

New results show that the four-type Human Papillomavirus vaccine Gardasil® induces robust immune memory, a hallmark for long-term protection

Findings support vaccination programmes for girls and young women to reduce the burden of cervical cancer and its pre-cursors, of pre-cancerous vulvar lesions and of genital warts

Lyon, 21 June 2007 – New study results published today in the medical journal *Vaccine* suggest that the efficacy of the four-type (6,11,16,18) Human Papillomavirus vaccine Gardasil® will be long-lasting. In women, who had been vaccinated with Gardasil® five years before, a robust immune memory was observed when their immune system was exposed to the vaccine virus types. Immune memory is a hallmark for long-term protection.¹

Exposure to natural viruses was simulated through a challenge dose of Gardasil®, given five years after the first dose of the initial three dose vaccination series.* The immune system remembered very well the vaccine virus types and rapidly responded with a strong induction of specific neutralising antibodies. This immune memory was present regardless of the antibody level observed before exposure, and the antibody response exceeded the response observed right after the initial vaccination series.

Gardasil® is the first and only Human Papillomavirus vaccine to have demonstrated immune memory by challenging the immune system of women previously vaccinated. Previous results of this study had shown that Gardasil® prevented 100%[†] of cervical lesions and genital warts caused by the four vaccine virus types up to five years after the start of vaccination.²

"The duration of protection afforded by vaccines represents a critical test of their utility as public health interventions. Some vaccines induce long-term immunity, while others require booster doses. Vaccines that induce long-term protection are usually characterised by the generation of immune memory. The new findings suggest that the efficacy of this vaccine will be long lasting", commented the authors in their article in *Vaccine*.

"Many health authorities have already recommended Human Papillomavirus vaccination of girls and young women because maximal benefit is expected when vaccination is completed before exposure to the virus, thus before sexual debut. The demonstration of immune memory for Gardasil® further supports this decision. Girls and women who receive the vaccine in their teens or early adulthood can be expected to be protected when exposed to the virus later on in life", comments Patrick Poirot, vice-president Medical and Scientific Affairs at Sanofi Pasteur MSD.

To date, health authorities in the US, Australia, Canada, Germany, France, Italy, Belgium, Austria, Norway, Luxemburg and Switzerland have already recommended universal Human Papillomavirus vaccination of young girls, often coupled with catch-up programmes for additional age groups of girls and young women. Decisions were taken after accelerated review times compared to decisions upon recommendations and funding for vaccination programmes against other diseases in the past.

The virus types 6, 11, 16 and 18 directly targeted by Gardasil® cause the vast majority of genital Human Papillomavirus diseases. It is estimated that among Human Papillomavirus diseases in Europe, they cause 75% of cervical cancer,³ 95% of vulvar and vaginal cancers,^{4,5} 70% of pre-cancerous (CIN[‡]2/3)^{6,7} and 50% of potentially pre-cancerous cervical lesions (CIN[‡]1)⁸, 80% of pre-cancerous vulvar and vaginal lesions (VIN[‡]2/3 and VaIN[‡]2/3)^{4,5,9,10}, and 90% of genital warts.^{11,12}

* It would have been unethical to expose the women to natural viruses.

† 95% CI [12,100]

‡ CIN = Cervical Intraepithelial Neoplasia / VIN = Vulvar Intraepithelial Neoplasia / VaIN = Vaginal Intraepithelial Neoplasia

In large clinical studies, Gardasil® provided also benefits against pre-cancerous (CIN2/3) and potentially pre-cancerous cervical lesions (CIN1) caused by additional virus types not directly targeted by the vaccine. The additional virus types cause more than 10% of cervical cancer and substantial proportions of pre-cancerous and potentially pre-cancerous cervical lesions. The data have recently been submitted to the European Medicines Agency (EMA) and the US FDA in order to update the marketing authorisation for Gardasil®.

Gardasil® is the only licensed vaccine in Europe for the prevention of cervical cancer and its precursors as well as pre-cancerous vulvar lesions and genital warts caused by Human Papillomavirus types 6, 11, 16 and 18.

Gardasil® has been approved in 76 countries (many under accelerated review timelines), including the European Union (EU), the US, Canada and Australia and has met with very broad acceptance. Additional applications are currently under review with regulatory agencies in many more countries around the world. The EU licensed Gardasil® within just 9 months compared to a usual review time of 13-15 months.

