VOISIN/PHANIE/REX FEATURES

CLINICAL APPROVAL

Trials of an anticancer jab

Two vaccines seem to be so effective in preventing HPV infection that mass vaccination has been introduced for girls. But will long-term studies show falls in cervical cancer.

BY JULIE CLAYTON

For Matti Lehtinen, a virologist and professor of public health at the University of Tampere, Finland, it was a setback to hear that the cause of cervical cancer was the human papillomavirus (HPV). He had spent several years on the wrong track — as had many scientists during the 1970s — investigating a different virus altogether: the herpes simplex virus (HSV). "It was very disappointing," he admits.

But Lehtinen turned adversity to advantage, and embarked on a career that is now seeing the science of HPV through to its ultimate application: cancer prevention. He was lead author on a paper that showed that infection with HPV type 16 is a risk factor for cervical cancer, and for the past ten years he has been lead scientific investigator on the Finnish arms of clinical trials for the two vaccines against HPV.

Both vaccines have now been approved, with the stated aim of preventing cervical cancer, which kills about a quarter-of-a-million women each year. Although successful, the vaccine trials did not demonstrate anticancer activity; approval was based on the assumption that eradicating HPV infection would reduce or eliminate the risk of cervical cancer. Lehtinen admits that proving this final step will require a long-term human study.

EARLY RESULTS

The first vaccine to enter phase III efficacy trials was Gardasil, produced by pharmaceutical giant Merck, based in Whitehouse Station, New Jersey. Gardasil contains peptides from four HPV types: 16 and 18, which account for at least 70% of cervical cancer cases globally; and 6 and 11, which are commonly associated with anogenital warts (see 'The global burden', page S2). The two Gardasil trials (Future I and II) enrolled 17,600 women across the Americas, Europe and the Asia–Pacific region, who received jabs between December 2001 and May 2003.

The second vaccine is Cervarix from GlaxoSmithKline, based in London, which began its phase III trial (Patricia) in May 2003. In total, 18,600 women were enrolled in 14 countries across the Asia–Pacific region, Europe, Latin America and North America.

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Cervarix contains peptides from HPV types 16 and 18 only, plus an adjuvant to boost the immune response.

The minimum age for enrolment in either trial was 15. Many girls become sexually active — and hence potentially exposed to HPV — in their mid-teens, so it is important to reach them beforehand. Younger girls were not enrolled because this would require longer trials to gain sufficient data to determine vaccination efficacy.

In both the Future and Patricia trials, participants were examined at least once each year for signs of HPV infection or epithelial lesions. Lesions are classified as either cervical intraepithelial neoplasia (CIN) grade 1, 2 or 3 (abnormal cell growth), or adenocarcinoma in situ (AIS) — a localized tumour that has yet to become invasive. Trial participants who developed CIN2 or higher-grade lesions (CIN2+) were treated, so their natural disease outcome is not known. However, the trials also differed in important ways.

The trials gathered data for four years after vaccination, although both Merck and GSK reported early results as soon as they had enough data to reach statistical significance. After an average of 3 years of follow-up, results for the two vaccines were similar: both were at least 98% effective in preventing CIN2+ associated with HPV types 16 or 18 (refs 1,2,3). Gardasil also had 100% efficacy against genital warts[2]. At this stage, the number of subjects diagnosed with CIN3 and AIS in any of the trials was too low to draw firm conclusions about the vaccines' efficacy on these measures, says Lehtinen. There were no serious side effects.

In the absence of a head-to-head trial, "it would be unfair to compare the two vaccines because the trials were not identical", says Jorma Paavonen, professor of obstetrics and gynaecology at the University of Helsinki, Finland, and medical investigator for the Finnish trials. Based on the initial efficacy and safety data, the US Food and Drug Administration (FDA) approved Gardasil in 2006 and Cervarix in 2009.

However, neither vaccine was able to clear established HPV infection; in other words, there was no therapeutic effect. From a public-health viewpoint, this reinforced the notion that the vaccines should be given to individuals before they become sexually active (although how long before — that is, the earliest age the vaccine can be given — has not yet been determined).

INTO THE REAL WORLD

Full results covering four years for all trial subjects have now been reported. The latest data, which have more statistical power, were published in 2010 for Gardasil[4,5] and 2011 for Cervarix[6]. So far, immunity has endured: antibody levels in the vaccinated women are as high as they were immediately post-vaccination. The final efficacy data against persistent infection with HPV types 16 and 18, and against premalignant lesions, confirm earlier findings (and are most impressive for women aged less than 20). Furthermore, in an entirely separate trial in Costa Rica, Cervarix showed 84% efficacy against anal infection by HPV types 16 and 18 (ref. 7).

