

HPV vaccine promises much but screening remains vital

→ Peter McIntyre

The new HPV vaccines have shown impressive results in their target population, but if immunisation programmes come at the expense of existing or planned cytological screening, deaths from cervical cancer may increase.

It is more than two years since GlaxoSmithKline and Merck first announced sensational results of separate trials of vaccines designed to protect women against two types of human papillomavirus (HPV). HPV 16 & 18 together cause 70% of cervical cancer, a disease that kills about 250,000 women each year worldwide.

GlaxoSmithKline reported outstanding results for its vaccine Cervarix in November 2004. In May 2005, Merck reported similar results for its vaccine Gardasil. The Merck version is now on the market in many countries of the world, while Cervarix awaits approval in both Europe and the US.

Initial results showed 100% protection against infection in uninfected girls and women. Some health professionals talked of the virtual elimination of cervical cancer. In October 2005, Kevin Ault, a gynaecologist on the Merck research panel, told CNN television news: "We are talking about maybe a generation or

two of women to receive this vaccine before we get to no more Pap smears."

The vaccines still show strong protection against target HPV types in girls and women who are free of the virus. However, it is becoming clear that they are nowhere near as effective at stopping cervical cancer in the real world where infection rates are high. Moreover, the cost of Gardasil, \$360 in the US and €300 in Europe for a three-dose course, raises fears that money could be diverted from screening programmes.

Merck and its European partner Sanofi Pasteur MSD have been accused of over-aggressive marketing. In the US, Merck called off its lobbying of state authorities after questions were raised over some of the claims being made on behalf of the vaccine and after it was revealed that Merck had made payments to the group coordinating efforts to win State legislation for school vaccination programmes.

In Europe, the First Global Summit on Cervical Cancer, held in Paris in

March 2007, attracted criticism for its reliance on Sanofi Pasteur. The British newspaper, *The Guardian*, revealed that Sanofi Pasteur had funded the whole event, paid for sports stars to attend and even paid some freelance journalists to cover it. It also published a claim that consultants had been offered money to attend meetings as 'opinion leaders'.

The Summit, held under the patronage of the French President Jacques Chirac, called on governments to "educate and communicate to all women worldwide about cervical cancer – its cause and prevention through vaccination and regular cervical cancer screening." Justine Henin, the Belgian tennis star, said she would campaign to raise awareness about HPV and the need for screening and "to urge governments that mothers should be able to protect their daughters with a vaccine."

EFFICACY IN THE REAL WORLD

The striking performance of Gardasil in its primary target group and the



Prevention is better than cure. For greatest preventive effect, immunisation programmes need to vaccinate young people before they become sexually active

relative lack of impact in a wider population of women is seen in the latest results from the FUTURE study group, published in the *New England Journal of Medicine* (10 May 2007). These extend the phase III study results of Gardasil to three years, up to 15 June 2006.

In the Merck-sponsored study, more than 12,000 women aged 15–26 were randomised to receive Gardasil or placebo. After three years, vaccine efficacy against pre-cancerous high-grade cervical lesions (CIN 2 & 3) caused by HPV types 16&18 was 98% amongst uninfected girls and women. The study says: “These findings suggest that widespread immunisation of female adolescents and young women could lead to reductions in HPV-16-related and

HPV-18-related high-grade lesions that would be apparent within years, rather than decades.”

However, there was no clear evidence that vaccination altered the course of existing HPV infection. Efficacy drops to 44% in the “intention to treat population” – defined as all women regardless of their HPV status at the start of the trial. In this wider population, 83 women in the vaccine group developed high-grade cervical disease related to HPV 16 or 18, against 148 in the placebo group.

When all high-grade cervical lesions are taken into account, efficacy drops to just 17%: cervical disease related to any HPV type (not just 16&18) was found in 219 women in the vaccine group and 266 in the placebo group.

There were parallel results in a separate study of the effectiveness of the vaccine in preventing anogenital disease (genital warts or vulvar or vaginal intraepithelial neoplasia).

It can be seen that the impact of introducing the vaccine is highly significant in uninfected girls and women, but far smaller in the general population.

Vaccine manufacturers argue that the vaccine is prophylactic, not therapeutic, and is not supposed to protect women who are already infected. That is the very reason for targeting vaccination programmes on girls before sexual activity begins. Many specialists welcome the vaccine as an extra weapon and some believe that a vaccine programme could even sharpen the focus on screening. However, they do not want the vaccine to undermine attempts to strengthen screening programmes.

POLAND – FIVE DIE EACH DAY

Poland has one of the highest cervical cancer rates in Europe, with up to 4,000 new cases of invasive cervical cancer a year. Half of these women currently die, at a rate of five women a day.

