



# The HPV vaccine market: Cervarix™ competes with Gardasil®

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Last month's US FDA and WHO approval of Cervarix™, GlaxoSmithKline's (GSK [London, UK]) vaccine against human papillomavirus (HPV) types 16 and 18 [101], boosted GSK's position in the global HPV vaccine market. Gardasil®, Merck's vaccine against HPV types 6, 11, 16 and 18, obtained US FDA and WHO approvals in 2006. US FDA rejection of Cervarix 2 years ago, together with Cervarix's lack of protection against HPV 6 and 11, led health authorities in many countries to approve Gardasil long before Cervarix. Now that the tenders are out, policy makers need to choose between the vaccines. The competition is fraught with biased interpretation of the available data and accusations of unbalanced delivery of recommendations, risks and benefits.

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## Current global registration & approval status of both vaccines

Both vaccines have been widely approved for prevention of cervical cancer and its precursors – Gardasil in 126 countries, and Cervarix in 100 countries. The US FDA recently approved Gardasil for prevention of vulvar and vaginal cancers [102] and for use in boys and men aged 9–26 years [103]. In several countries Cervarix approval includes the over 26-year-age group. The high costs of both vaccines have stimulated discussion of cost-effective models of vaccination. Although effective for boys and adult women, administration to girls before sexual debut is considered most cost-effective. The proposition of publicly funded vaccination programs of girls aged 12–13 years has been met with heated debates due to high costs and

political considerations [1]. Consequently, both companies have invested massive sums of money into convincing opinion leaders of the benefits of their product. Merck's educational pitch for professional medical associations has been criticized for not providing a balanced recommendation on risks and benefits [2]. However, the American Society for Colposcopy and Cervical Pathology refuted such claims, stating that the messages were balanced and reflective of US FDA approval.

Currently, governments in 27 countries have decided to publicly fund HPV vaccination:

- In the Asia/Pacific region – Australia and New Zealand;
- In Latin America and the Caribbean – Cayman Islands, Mexico and Panama;
- In the Middle East – United Arab Emirates and Abu Dhabi;
- In North America – Canada and the USA;
- In Europe – Belgium, Denmark, France, Germany, Greece, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland and the UK.

Recommendations in Denmark and France state a preference for Gardasil, while Cervarix was selected for vaccination in the vaccine program in the UK, Holland, Italy, Poland and Spain.

When selecting a vaccine, policy makers need to consider which vaccine is more effective and safe, both for the short and long term, which provides the widest coverage, and the costs.

## The driving force behind the development of the vaccines

The incentive for developing a vaccine against HPV derives from the serious nature of the associated diseases – cancer, precancer and sexually



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transmitted infections; and the high costs of precancer screening and treatment. The annual worldwide incidence for cervical cancer is almost 0.5 million; for cancers of the vulva and vagina, the incidence is approximately 40,000 [3,4]. In addition, annual worldwide incidence for high-grade cervical intraepithelial neoplasia (CIN), the precancerous condition of cervical cancer, is almost 0.5 million; and for both low-grade CIN and genital warts (condylomata acuminata), 30 million cases each. The International Agency for Research on Cancer (IARC [Lyon, France]) predicts this rate to rise 40% if efficient preventative measures are not implemented soon [3]. The implementation of a vaccine will likely lead to a significant decrease in the health, emotional and financial burden associated with these pathologies [5].

### Is one of the vaccines preferable over the other?

The main advantage of Gardasil, the quadrivalent vaccine, is that it is directed against four common HPV types: HPV 6 and HPV 11, which cause genital warts and low-grade premalignant conditions in the cervix, and HPV 16 and HPV 18, which cause premalignant and malignant conditions in the cervix, vulva, vagina, anus and oropharynx [6].

While Cervarix, the bivalent vaccine, is directed only against HPV 16 and HPV 18, its potent adjuvant, adjuvant system 04 (AS04), accelerates a more sustained and stronger immune response [7] than that of the conventional adjuvant aluminum hydroxyphosphate sulfate in Gardasil. While the novel AS04 adjuvant has demonstrated safety in many recipients of various AS04-containing vaccines, its experience is meager compared with the 20-year use of the adjuvant in Gardasil [8].

According to GSK, the maintenance of a high level of antibodies for 6 years following vaccination highlights the long-lasting clinical success of Cervarix. This contrasts to the decrease in the level of antibodies against HPV 18 detected 2 years subsequent to the three-dose regimen of Gardasil. However, now more than 7 years after the initiation of controlled studies, the two vaccines exhibit similar effectiveness in preventing premalignant conditions. Moreover, injection of a fourth dose of Gardasil, 5 years after the three initial doses, induced an immediate, sharp increase in the level of antibodies to a level twice as high as the level achieved following the three initial doses [9], indicating a strong immune memory even 5 years after the initial

vaccination. The duration of vaccine effectiveness and the necessity of a booster dose are not known for either vaccine.

