Challenges of implementing human papillomavirus (HPV) vaccination policy

Angela E Raffle argues that in countries with established cervical screening programmes, HPV vaccination of pre-adolescent girls could bring additional benefit at an affordable cost, but careful planning, adequate education, and integral evaluation will be needed

In affluent countries, cervical screening programmes are reducing deaths from cervical cancer, but screening is labour intensive and needs meticulous attention to quality to ensure benefits exceed harms.¹⁻³ Vaccines against human papillomavirus (HPV) provide a new approach to preventing cervical cancer, particularly in countries with a high incidence of the disease and no or poorly developed screening programmes. In the United Kingdom, universal HPV vaccination of girls aged 12-13 will be introduced subject to an independent review of its costs and benefits. Implementation will be complex, and careful planning and education for the public, participants, and health service staff is essential. The challenge for the UK and other countries with established cervical screening programmes is to switch to new and affordable programmes of cancer control that will do more good and less harm than existing ones.

Development of HPV vaccines

The association between cervical cancer and HPV was discovered in the 1970s, HPV type 16 DNA was identified in biopsy samples in the early 1980s, and by 2003 the classification of the seven most prevalent HPV types that cause 87% of cervical cancers was described.⁴ The creation of preventive vaccines soon followed. At present no vaccines can treat existing HPV infection.

Two vaccines have been developed so far and one, Gardasil, is already licensed for prevention of cervical cancer. Gardasil is a quadrivalent vaccine active against four HPV types—HPV-16 and HPV-18, associated with 70% of cervical cancers, and HPV-6 and HPV-11, associated with most cases of genital warts. The second vaccine, Cervarix will probably be licensed later this year. It is bivalent and protects against HPV-16 and HPV-18. Vaccines protecting against other oncogenic types of HPV may possibly be developed within 10 years.

Public policy on preventing cervical cancer

A transatlantic visit by newspaper editor Harold Evans triggered the media campaign that culminated in the start of cervical screening in the UK in the 1960s. Few people had heard of cervical cancer, and as public concern mounted, a screening programme was introduced rapidly before the many uncertainties it raised were resolved. In particular, Archie Cochrane's call for randomised controlled trials was ignored.⁵ By 1985 around 40 million tests and around 200 000 cone excisions had taken place.⁶

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Many women were left infertile after surgery, some had complications, and some died. Yet deaths from cervical cancer hardly changed.

Eventually, after a media storm when a woman died from cervical cancer having never received her abnormal screening result, the programme was overhauled. Training and quality standards were introduced for all aspects,⁷ resulting in a fall in death rates.⁸ Incidence went from 15.4 per 100 000 in 1986 to 9.6 in 2000, and mortality from 10.9 per 100 000 in 1950 to 3.4 in 2004.⁹ Fewer than 1000 women now die from cervical cancer annually in England, and a further decline is expected as screened cohorts age. There is a downside to screening though, in the form of overdiagnosis and overtreatment. For each death averted, more than 150 women have an abnormal screening result and over 80 are referred for investigation.³

Faced with the challenge of devising and implementing a completely new programme to prevent cervical cancer based on HPV vaccination it is essential to determine what combination of vaccination, testing, and treatment is needed.⁷ In the past, the National Health Service (NHS) cervical screening programme has dealt successfully with difficult policy decisions on Papnet (computer assisted cytology testing), HPV testing, and liquid based cytology, despite aggressive marketing aimed at forcing immediate adoption. The introduction of HPV vaccination requires similar careful planning. Launching a programme prematurely could result in low uptake of vaccine, low uptake of screening, considerable public confusion, scaremongering about side effects,¹⁰ and no extra effect on disease rates.

In the UK, policy making is being led by the Department of Health's joint committee on vaccination and immunisation,¹¹ and on the basis of their deliberations, an announcement was made on 20 June 2007 that an HPV vaccine programme would be introduced subject to an independent cost-benefit analysis.