Slawomir Majewski, President of the Polish Society for HPV Prevention, said, “The main reason is late diagnosis. We never had a good screening programme.” He cites as contributory factors lack of education at school about sexually transmitted diseases, stigma attached to going for gynaecological examination, and the poor state of the economy.

In 2006, Poland introduced a national cervical screening programme, inviting five million women a year for screening. In June 2006, the vaccine (called SILGARD in central and eastern Europe) was approved for use in

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Poland, and several local authorities have since decided to fund vaccination for girls in local schools.

The Polish Society for HPV Prevention, formed by gynaecologists, vaccinologists, paediatricians, general practitioners and specialists in sexually transmitted infections, has organised training for 5,000 doctors over the past two years. There has been a mass media campaign to raise awareness in the public (details can be seen in Polish at www.hpv.pl). Merck was involved in funding and planning some of this work as was GlaxoSmithKline, but

Majewski says that they did not put doctors under pressure.

“Before the vaccine was approved, Merck supported a very good educational campaign speaking only about the HPV problem and cytology and so on. So they were very clever and then when the vaccine was approved and was on the market, they just added this information.

“From a medical and scientific point of view, we were not put under pressure. In Poland, it was necessary to start to talk about this problem. Of

course, these companies always think about business, but the most important thing is to be fair, to tell the truth and not exaggerate and to be objective.

“I would say we have made a huge effort in Poland. We have definitely shifted public opinion and provoked huge discussions. We have done a very good job, for doctors, general society and policy makers and also for general authorities.”

He said that vaccine and screening programmes could strengthen each other. “I am sure that many more

HOW EUROPE IS USING THE VACCINE

Gardasil

The Merck vaccine Gardasil (also marketed as SILGARD) protects against HPV types 6,11, 16 & 18.

The US regulatory agency, the FDA, approved its use in June 2006. The Centers for Disease Control and Prevention recommended vaccination for all girls and women aged 11–26 years. Texas and Virginia have made laws for mandatory school vaccination, and 20 States are considering similar measures.

The European Medicines Agency approved its use in EU countries in September 2006. Sanofi Pasteur MSD, which is marketing and distributing Gardasil in the EU, hopes to introduce it into every EU country by the end of 2007.

Germany has added HPV vaccine to the national vaccination schedule. The German Standing Commission for Vaccination recommended universal vaccination for girls aged 12–17 years.

The Italian Pharmaceutical Agency (AIFA) has recommended universal vaccination for 12-year-old girls, and the Ministry of Health will fund the programme.

The Conseil Supérieur d'Hygiène Publique de France has recommended universal vaccination for 14-year-old girls, and a programme for 15- to 23-year-olds. A decision on funding is awaited.

Austria has recommended vaccination for girls and boys aged 9–15 years, and a programme for older girls and women.

The Norwegian Institute of Public Health (FHI) has recommended a national programme for girls aged 11–12, with a catch up programme up to the age of 16. The Minister for Health is considering funding.

The Luxembourg High Council for Public Health (CSH) has recommended vaccination for all 11- and 12-year-old girls, with a catch up programme up to the age of 18.

The Pharmaceutical Benefits Board in Sweden has included the vaccine in the na-

tional Pharmaceutical Benefits Scheme to cover the cost for girls aged 13–17 years.

Belgium has recommended universal vaccination for girls aged 10–13 and will consider the benefits of a catch up programme for girls up to the age of 15.

All these countries have emphasised the need for continued or improved screening programmes.

Cervarix

Cervarix protects against HPV 16, 18, 31 & 45.

GlaxoSmithKline applied for European approval for Cervarix in May 2006 and for US approval in March 2007.

The Australian Therapeutic Goods Administration's drug evaluation committee has recommended approval of Cervarix for girls and women aged 10–45.

GSK has embarked on a trial to compare Cervarix with Gardasil, believing that its own vaccine will show longer lasting protection.



KELLY MOONEY PHOTOGRAPHY/CORBIS

Twin-track approach. However effective HPV vaccination programmes turn out to be for today's target population of 12- to 17-year-olds, young women who are now in their late teens and early 20s will probably need an effective national screening programme for at least the next 50 years

women will attend the cervical screening. In our educational campaigns, we stress from the very first moment that, despite vaccination, women have to go for cytological screening.

“Of course, the vaccine is expensive and we need to convince policy makers to pay at least for vaccinating the young population – children and young adolescents. The sexually active population can also greatly benefit. Almost 85% of the sexually active population aged between 18 and 45 is HPV negative.”

SERBIA – SCREENING IS A PRIORITY
Serbia has an even higher rate of cervical cancer, one that has risen over two decades. In 2002, the national rate was 27.2 per 100,000 women

(1,089 new cases), with regional rates as high as 38.1 women per 100,000. Similar rates are seen in Romania, Albania and Bosnia & Herzegovina. At 7.2 deaths per 100,000 women, mortality in Serbia is not as high as in some other countries due to better treatment, but cervical cancer cost 452 women their lives in 2002.

