HPV vaccines: peering through the fog

Anne Szarewski

Background

The UK's human papillomavirus (HPV) vaccination programme should now be underway: vaccination of 12–13-year-old girls against HPV was due to begin in September 2008, with a recent announcement that 17–18-year-olds will also be vaccinated in this academic year.[1] From September 2009, a further catch-up programme for girls up to the age of 18 years will commence. The Department of Health (DH) has decided that the HPV vaccine to be used for the programme will be Cervarix® (GlaxoSmithKline), which is the bivalent vaccine against the cervical cancer-causing HPV types 16 and 18. This decision has surprised many, in view of the fact that the other available vaccine, Gardasil® (Merck), would protect against genital warts (HPV types 6 and 11) as well as cervical cancer.

It is unfortunate that there has not been a proper disclosure of the factors that led to the decision, resulting in widespread speculation amongst health professionals and the media, particularly relating to the cost of the vaccine. A list of the pre-agreed evaluation criteria against which the bids were evaluated has recently been released (Table 1), and includes many factors, which have been weighted, though details of cost are still not given. When questioned, the Secretary of State for Health stated that both published and unpublished data were considered.[2] The suggestion in the media that girls in the UK will receive an inferior vaccine may undermine the success of the vaccination programme, as parents become unsure whether it is worth vaccinating their daughter with such a product.[3,4] Adding fuel to this debate is a mathematical model published in the *BMJ*, which was considered by the DH when making its decision.[5] This suggests that Cervarix must be £13–£21 cheaper than Gardasil in order to be cost effective. However, it should be noted that a number of assumptions were made in this model; it was assumed both vaccines were identical in terms of efficacy, duration of immunity, cross-protection against non-vaccine HPV types, and that uptake amongst girls would be at least 80%. This last assumption is the least likely to be correct; a pilot study in a primary care trust (PCT) in Manchester found uptake was only 70% overall, and significantly lower in schools with a greater proportion of girls from ethnic minority groups and poorer families. In addition, the Catholic schools in the PCT refused to participate in the pilot.[6] One could speculate that another factor influencing the DH decision might have been the possibility of greater acceptability of a 'cervical cancer vaccine' (without the need to mention genital warts) in certain ethnic and religious groups.[7]

Table 1 Pre-agreed award criteria for the evaluation of the contract to supply human papillomavirus (HPV) vaccine[2]

Criteria	Points (maximum)
Quality of protection against cervical cancers caused by HPV strains 16/18	5000
Duration of protection against cervical cancers caused by HPV strains 16/18 for more than 10 years' duration	3000
Quality of protection against anogenital warts caused by HPV strains 6/11	1300
Duration of protection against anogenital warts caused by HPV strains 6/11 for more than 10 years' duration	500
Quality of protection against HPV strains not included in the vaccine formulation	1000
Other evidence of additional clinical benefits	500
Effective price per dose excluding VAT	Commercially confidential
Supply of the vaccine as single pre-filled syringe pack presentation	10
Quality of labelling, leaflets and presentation	5
Shelf-life	120
Flexibility in the vaccine dosage schedule	70
Offers that reduce the risk of wastage if the vaccine is subject to temperatures above 8°C[a]	200
Closeness of proposed delivery schedule to authority requirements	200
Pallet configuration including a preference for the use of Euro pallets	5
Impact of proposed amendments on the terms and conditions	(–500) [Offerors may lose up to 500 points]
Quality/robustness of manufacturing contingency arrangements	10
Quality/robustness of the risk management of storage and distribution	10
Information provided relating to pack sizes, cold chain delivery, batch numbering systems and production capacity	5

[a]Includes the provision of temperature indicators and evidence-based guidance on the stability of the vaccines at higher storage temperatures and subsequent safe administration.

Age for vaccination

For optimal protection, the vaccines should be administered prior to the onset of sexual activity. In general, antibody responses induced by vaccines are higher pre-puberty compared to post-puberty, a feature that has also been shown for the HPV vaccines. Currently follow-up data are available only up to 6.4 years, but modelling suggests that immunity may persist for 30 years.[8] Ideally, such a vaccine would be administered with other childhood vaccines, removing any link with sexual activity in the minds of parents.

The vaccines

Both Gardasil and Cervarix have shown high efficacy, approaching 100%, against HPV 16 and 18-related high-grade cervical intraepithelial neoplasia (CIN) and Gardasil has shown similar efficacy against genital warts.[8] Although

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Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, London, UK

Anne Szarewski, PhD, FFSRH, *Clinical Consultant and Honorary Senior Lecturer, and Editor-in-Chief, Journal of Family Planning and Reproductive Health Care*

Correspondence to: Dr Anne Szarewksi, Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, UK. E-mail: anne.szarewski@cancer.org.uk

superficially similar, there are differences between the two vaccines, which may turn out to be relevant. Both consist of virus-like particles (VLPs) using the L1 virus coat proteins. VLPs have the outward appearance of the actual virus and generate a powerful immune response (much stronger than natural immunity) but are harmless as they contain no DNA.