In Europe, a survey initiated in January 2007 by the Vaccine European New Integrated Collaboration Effort paved the way for sharing epidemiological data and analysis to help policy making.¹² The report emphasised the complexity of the problems and questioned the assumed benefit of vaccination over high coverage screening, yet it found that by March 2007 four countries had already made policy decisions. The vaccine recommendations were for pre-adolescent girls in Austria, for girls age 12-17 in Germany, for girls age 14 with catch up to 23 in

France, and for girls age 12 in Italy. Only Italy had agreed how to fund it.

The Advisory Council on Immunisation Practices in the United States recommends HPV vaccination for various groups, including women up to 26.¹³ Texas was the first state to make HPV vaccination in girls legally compulsory for students entering sixth grade, and others are considering such legislation. Australia has a government funded programme offering vaccination to girls age 12-26. Introduction of state funded vaccination is also being considered in Canada.

What is the evidence so far?

Vaccine studies

Four phase II randomised controlled trials have examined safety and efficacy of HPV vaccines in women, and several phase III trials are in progress. The evidence is summarised in a Canadian Health Technology¹⁴ review, a summary by Koutsky and Harper, and in reports from two phase III studies, the future II trial and the HPV PATRICIA study.¹⁵⁻¹⁹ No major adverse events have occurred. Vaccination gives 88-100% protection against HPV infections and cervical intraepithelial lesions for the HPV types vaccinated against in participants with no evidence of HPV infection at recruitment. Results of the future II trial of 16-26 year old women confirm high (98%) protection against cervical intraepithelial neoplasia related to vaccine types in non-infected women. When all participants and all lesions are considered, the difference is 17%, with 266 cervical epithelial lesions in the control group and 219 in the vaccine group. Women with a previous screening abnormality or more than four sex partners were excluded, so protection may be even lower in non-research populations.¹⁶ Overall protection in the PATRICIA study is not reported.¹⁸

Attitudes to vaccination

Studies from different countries, including two from the UK,^{20,21} have examined women's and parents' knowledge and attitudes about HPV and vaccination. People generally know little about HPV but when given information most support a vaccine that prevents cancer provided it is effective and safe. Thus, we need a comprehensive information programme to enable informed choice.

Will HPV vaccination be cost effective?

Modelling of impact on HPV prevalence and cancer incidence
Several modelling studies have been published and more are in progress. The models are valuable if based on sound assumptions but do not preclude the need for ongoing evaluation of true life implementation.

Things we still don't know

Because studies have been followed up for five years only, we do not know how long immunity from vaccination lasts. Further evidence will continue to emerge, so we may need to adjust our policies. For example, booster vaccinations may be needed. Nor do we know for certain that protection against cervical intraepithelial lesions translates to protection against fatal invasive cancers, although this is likely. This means that research follow-up for vaccinated girls and young women will be needed for several decades,²² including monitoring of HPV types in cervical intraepithelial lesions. In the longer term, vaccination history will need to be part of the UK audit of cervical cancers.²³

Further questions that need to be answered are how much cross protection the vaccines give against HPV types not included in the vaccine and what the uptake of vaccination will be. High uptake of vaccination in lower socioeconomic groups is important for they are at the greatest risk of developing cervical cancer. Compliance with subsequent screening of vaccinated cohorts is also important. The effectiveness of vaccinating men is not known, and until studies evaluating this are concluded vaccination of boys is not indicated.

Things we do know

Vaccination of girls before they are exposed to HPV provides immunity to infection with the vaccine types, and it protects against cervical intraepithelial lesions associated with these HPV types, for at least five years. Vaccinating pre-adolescent girls will probably reduce their risk of developing cervical cancer related to HPV-16 and HPV-18. Such vaccination can be recommended once the infrastructure for service delivery—including information technology for scheduling invitations and recording vaccination history—is in place.