Serbia has never had a national strategy for cancer prevention or centralised screening. The Balkan conflict and subsequent economic collapse eroded what opportunistic screening there was, as health spending fell from €150 per person in 1997 to less than € 50 in 1999.

In 2003, the Ministry of Health appointed an expert group for the pre-

vention and early detection of cervical cancer. A survey sponsored by the Alliance for Cervical Cancer Prevention (ACCP) identified lack of knowledge, embarrassment, a sense of fatalism about cancer and unwillingness to talk about the disease as barriers to screening, as well as lack of patient-friendly health services.

In 2004, a WHO pilot programme – funded by the French Government – was launched in Branicevo in eastern Serbia. This screened 12,763 women aged 30–49, almost 60% of the target population. Sixty-three high-grade squamous intraepithelial lesions and six invasive cancers were detected – a cervical cancer incidence of 47 per 100,000.

A national programme for cervical

Vaccination before onset of sexual activity will be 'of primary importance' in under-screened populations

cancer screening will be finalised this year and introduced to cover all Serbian women aged 25–64 over the next three years. Meanwhile the vaccine was approved for use in Serbia in October 2006, although it is not yet on the market.

Vesna Kesić, professor of gynaecological oncology at the Clinical Centre of Serbia in Belgrade, is the Ministry of Health adviser for the prevention and detection of cervical cancer, and has been centrally involved in the efforts to introduce screening. She describes the vaccine study results as encouraging and fascinating. However, she says, "At present, the HPV vaccination would be a great opportunity and benefit in areas of the world where cervical screening is not available or feasible. The implementation of a nationwide screening programme in a country like Serbia is a realistic goal, can be achieved and will remain pivotal in the prevention of cervical cancer. We cannot forget women who already have cervical cancer and do not know it, and the women who have pre-cancer that should be treated.

"I do not mean that vaccination should not be started as well, but in these economic circumstances, it cannot be made available on a national scale. For me, it is hard to imagine that a low-resource country should concentrate efforts and financial resources on trying to implement compulsory vaccination just when it is about to provide and pay for the regular, organised screening for its women that has been fought for so hard."

LOW-INCOME COUNTRIES

The International Union Against Cancer (UICC) has a global vision to

eliminate cervical cancer, but notes that 83% of cervical cancers occur in resource-constrained countries, with high mortality rates, in sub-Saharan Africa, Central and South America and some regions of Southeast Asia. Few effective screening programmes exist in these countries.

The UICC says that screening programmes remain important, but early vaccination prior to the onset of sexual activity will be "of primary importance" in under-screened populations. To achieve this, the cost of vaccinations in these countries will have to come down.

Virologist Harald zur Hausen, who first identified HPV as the viral cause of cervical cancer, has helped the UICC to draft a new position statement. He told *CancerWorld*, "I think screening must continue, as the vaccines only cover 70% of the cervical cancer cases. However, in countries with no screening facilities and no gynaecological tests, the vaccine needs to be introduced so that it is available prior to the onset of sexual activity. The message from the NEJM papers is that women who are not already infected are highly protected."

A TWIN-TRACK APPROACH

So long as HPV virus continues to exist in the population, so will the need for screening. Whether Pap smears become unnecessary in a generation or two depends on a number of variables, including vaccination levels in the target group, the longevity of vaccine protection, the extent to which the virus lives on in men, the effect of HPV types not covered by the vaccine and factors such as population movements.

Will a country that does not have the infrastructure or money to implement and maintain a cervical screening programme be able to maintain vaccination at or near 100%, especially if there is opposition to giving this vaccine to adolescent girls? A vaccine programme has its own organisational problems, such as the need for an up-to-date vaccination registry, for revaccination, for regular follow-up of vaccinated girls and for continued screening for the 30% of problems caused by HPV types not covered by the vaccine. Further surveillance is also needed to investigate long-term safety; reports of fainting, numbness and rare cases of Guillain-Barré syndrome occurred during the Gardasil trial.

The Bill and Melinda Gates Foundation has funded the Alliance for Cervical Cancer Prevention to work with low-income countries on a strategy to combat cervical cancer. The ACCP and GAVI (Global Alliance for Vaccination and Immunisation) are talking to the drug companies about ways to make vaccines affordable to developing countries. So far there are no firm proposals.

It seems unthinkable that any country with an advanced healthcare system will want to abandon cervical screening in the foreseeable future. Indeed many countries now need to strengthen their national programmes. Countries with little or no cervical screening need something that is affordable and that works. At present, the vaccine is not affordable. It has great potential to save life – but only if adds to existing protection, rather than weakening it.