Joint Committee on Vaccination and Immunisation

Minutes of the HPV Sub-group meeting, Wednesday 28 February 2007

Attending:

Professor Andrew Hall (CHAIR)
Professor Margaret Stanley
Dr Katherine French
Professor Paul Griffiths
Professor Leszek Borysiewicz
Julietta Patnick
Professor Jack Cuzick
Dr Charles Lacey
Dr Richard Roberts

Health Protection Agency
Professor Elizabeth Miller
Dr John Edmunds
Dr Mark Jit
Dr Kate Soldan

Health Protection Scotland
Dr Martin Donaghy

NIBSC
Dr Stephen Inglis

Scottish Executive
Dr Elizabeth Stewart

DHSS Northern Ireland
Dr Lorraine Doherty

DH
Joanne Yarwood
Dr Peter Grove
Dr Sowsan Atabani
Dr Karen Noakes (minutes)

Executive summary

1. The group's view was that there is sufficient evidence on the protective effect of HPV vaccines on cervical cancer in the UK to suggest vaccination of girls at 11-12 years of age (in the first year of secondary school) as part of a school-based programme in conjunction with a sexual education programme (through Personal & Social Education-PSE).

2. The sub-group considered that a catch-up campaign to include all girls up to the age of 15/16 years would be beneficial. However, additional cost-effectiveness analysis to determine the extent of catch-up was required for a recommendation by the main Committee.

3. The committee strongly recommended the implementation of procedures to record individual vaccination and other disease surveillance measures to facilitate subsequent assessment of the impact of the vaccination programme.

4. The sub-group agreed that the effectiveness and cost-effectiveness model developed by the HPA needed to be peer reviewed by biologists, mathematical modelers and economists to ensure that the model was robust.

5. The committee noted that with any introduction of routine HPV vaccination the national cervical screening programme should continue unchanged until further investigation assesses the impact of immunization on its cost-effectiveness. This w ill also help to identify HPV related cervical lesions that are not covered in the current HPV vaccines and to evaluate the impact of the vaccination programme. It was suggested that as the vaccinated individuals reach screening age, the frequency of screening might be amended.

6. Based on the data provided, the subgroup committee felt that further analysis of the benefits of warts prevention was necessary to make an informed decision on the choice of vaccine (bivalent vs. quadrivalent). This was not essential to forming a recommendation on vaccination in general, as the main objectives relate to the prevention of cervical cancer. The sub-group favoured the use of the most cost-effective vaccine against all endpoints, including genital warts.

MINUTES

1. Announcements and apologies

Members were welcomed to the third meeting of the JCVI subgroup on HPV vaccine. The main aim of this meeting was to consider new data from the vaccine manufacturers (and others) and further work that has been carried out by modelers at the Health Protection Agency and Imperial College, and to provide advice on the data and assumptions used in the models. New data from the HPA on age specific seroprevalence of HPV 6, 11, 16 and 18 in young females were also to be considered.

Apologies were received from: Professor Henry Kitchener, Professor Geoffrey Garnett, Dr Syed Ahmed, Derinda Fitton, Dr Paul Jackson,Dr Ruanne Barnabas, Dr Mair Powell, Neil Robbins, Dr Claire Cameron, Dr David Salisbury, Dr Dorian Kennedy and Tim Elliot

The following members declared interests in GSK or Merck (Sanofi Pasteur in the UK).

Stephen Inglis specific, non personal
Katherine French specific, non personal
Geoffrey Garnett personal, specific (not present at the meeting)
Paul Griffiths non personal, non specific
Charles Lacey non personal, specific
Liz Miller non personal, non specific
John Edmunds personal, non specific
Margaret Stanley non personal, specific
Martin Donaghy personal, non specific

It was noted that all members present were permitted to take part in the discussions.