Around a third of cervical cancers are caused by types other than HPV-16 and HPV-18 and will not be prevented by current vaccines. Also, girls who were sexually abused as children may have been exposed to the vaccine types. Some form of screening will therefore be necessary, possibly at around age 25, even for women who were vaccinated before adolescence. Vaccination at age 16-26 in the future II study gave only 17% overall protection against cervical intraepithelial neoplasia. Screening, which gives 80% protection, is more effective so is the policy of choice for females 16 and over.

More than 80% of lesions with borderline and mildly abnormal cytology and more than 70% with low grade abnormality on histology (cervical intraepithelial neoplasia 1 and 2) are not related to HPV-16 or HPV-18 so will not be prevented by vaccination.²⁴ Screening in cohorts vaccinated before adolescence will therefore yield a very high ratio of inconsequential abnormalities relative to lesions where intervention brings genuine health ben-

efit. Trials are needed to ascertain the optimum cervical screening regimen for vaccinated cohorts.

Vaccination has been shown to be safe in girls from age 9. Ongoing follow-up will continue to monitor safety—for example, in relation to inadvertent vaccination during pregnancy—and duration of immunity. The Department of Health based its choice of vaccination age on views of parents and girls about acceptability, practical considerations relating to likelihood of high coverage, and duration of immunity.

The quadrivalent vaccine provides immunity to HPV-6 and HPV-11, which cause genital warts. Although not life threatening these cause substantial distress. Their prevention would be an extra benefit of vaccination, although the relative price of bivalent and quadrivalent vaccine, and evidence of cross protection—should this be confirmed—must be taken into account.

Cost implications of universal vaccination

The cost of a vaccination programme includes the cost of information and education for parents and girls, the staffing and information technology infrastructure for delivering a school based programme offered to all girls, and the cost of the vaccine. In a total population of a million, around 7000 girls will need to be vaccinated each year. Staffing costs are likely to be at least £100 000 (£147 800; \$201 800) each year and vaccine costs will depend on both price and uptake. If vaccines cost £80 per dose (February 2007 *Monthly Index of Medical Specialties (MIMS)* price, excluding value added tax) and uptake is 80%, delivery for a million population will cost around £1.44m annually. Education and information technology costs and booster doses will add to the cost. For England as a whole, vaccination of pre-adolescent girls could add more than £72m annually to the existing cervical cancer control programme, which in 1998 cost £132m,²⁵ and may now be around £198m.

If vaccination is simply an “add-on” to the screening programme then attributable additional lives saved will be few, because deaths from cervical cancer will continue to fall even without vaccination as the impact of the screening improvements in the 1980s take full effect. For a million population, around 15 deaths occur annually, 10 of which are in women under 75. Thus, a policy of simply adding vaccination may not be a good use of resources. If vaccination can be accompanied by replacing existing screening with a regimen involving fewer tests—incorporating surveillance only for those with persistent infection—then eventually the programme cost might be only marginally higher than now, and the harm from the high rates of positive tests through screening might reduce.

Conclusion

The only certain way of determining the long term impact of vaccination will be to follow vaccinated women for several decades. This follow-up can be achieved as part of an NHS-wide evaluation of vaccination and subsequent testing. Research and development experts should help plan and implement the new policy and undertake ongoing

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evaluation. In addition, vaccination records, likely to be held on the child health system, should be linked to the Exeter general practitioner registration database, which schedules and records cervical screening tests.

Contributors and sources: AER has been involved in cervical screening policy making, quality improvement, and research since 1985. This article is based on discussions at a national meeting convened by the Department of Health in November 2005, discussions with members of the joint committee on vaccination and immunisation's HPV subgroup, and literature search for published vaccine studies and attitude surveys.

Competing interest: AER is responsible for the cervical screening programme in her local area.

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SUMMARY POINTS

High quality cervical screening reduces deaths from cervical cancer by around 80%

Vaccines against HPV should improve prevention of cervical cancer in countries without screening
Vaccination is less effective than high quality screening in females over 16 years

Vaccination for pre-adolescent girls, with proper education and planning, could improve overall benefit compared with existing screening