The VLPs in the two vaccines have been manufactured using different systems, and the adjuvants used are also different. While Gardasil contains aluminium hydroxyphosphate sulphate, Cervarix is adjuvanted with ASO4, which is aluminium hydroxide with monophosphoryl lipid A. The ASO4 adjuvant has been used previously in a hepatitis B vaccine (Fendrix®), where it was shown to generate a stronger and longer-lasting immune response than the vaccine containing aluminium hydroxide alone.[9] In this context, it is interesting that the antibody response to HPV 18 appears to be maintained at high levels for longer with Cervarix than Gardasil[9] though the clinical significance of this is still uncertain. One could speculate that higher antibody levels might translate into longer lasting immunity, a criterion weighted heavily in the UK evaluation (Table 1) and in a recent economic evaluation in the USA.[10] Clearly, if one vaccine required a booster after a certain length of time while the other did not, the difference in costs to a vaccination programme would be very significant. A direct comparison study of the two vaccines is underway, using a non-proprietary neutralising antibody assay; interim results should be available before the end of this year and are awaited with interest.

Cross-protection

A related issue is that of cross-protection. It had been thought unlikely that this would occur, yet both vaccines have shown early evidence of such an effect. In the extended Phase II trials at 6.4 years, Cervarix has shown 78% (95% CI 39–93) protection against incident infections with HPV 45, which is HPV 18-related, and 60% (95% CI 20–81) protection against incident infections with HPV 31, which is HPV 16-related.[11] In the interim analysis of the Phase III trial, Cervarix has shown cross-protection against persistent infections at 6 months for HPV type 45 (59.9%, 95% CI 2.6–85.2), type 31 (36.1%, 95% CI 0.5–59.5) and type 52 (31.6%, 95% CI 3.5–51.9). The extent of sustained cross-protection against persistent infections, abnormal cytology and pre-cancerous lesions remains to be determined. A laboratory study of antibody cross-neutralisation with Gardasil suggested cross-protection against types 31, 45, 52 and 58,[8] while more recently data have been presented suggesting protection against both persistent HPV infection and CIN associated with a bank (31/33/45/52/58) of non-vaccine HPV types.[12] However, interestingly, in the Canadian Summary of Product Characteristics, dated March 2008, the level of protection against individual HPV types is given; here there is no cross-protection against HPV type 45.[13] Although the clinical significance of this is not yet known, it is interesting that there appears to be a consistently weaker effect of Gardasil on HPV 18 and its related type, 45 (see above). Cross-protection is an important issue, as it may raise the overall protection level significantly.

Other issues

Vaccinating older women

Studies are underway to evaluate the benefit of vaccinating older women (i.e. those over 25 years of age). In a group of previously HPV-negative women aged 24–45 years, recently presented data suggest that Gardasil was highly effective in preventing both persistent HPV infection and disease associated with the HPV types in the vaccine.[14] If efficacy in older women is confirmed, vaccination of a wider age range could have a more immediate impact on cervical cancer.

Need for third vaccine dose?

Is the third dose of vaccine actually necessary? A three-dose schedule is complicated and particularly problematic in developing countries. Could one 'mix and match' the two vaccines to try and reap the benefits of both? We do not have answers to these questions at present but they are urgently needed.

Future of cervical screening?

In theory, an HPV vaccine could prevent almost all cervical cancer, eventually removing the need for cervical smears. It is noteworthy that the vaccines should be effective against cervical adenocarcinoma (of which a relatively higher proportion are associated with HPV 18 and 45), which is not detected effectively in current screening programmes and which appears to be increasing in incidence. There is potential for a very significant reduction in this cancer, which now accounts for up to 20% of cervical cancers. However, until the number of HPV types in the vaccine is increased, there will still be cancers not prevented by vaccination. In addition, there is at least one whole generation of women for whom the vaccines have come too late to precede sexual activity, and who will continue to require screening. It is, however, clear that screening programmes, where they exist, will need to adapt when HPV vaccination becomes widespread. It is likely that cytology will become less useful as the number of abnormalities in the population decreases, and cytologists struggle to maintain their skills. HPV testing of some kind is likely to be the way forward, but this raises many issues – not least the high transient positivity rates in women under 35 years, and the probable need for HPV typing tests, which are not yet commercially available, to monitor long-term vaccine efficacy. These are issues that will need to be addressed in the next 15 years in the UK.

Vaccinating boys

Data on efficacy in men are awaited, as the issue of whether to vaccinate boys as well as girls is still under debate. Most mathematical models suggest that vaccination of girls alone is the most cost-effective strategy, assuming high uptake amongst girls. However, if boys are not vaccinated, men who have sex with men (MSM), and who are at increased risk of HPV infections and anal cancer, will not benefit from the vaccine. Another unfortunate aspect of restricting vaccination to girls is that it focuses attention on women in relation to a sexually transmitted virus; this is not a useful social message in any context and there are some cultures in which the strategy may prove unacceptable.

Assuming efficacy in men is shown, I suggest that an ideal solution would be to vaccinate girls with Cervarix and boys with Gardasil. Evidence is accumulating to suggest that Cervarix may offer greater protection against cervical cancer, which would make it the more logical choice for girls. If boys were vaccinated with Gardasil they would improve herd immunity against the cancer-causing HPV types, while also being protected themselves (a particular benefit for MSM). Meanwhile, their vaccination against HPV types 6 and 11 would, again via herd immunity, protect both sexes. Finally, both sexes would be seen as susceptible, which, in my view, would be a far more equitable public health message.

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