2. Minutes of meeting 22 September 2006

Elizabeth Stewart did not attend this meeting, Martin Donaghy attended for the Scottish Executive, Julietta Patnick's title is not Doctor, Jack Cuzick is a Professor, Paul Griffiths is noted twice as attending. It should be noted on page 5, second paragraph that the NHS Screening programme are a partner, with the Health Protection Agency and Manchester ARTISTIC group, in the study to test biopsies for type-specific HPV infections and are funding this work. On page 5, paragraph 4 it is noted that Cancer Research UK plan to type 1000 abnormal cytology samples referred for colposcopy. This is in women of all ages so reference to this being in 'women in their 20's' should be removed. With these amendments, the minutes were agreed as a true record.

3. Matters arising

Three actions were noted from the minutes of the last meeting:

(i) Page 7, paragraph 6. Screening history data from the Manchester ARTISTIC group is to be made available to modelers at the Health Protection Agency. This was reported as in progress and these data should be included in the models in future.
(ii) Page 8, paragraph 4. Members had yet to see the WHO document on the possible clinical study designs that might support addition of serotypes to the current HPV vaccines that had been due to be published in 2006. The Secretariat would check whether this has been published and circulate this document.

(iii) Page 8, paragraph 6. It was confirmed that DH Press Office would keep other Press Offices (including that of the National Cancer Screening Office) informed of any media plans and ensure that draft press releases are circulated for comment.

4. Additional data on vaccine clinical efficacy trials

It was noted at the start of this item that the papers provided by Sanofi Pasteur MSD and GlaxoSmithKline were commercially confidential and must not be circulated or discussed outside this meeting.

The additional data provided by Sanofi Pasteur with regards to Gardasil included an executive summary in response to questions raised in the past HPV subgroup meeting held in Sept 2006. The summary addressed the following issues:

-cross-reactive antibodies induced by the vaccine (detected in vitro using a binding immunoassay & pseudovirus neutralization assay)
-enhanced immunogenicity and longevity of antibody response of Gardasil by providing the 5 year follow up phase II clinical trial publication by Villa et al, 2006) and also a submitted manuscript describing HPV-specific antibody responses following immunisation with various aluminium adjuvants (Caulfield et al, unpublished).
- the commitment of the manufacturer to continued research and development of HPV vaccines, which may lead to the inclusion of further HPV types in their vaccine formulation.

Further published papers and meeting abstracts were provided on the immunogenicity of Gardasil in adolescent males and females, comparing the magnitude of the response to that in young women (Block et al, 2006) and the duration of the immune response up to 12 months post 3rd dose (Reisinger et al, 2007), impact of Gardasil on prevention of cervical lesions in women recently infected with a vaccine type HPV (DNA positive, seronegative) on enrolment and a 3 year follow-up data on the impact of Gardasil on the development of vaginal and vulvar pre-cancerous lesions.

Additional data provided by GSK included published papers showing sustained efficacy up to 4.5 years of the bivalent vaccine (Harper et al, 2006), an unpublished report of efficacy data representing 5.5 years of total follow up as continuation of the Harper paper. This includes an interim analysis of a multi-centre study carried out in women regardless of their HPV status at enrolment. This provides some in vivo cross-protection data against infection with HPV types 31, 45 & 52.

The group agreed that there was not yet any evidence of greater cross protection against any non-vaccine HPV types 31 and 45 in one vaccine compared to the other. The results so far were based on a small phase II clinical trial or by using in vitro immunoassays. It was noted that the results of the assays did show the sera to be cross neutralizing rather than just cross reactive which was encouraging. In the small phase II trial, the results presented provided evidence of protection against infection rather than protection against disease. It was noted that it would be difficult to show cross protection against 45 and potentially others in a clinical trial as the incidence of disease caused by these types is relatively low thus you would need a large number of women in the trial.

The group agreed that there was so far no evidence of any difference in duration of protection between the two vaccines.

The group also discussed whether multivalent vaccines, protecting against additional serotypes, would be available in the future and how these might be added to immunisation programmes. It was not known how many years away these multivalent vaccines are. Based on current HPV vaccination programmes, the future licensure of multivalent vaccines would likely be dependent on immunogenicity and possibly the prevention of incident infection (as a surrogate marker for persistent infection). It was suggested that one possibility would be the marketing of additional vaccines for other HPV types rather than the inclusion of these in the current vaccine. This might be necessary because of the protein load in polyvalent vaccines leading to increased reactogenicity.