More significant antibody neutralizing activity has been demonstrated in cervical epithelial cells following vaccination with Cervarix than with Gardasil [10]. Some claim that antibodies in the cervical mucosa can strike infecting HPV early, even before penetration into the epithelium. Others believe that the same level of protection occurs if the antibodies meet the virus at the basal cell layer.

### Comparison of clinical studies of both vaccines

Phase II research studies published in 2006 provided evidence of the safety and effectiveness of both vaccines against HPV 16 and 18 persistent infections, and against premalignant conditions CIN grade II and III caused by these strains. In addition, Gardasil demonstrated excellent effectiveness in the prevention of condylomata acuminata and CIN grade 1, vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia. Side effects were pain at the injection site, with no serious adverse events reported [11–13].

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Later, Phase III studies, which included tens of thousands of women, also documented the effectiveness of the vaccines. The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II trials [14–17] compared Gardasil with a placebo; the Papilloma Trial Against Cancer In Young Adults (PATRICIA) study [18] examined the effectiveness of Cervarix against hepatitis virus A.

A secondary aim of the vaccine trials was to show a reduction in referrals to colposcopy, cervical biopsy and cervical excision (loop excision) in the vaccinated versus the control group. Reduction in colposcopy referrals was 20% for Gardasil and 26.3% for Cervarix. Reduction in the number of cervical biopsies was 22% for Gardasil (unknown for Cervarix), and the reduction in therapeutic cervical excisions was 43% for Gardasil and 68.8% for Cervarix [14–18]. These variables were measured in the per-protocol groups. GSK highlights the seemingly greater reduction in diagnostic and therapeutic procedures for Cervarix.

### Can the trials of the two vaccines be truly compared?

Actually, true comparison of the Phase III studies is limited, due to differences in their goals, variables investigated, and inclusion criteria. Specifically, the populations differed: more were enrolled from Pacific and Asia regions in the Phase III Cervarix (PATRICIA) study [18] than in the Gardasil (FUTURE I/II) studies (34% of 18,644 and 4% of 20,541, respectively) [14–17]. This may explain the twofold prevalence of HPV 16 and HPV 18 carriers at enrollment in Gardasil studies (9% HPV 16 PCR-positive, 4% HPV 18 PCR-positive) compared with the Cervarix study (5 and 2%, respectively). A similar difference in HPV prevalence at study entry was evident in the CIN 2<sup>+</sup> incidence in the control arm of the two Gardasil studies: the time to event curves for CIN 2<sup>+</sup> for Gardasil, calculated for combined efficacy population–intent-to-treat population analysis, was 1.59 cases per 100 person-years. At the same time, in the Cervarix trial, which calculated for total vaccinated cohort (all women who received at least one vaccine dose, regardless of their serological and DNA status prior to vaccination [TVC]) analysis at month 36, there was only 1.19 cases per 100 person-years, representing a 34% lower incidence compared with Gardasil.

Could this explain the difference in effectiveness between the two vaccines? Indeed, differences in prevalence and incidence of infection and disease can have a major effect on effectiveness estimates (percent reductions), even if there was no actual impact on disease prevention.

### Cross-protection against additional HPV strains: which vaccine is more effective?

A secondary end point of most studies was the determination of antibodies generated in response to vaccine antigens against nonvaccine related viruses, and the prevention of CIN 2<sup>+</sup> caused by these viruses. HPV 16 is closely related phylogenetically to HPV 31 (both are part of the A9 group), and HPV 18 to HPV 45 (A7 group). HPV 45, HPV 31 and HPV 52 account for an additional 10% of cervical squamous cell carcinoma [13–17]. This is particularly important for prevention of adenocarcinoma, as more than 90% of cervical adenocarcinomas result from these five HPV types, compared with 80% of the more common cervical squamous cell carcinoma. Vaccine-induced protection against persistent infection with nonvaccine oncogenic HPV types is defined as cross-protection.

Cross-protection capability in Cervarix may result from modification of the proteins L1 of the VLP, enabling a less stringent antigen–antibody interaction, or from the more potent adjuvant, ASO4, leading to the production of a higher titer of HPV antibodies.

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*“Superior vaccine cross-protection potential may explain Cervarix’s efficacy.”*  
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An editorial previously published in *Therapy* asserted that cross-protection rarely reaches 100%, and that the level of this protection decreases with time [19]. More data has recently become available regarding this issue. In the Phase III end of study analyses, Cervarix was highly effective in preventing CIN 2<sup>+</sup> of all HPV types [18]. While HPV 16 and HPV 18 cause approximately 52% of CIN 2<sup>+</sup> lesions, GSK claims Cervarix’s efficacy against CIN 2<sup>+</sup>, irrespective of HPV DNA in lesions, to be 70.2% (range: 54.7–80.9%) in TVC-naïve women, versus only 42.7% (range: 23.7–57.3%) with Gardasil.