CORBIS

It is hoped that mass vaccination of girls will protect non-vaccinated groups, including men.

The near-complete protection conferred by both vaccines against infection with HPV types 16 and 18 "was an unexpected result — almost too good to be true", says Lehtinen. What's more, there was a surprisingly high level of effectiveness against HPV types not targeted by the vaccine — particularly with Cervarix, which seemed to protect against HPV types 31, 33 and 45. "The data regarding cross-protection were much stronger than expected — to everyone's delight," says Barbara Romanowski, clinical professor in infectious diseases at the University of Alberta in Edmonton, Canada, and principal investigator for the Canadian trials of Cervarix. But how these trial results translate into real-world protection against infection with non-vaccine types is yet to be determined, she adds, and monitoring is continuing.

As countries start mass HPV vaccination campaigns of girls, other effects might become apparent. Researchers in several countries, including Australia, the United Kingdom, the United States and some Scandinavian countries, are watching to see whether other HPV types begin to take over the niche previously occupied by types 16 and 18. A similar shift previously occurred with vaccines against pneumococcal infections, resulting in an increased circulation of pneumococcal serotype 19a, which the vaccine did not target. Such a shift in HPV could undermine any progress towards reducing cervical cancer cases. "We may see an overtaking of the ecological niche by non-vaccine types," Lehtinen warns, "but there is no evidence yet."

Researchers hope that mass vaccination will also lower the rate of infection in the unvaccinated population — in men, for example. Whether so-called herd immunity is achieved partly depends on the proportion of the population that receives the full vaccine dose (see "mass vaccination'). To this end vaccination for boys was recommended in the USA and Canada in November 2011, and plans to vaccinate 12- and 13-year-old boys in Australia from 2013 have also been announced.

Data on the impact of these population-based campaigns are beginning to trickle through, with Australia providing the first glimpse. More than 70% of eligible girls have completed all three courses, and there is already a marked decline in the prevalence of anogenital warts in both young women (59% fewer cases) and men (28% fewer)[8]. New data from cervical screening clinics in New South Wales and Victoria reveal that fewer young women have been infected with vaccine-related HPV types[9].

The state of Victoria has seen a decline of 0.38% in the incidence of high-grade (CIN2+) abnormalities in young women since vaccination began (number of new diagnoses within a 3-month period per 100 women tested)[10]. Perhaps more significantly, data for 2010 also reveal

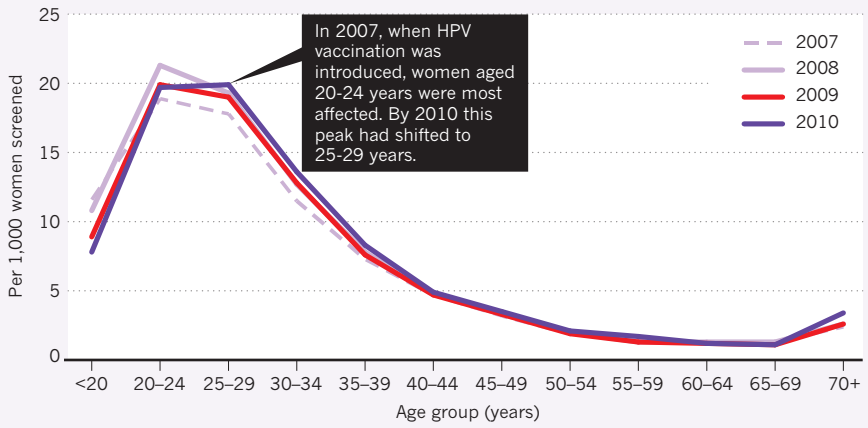
MASS VACCINATION

Few Western countries have achieved >50% coverage. For both vaccines, three doses are recommended, but several trials are investigating whether fewer doses are effective.