It was important to consider the WHO document on possible clinical study designs supporting addition of types to the current HPV vaccines in these discussions. It was stated that a Merck polyvalent vaccine was tested in a phase 1 clinical trial and the immunogenicity data was in press for scientific publication.

5. Prevalence and epidemiology of HPV in the UK

Provisional data from the Manchester ARTISTIC group on the distribution of HPV type by age and grade of cytology was provided at the meeting. Data were also provided on mixed infections where two or more HPV types were present. These data were provided in confidence. The data also confirms the point that the incidence of HPV type 45 causing disease in the UK is low.

6. Published mathematical models

The group were asked to comment on the following published models assessing the burden of cervical cancer, impact of HPV vaccination and its cost-effectiveness as a prevention strategy for HPV-infection and disease.

- Kohli M, Ferko N, Martin A, Franco EL, Jenkins D, Gallivan S, Sherlaw-Johnson C, Drummond M. Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK.
  Br J Cancer. 2007 96:143-50.
- Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease.
  Epidemiol Rev. 2006 28:88-100.
- Van de Velde N, Brisson M, Boily MC. Modeling Human Papillomavirus Vaccine Effectiveness: Quantifying the Impact of Parameter Uncertainty.
  Am J Epidemiol. 2007 Feb 1; [Epub ahead of print]
- French KM, Barnabas RV, Lehtinen M, Kontula O, Pukkala E, Dillner J, Garnett GP. Strategies for the introduction of human papillomavirus vaccination: modelling the optimum age- and sex-specific pattern of vaccination in Finland.
  Br J Cancer. 2007 96:514-8

It was noted that the Kohli paper used the same model as discussed previously (for USA) but now used UK data. The model was a static one (incapable of taking into account indirect effects) and was difficult to assess (or re-create) as not enough information had been included in the published paper on methods and parameters used.

The Elbasha paper used a similar model to the one being used by the Health Protection Agency as they have both been adapted from the model developed at Imperial College (Professor Geoff Garnett). It was difficult to understand the parameterization used and the group had not gone into the same level of analysis that the two groups presenting to JCVI were doing in looking in detail at the UK data from the ARTISTIC study. The paper by Van de Velde looks at the different model structures that can be used to assess the impact of HPV vaccination and analyses what factors are important in order for data to fit the model. It highlights the complexities of this work and the fact that different model structures produce different results. It was not a cost-effectiveness study. Similar to the Kohli paper, the model only takes account of the direct protection (i.e. did not consider herd immunity), and would therefore be expected to underestimate the impact of vaccination at the population level.

The ideal model to base a decision on uses UK parameters that have been adequately described and is one where we can be confident in the model structure, or in which uncertainty with regards biological assumptions (model structure) and parameter values has been thoroughly explored..

7. Age structured model of HPV-16 in the UK

An age structured dynamic transmission model of HPV-16 infection only and progression to cervical cancer was presented by Katherine French.of Imperial College. The model assumes that the vaccine has no effect on those already infected, assumes that the vaccine is 100% effective over a lifetime and explored different assumptions about natural immunity to fit the model.

The model uses data obtained from Natsal 2000 for sexual behaviour and age of sexual debut and the HPV progression and regression rates based on rates from the literature adjusted to improve model fit. HPV-16 DNA data has been obtained from the ARTISTIC study and serological data obtained from the Health Protection Agency (Preston sera bank). Cervical cancer incidence data was obtained from Cancer Research UK. Fitting the model to UK data has been more difficult than anticipated. If the model parameters from Finland are used, this dramatically overestimates HPV prevalence, detected by both DNA and serology. If the ARTISTIC data is used to parameterize the model, the predicted HPV DNA prevalence is overestimated but the seroprevalence data fits the model moderately well. The data, including cancer incidence, fits much better in the model if the duration of natural immunity is increased from 5 years to life long.