Superior vaccine cross-protection potential may explain Cervarix’s efficacy. In Phase III studies, Gardasil only demonstrated effectiveness against CIN 2<sup>+</sup> lesions caused by HPV 31 (70%; 95% CI: 32–88.2). In contrast, Cervarix was effective against CIN 2<sup>+</sup> lesions caused by HPV 31 (68.4%; 95% CI: 34.2–86.1), HPV 33 (49.8%; 95% CI: 4.8–74.6), and HPV 45 (100%; 95% CI: 7.0–100).

These differences in cross-protection favor Cervarix. However, Merck claims that cross-protection may be only short term, being dependent on existent antibody levels. True protection against these and other HPV types may be accomplished by a second-generation HPV vaccine targeted against specific HPV types. Such a vaccine is currently being developed.

### The head-to-head vaccines trial

A Phase IIIb blinded and randomized study of 1106 women, directly comparing (head-to-head) the two vaccines, has been recently completed [10]. However, this study only included immunogenicity and safety analyses, and not a clinical comparison between the vaccines. The participants were stratified by age (18–26, 27–35 and 36–45 years) and randomized (1:1) to receive Cervarix (months: 0, 1 and 6) or Gardasil (months: 0, 2 and 6). A total of 7 months after the first vaccination, all women who were seronegative and cervical

HPV-DNA-negative before vaccination for the HPV type analyzed had seroconverted for HPV 16 and HPV 18, except for two women in the Gardasil 27–35 year age group who did not seroconvert for HPV 18 (98%). Geometric mean titer ranged from 2.3- to 4.8-fold higher for HPV 16 and 6.8- to 9.1-fold higher for HPV 18 after vaccination with Cervarix than with Gardasil, across all age strata. Similarly, in the TVC, Cervarix induced significantly higher serum neutralizing antibody titers in all age strata ( $p < 0.0001$ ). Positivity rates for anti-HPV 16 and 18 neutralizing antibodies in cervicovaginal secretions, circulating HPV 16 and 18 specific memory B-cell frequencies, and CD4<sup>+</sup> T cell counts were also higher after vaccination with Cervarix compared with Gardasil. GSK concluded that Cervarix affords a longer duration of protection against HPV 16/18.

Merck does not concur with this conclusion on the grounds that the head-to-head trial did not measure clinical efficacy. Efficacy or duration of protection, they claim, cannot be predicted only by comparing antibody levels or immune responses between two vaccines. Furthermore, seroconversion rates for both vaccines were high, and memory B cell counts for HPV 16/18/31/45 were similar for both vaccines at month 12 [104]. Data for month 12 of the head-to-head study have not yet been officially presented.

### Is one of the vaccines effective for a longer period than the other?

In Phase II follow-up studies, both vaccines demonstrated high immunogenic levels for more than 7 years [11–13]. An 8.5-year follow-up for Merck's monovalent HPV 16 vaccine shows 100% vaccine efficacy [20]. It is not clear if there will be a need for an additional fourth dose (booster) in the future. Similarly, the hepatitis B vaccine demonstrates long-term effectiveness, despite the continual decrease in antibody levels, which become immeasurable [21]. The claim that Cervarix, due to its use of AS04 type adjuvant,

will establish a long-term memory of the vaccine beyond that achieved by the quadrivalent vaccine has yet to be proven.

### Conclusion

Competition between Gardasil and Cervarix on the HPV vaccine market is based on proof of efficacy and cost-effectiveness. Large-scale Phase III studies and a Phase IIIb head-to-head study are now available, showing that both vaccines are safe and effective against cervical cancer and high-grade CIN caused by HPV 16 and HPV 18, if administered prior to first exposure to these sexually transmitted viruses.

Differences between the vaccines exist: namely, only Gardasil protects against condylomata acuminata and low-grade CIN caused by HPV 6 and HPV 11. This vaccine has been shown to be effective in preventing vulvar and vaginal precancer and lesions.

Cervarix has higher capability of preventing HPV 45 and HPV 52 infection than Gardasil, and similar potential against HPV 31. These viruses also cause cervical cancer.

When deciding between the vaccines, an individual or a health authority should take into account the effectiveness against CIN 2<sup>+</sup> lesions of all types, genital condylomata, vaccine safety and cost. The age of the individual to be vaccinated is also important; in some countries each vaccine is licensed for different age groups.

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