Country	Date vaccination campaign started	Uptake – at least 1 dose	Uptake – all 3 doses	Vaccine used
Australia	2007 (Gardasil), 2008 (Cervarix); (12–13 year olds)	83%	70.8% Range: 63.7% (Tasmania) to 79.6% (Australian Capital Territory) [11]	Gardasil and Cervarix
Canada	2007 to 2009, (9–14 year olds)	n/a	50% (Alberta and Manitoba) to 85% (Newfoundland, Nova Scotia and Quebec, for 2 or 3 doses.) [12]	Gardasil
Denmark	2009	80%	62% [ref. 13]	Gardasil
United Kingdom	2008, (12–13 year olds)	89%	83.8% [ref. 14]	Cervarix (changing to Gardasil in September 2012)
United States	2007, (13–17 year olds)	48.7%	32% [ref. 15]	Gardasil and Cervarix

HIGH-GRADE LESIONS IN AUSTRALIA

The number of women with high-grade abnormalities detected by histology screening dropped in women aged 20-24 years. Futher study will reveal whether this is the result of vaccination.



AUSTRALIAN DEPT. HEALTH AND AGEING.

that prevalence of CIN2+ abnormalities is now highest in the 25–29 age group, rather than in younger women. In women aged 20 to 24 years old — a group that contains the first girls to be immunized, including 14–18-year-olds on 'catch-up' immunization — the prevalence of high-grade lesions is "flattening out", says Julia Brotherton, epidemiologist and medical director of Australia's National HPV Vaccination Program Register in Carlton South (see graph).

Rather than rely on national averages, Australian researchers are in the process of linking cervical screening data to the national vaccination register to compare outcomes for individual women who received one, two or three doses against outcomes for unvaccinated women. "We hope by the end of this year to have more definitive results showing that it's specifically the vaccinated women who are getting most of the benefit," says Brotherton. Similar data for the United Kingdom and the United states are due out soon.

In Finland, by contrast, the success of the screening campaign in preventing cervical cancer has reduced the urgency to introduce the HPV vaccine. The National Institute for Health and Welfare has only recently recommended mass vaccination for girls, and the government has not yet given the campaign the go-ahead. In the meantime, researchers have an opportunity for a different kind of trial that would not be possible in countries where vaccination campaigns are already underway. Lehtinen and his colleagues are embarking on a new phase IV trial of Cervarix that will directly test the benefits of vaccinating boys as well as girls (see 'Vaccinate boys too', page S10). Depending on the results, "we could correct the decision to vaccinate only girls if we get data showing that vaccination of girls and boys is even better", says Lehtinen.

All these results are about preventing infection and abnormal cervical cell swabs. Data that might show efficacy against cervical cancer will take longer. "We'll need to wait for women who were vaccinated in their early teens to move through to their late twenties and onwards before we're truly able to see it," Brotherton adds.

So the long-term human study continues. Researchers are waiting to see whether vaccination leads to enduring immunity at the population level, and against which HPV types. But as Lehtinen says, the real test of the vaccines will be not in the data the clinical trials were designed to reveal. Ultimately, it's about whether the vaccine can prevent cancer and save lives. Those, he says, are "the most stringent end-points". ■

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REGISTERING LONG-TERM TRENDS

Clinical trials of the two HPV vaccines may have finished, but data are still accumulating.

Now the trials of Gardasil and Cervarix have formally ended, participants are back with their normal healthcare systems for routine cervical cancer screening and care. But those in Scandinavian countries such as Finland and Sweden can continue to provide information. These countries run national registries that routinely gather data on conditions such as autoimmune disease, pregnancy outcomes and cancer that are linked to personal identification numbers, helping researchers gather long-term vaccine efficacy data against cervical cancer and other HPV-related diseases. "Finland is a paradise of health registries," says Jorma Paavonen, professor of obstetrics and gynaecology at the University of Helsinki and medical investigator for the Finnish trials. Such a system will help illuminate the vaccines' long-term anticancer potential. "We can link vaccinated and unvaccinated individuals to the cancer registry to answer the question in a couple of years," he adds.

And they should have sufficient numbers. High interest levels meant that more girls volunteered for the Finnish trials than were needed. These girls now comprise an additional unvaccinated cohort of about 15,000 individuals. In the original trials, the control groups in Finland — 874 for Gardasil and 2,400 for Cervarix — were offered the vaccine once the trials were completed; approximately half accepted the offer, shrinking the control groups. In the new unvaccinated cohort, "we already have early results that there are a few cancer cases versus zero cases in the vaccine arm", Paavonen says. "The numbers are small, but the cases will accumulate rapidly."

The registries will also be useful in gathering data on adverse events. Despite a handful of media scares about their safety, "there's no evidence that these vaccines cause any harm", he adds. Nonetheless, he and other trial investigators are keen to continue monitoring at least for the next decade. ***J. C.***