The model assumed that girls are vaccinated at age 12, 15, 18 or 21 and that 70% coverage is achieved in the first year of the programme. A catch-up programme of 3, 6, 9 and 12 years worth of cohorts is evaluated in the model. A discount rate of 3% was used for both vaccinations and cases prevented. Results from these scenarios show:

- Vaccination for HPV 16 is more beneficial at young ages, before sexual debut. There is little difference in vaccinating girls at 12 or 15 years as only a small number of girls show evidence of infection before age 15 years
- Vaccinating males increases the number of cases prevented, especially if vaccinating at younger ages. This is dependent on vaccine coverage in girls. The benefit of vaccinating males as well as females is greatest at mid vaccine coverage (between 50-70%).
- Vaccinating males as well as females prevents fewer cases per 100 vaccinations given.
- A Catch-up programme has more impact when vaccinating younger ages. If 12 year olds are vaccinated, there is benefit from a catch up to the age of 18 years but additional ages beyond this showed a plateau in benefit
- A Catch-up vaccination programme increases the speed with which a decrease in HPV incidence is observed but overall increasing the number of ages included in catch-up does not have a great impact on number of cases prevented per 100 vaccinations given over 50 years.
- Duration of vaccine protection has a large impact on number of cases prevented per 100 vaccination
- The assumption of natural immunity is important. The shorter the duration of natural immunity the greater the impact of vaccination

The group commented that on the issue of whether to vaccinate at age 12 or 15 years, the antibody titres following vaccination are likely to be higher at age 12 rather than 15 years as younger people respond better to the vaccine.
Immunogenicity studies whereby geometric mean antibody titres (GMTs) were stratified by age have shown that the highest GMT was detectable following vaccination at age 12 and declined by up to half a log thereafter. From 16 years onwards, antibody levels following vaccination quickly fall and plateaus.

Regarding the assumptions made in the age-structured model. It is assumed that infected individuals remain infectious throughout but there are published papers to suggest that individuals are mainly infectious during the acute period and therefore the herd immunity effects are potentially overestimated in the model. A separate point was made that there is also likely to be a birth cohort effect which means that the data may not fit the model as well. The group were asked whether they could contribute to the issue of duration of natural immunity. This group agreed that the duration is unknown but there is a clear possibility of virus reactivation in older women (possibly due to immune senescence or alterations in immune responses associated with the menopause) and for some individuals their natural immunity will wane overtime and a large dose of virus could lead to them becoming reinfected. In natural infection it is not surprising that antibody levels are low as virus shedding occurs locally and in the absence of viraemia, a robust specific (IgG) immune response will not be induced. This is not the case for HPV vaccination where antibody responses are high as the virus-like particles are administered intramuscularly with easy access to antigen-presenting cells which will induce a strong immune response.

8. HPA modeling of cost effectiveness of HPV vaccination

The Health Protection Agency have tested a cross-sectional panel of serum samples from the Preston Serology Collection from women aged 10 - 29 years old for HPV types 6, 11, 16 and 18. Samples were tested by Merck laboratories in the US, using their neutralising antibodies assay. Results show that HPV seroprevalence is low up to age 14 and then increases rapidly. However, there is a fall in HPV seroprevalence at about age 25, which raised concerns about the use of these data to derive force of infection estimates to parameterise the models.

Somewhere in the range of 65% - 85% of women with an HPV infection seroconvert, so the actual incidence of HPV cannot be accurately determined from this data set. It also takes about 6-12 months for an incident HPV infection to produce an antibody response.

When compared to the type-specific HPV DNA prevalence data from the ARTISTIC study, the seroprevalence in 20+year old females was higher. This is consistent with detectable antibody response being a marker of past/cumulative exposures to HPV infection rather than representing current infections.

The data are useful as they contribute two important parameters. The first is the risk of exposure to HPV infection by age, within the candidate age range for vaccination. Results show that HPV seroprevalence is low up to age 14 and then increases rapidly from age 15, and therefore suggest that vaccination at age 14 or older would be too late to offer protection prior to substantial risk of infection. Conversely, there appears to be little additional protection to be gained by lowering the age of vaccination below age 13 (allowing 6-12 months for seroconversion).