Notes to editors

About the study

In a randomised, double-blind, placebo-controlled phase IIb study, 552 women aged 16 to 23 years old received either vaccine or placebo at day 1, month 2, and month 6. During three years of follow up, all women underwent gynaecologic examination, cervico-vaginal sampling for Human Papillomavirus DNA, serum anti-Human Papillomavirus testing, and Pap[§] testing, with follow-up biopsy as indicated. A subset of 241 women (all women who were enrolled in Brazil and Europe) were followed for an additional two years. The primary efficacy analysis was performed in women who were not infected with Human Papillomavirus 6, 11, 16 or 18 through month 7 (one month following dose 3), received all doses of vaccine/placebo, and were not protocol violators. The primary endpoint was the combined incidence of Human Papillomavirus 6-, 11-, 16- or 18- persistent infection or related disease, defined as Human Papillomavirus DNA detected in samples collected at ≥ 2 consecutive visits ≥ 4 months apart, or Human Papillomavirus DNA detection at the last recorded visit, or biopsies in which Human Papillomavirus DNA was detected and cervical, vulvar, vaginal dysplasia or genital warts was diagnosed.

5 years after the start of vaccination the exposure to the vaccine virus types was simulated in the same study population. Because it was not ethically feasible to expose subjects to natural viruses, the antigen challenge was given as a dose of Gardasil® to simulate exposure. All extension subjects received one dose at month 60 to examine the extent of immune memory in response to the initial vaccination series. Antibody levels 1 week post-challenge reached levels observed 1 month following the completion of the three-dose primary series. At 1 month post-challenge, antibody levels were higher than those observed 1-month post-dose 3.

The burden of cervical cancer and other Human Papillomavirus diseases

Despite screening for early detection, cervical cancer remains the second most common cause of death from cancer (after breast cancer) among young women (15-44 years) in Europe^{**}.¹³ Around 33,500 women are diagnosed with, and 15,000 women die from cervical cancer each year (the equivalent of 40 women per day or nearly 2 per hour).¹⁴

In addition, hundreds of thousands of women are diagnosed with other Human Papillomavirus diseases that start before cervical cancer and go beyond the cervix. These diseases include pre-cancerous and potentially pre-cancerous cervical lesions^{‡,8,15}, vulvar and vaginal cancer^{4,5,16}, pre-cancerous vulvar and vaginal lesions^{9,10,17,18} and genital warts.¹⁹

Cervical cancer is caused by Human Papillomavirus.^{††20,21} The virus is very common, with 70% of sexually active people estimated to become exposed at some point in life.^{22,23,24} Genital infections with Human Papillomavirus are very common with the majority of infections occurring in adolescence or early adulthood.^{25,26} In general the virus will be cleared by the body within about one year with no symptoms.

[§] Named after its inventor George Papanicolaou

^{**} European Union 25 member states plus Iceland, Norway & Switzerland

^{††} 99.7% of cervical cancers contain the genetic material (DNA) of the virus

However, in a significant number of cases the virus can cause cervical and genital lesions, including vulvar and vaginal lesions and genital warts. Cervical, vulvar and vaginal lesions may go on to cancer.²⁷

EU indication of Gardasil®

According to the licence in the EU, Gardasil®, Human Papillomavirus Vaccine [types 6,11,16,18] (Recombinant, adsorbed), can be given to children and adolescents 9 to 15 years and adult females 16 to 26 years of age and is indicated for the prevention of cervical carcinoma (cervical cancer), high grade cervical dysplasia CIN2/3 (precancerous cervical lesions), high grade vulvar dysplastic lesions VIN 2/3 (precancerous vulvar lesions) and external genital warts (condyloma acuminata) caused by Human Papillomavirus types 6, 11, 16 and 18.

Worldwide availability of Gardasil®

Gardasil® has been developed by Merck & Co., Inc. and Sanofi Pasteur MSD. In Europe, the vaccine is marketed by Sanofi Pasteur MSD.

Merck is actively working to accelerate the availability of Gardasil® in the developing world. Clinical trials for the development of Gardasil® have already included participants from 33 countries on 5 continents in a variety of settings. Clinical studies in developing world countries are being initiated to assess the efficacy of Gardasil® in other environments. Merck will donate free vaccine to the non-profit organisation PATH^{††} to support demonstration studies to accelerate the availability of Human Papillomavirus vaccines in the most impoverished countries. Merck is also working with India's Council of Medical Research to study Gardasil® in India. Merck will make our new vaccines, including Gardasil®, available to developing world countries at dramatically lower prices.

About Sanofi Pasteur MSD

Sanofi Pasteur MSD is a joint venture between sanofi pasteur, the vaccine division of sanofi-aventis, and Merck & Co., Inc. Combining innovation and expertise, Sanofi Pasteur MSD is the only company in Europe dedicated exclusively to vaccines. Sanofi Pasteur MSD is able to draw on the research expertise of sanofi pasteur and Merck & Co., Inc., together with their teams throughout the world, to focus on the development of new vaccines for Europe, which aim to extend protection to other diseases and perfect existing vaccines in order to improve the acceptability, efficacy and tolerability of vaccination.

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