invasive disease (by 40%) can be expected within the next few years, if the vaccination programmes provide good coverage. However, it will take about two decades until a reduction in invasive cancer rates and mortality can be seen. A recent report from Melbourne, Australia, a country with HPV vaccine coverage of 80% in girls and younger women, has shown a significant reduction of genital warts in the target population (relative risk 0.52, 95% CI 44–63), soon after the initiation of the programme (Fairley C, IPC 2009, Malmö). Since with this generation of vaccines only 70% of cancer cases can be prevented in the long term, the continuation of national screening programmes is mandatory.

## Conflict of interest statement

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