The second parameter that can be estimated from seroprevalence curves is the type-specific force of infection for HPV. However, this is more complicated, as is evidenced by the drop in the proportion of women with serum HPV antibodies after the age of ~23. This suggests that estimation of the force of infection from HPV seroprevalence data may need to take into account some waning of antibody levels (and seroreversion) after incident HPV infection or a possible cohort effect. It is unlikely that cohort effects alone would have such an impact on seroprevalence within the age-range under consideration and the fall was considered more likely to be due to waning antibodies. It was also noted that the population from which the samples in the serum database were obtained may affect the findings. In younger age groups, the samples received are mostly for diagnostic purposes. In the older age groups, the samples are most likely to come from antenatal screening and are not representative of the general population, in particular in relation to sexual history.

It was noted by the group that there are studies that show that in women with cervical cancer, only 50% are seropositive. .

Due to these uncertainties, the force of infection derived from this dataset has not currently been incorporated into the modelling.

Several natural history models with different assumptions about type-specific HPV natural immunity appear to fit population-based cytological and HPV DNA data well. Three Markov models have been used:

SIS - after infection with a single HPV type, no natural immunity and therefore can be reinfected
SIR - after infection with a single HPV type, goes to an immune state and can't ever be infected again with that HPV type
SIRS -after infection with a single HPV type, goes to immune state, but immunity can wane

Genital warts incidence data were used to derive force of infection to parameterize the models as the seroprevalence dataset contained uncertainities in the older age groups, as discussed above

Transmission models, based on the model from Imperial College are also able to fit data well except for the DNA prevalence in older women.

The group discussed the assumptions made in the models. They noted that biologically, the SIRS model is probably the most accurate. SIS models may be the most appropriate approximation when types have to be bundled, e.g. when modelling 'all/other high risk types'. It was noted that for type 16, progression from infection to CIN3 is rapid but this is accounted for in the model, as all progression rates were type (or group of types)-specific. Whether or not there is lifelong immunity to natural infection affects the outputs of the model, however the affect did not change the key conclusions . From a biological viewpoint it was noted that following natural infection it is difficult to measure cross-neutralizing antibodies with the available assays as the antibody response induced is not of a great magnitude.

It was suggested that trends in the National Screening Programme, with a decrease in coverage over time (as is currently being seen) should be included in the modelling scenarios. This could also include Modelling the effect of reducing the frequency of screening post implementation of HPV vaccination . This is something that could be considered in the future. The group noted that these changes would all lead to an increase in the cost effectiveness of vaccination.

The models with base case parameter values give a cost effectiveness per QALY below £20,000 after discounting, assuming lifelong vaccine protection and 100% vaccine efficacy. This is below the threshold of £20,000-30,000 generally used by NICE. The most influential parameter was the duration of vaccine-induced protection. In addition, it was pointed out that there are many other biological assumptions (apart from those related to development of natural immunity) that were not assessed as part of the sensitivity analysis. The combined structural and parameter uncertainty could potentially affect conclusions. A substantial part of the cost effectiveness of such an intervention is in the prevention of genital warts. This element of the model is currently based on limited data, hence a study

looking at the burden of genital warts in the UK is ongoing. This should provide better estimates of the episode lengths, costs and quality of life weights associated with anogenital warts.
It was noted that all of the models considered gave a base case cost per QALY below £20,000 and hence the literature was consistent on this point.

The group noted that the additional benefits in vaccinating boys to reduce the incidence of warts is low. This is because with a sustained high vaccine coverage in women, eventually all cases of warts would be eliminated because of herd immunity and the indirect protection of men. It was previously noted that, with high vaccine coverage, the vaccination of boys does not add any additional benefit to the prevention of cervical cancer.
The modelling group have yet to include a 10 year booster into the model or include other HPV-related cancers such as vulva and anal cancers. Work on the catch-up vaccination strategies is not yet complete.. Based on the effectiveness data from the Imperial model it would indicate a catch-up programme from 12-18 years.

Due to discounting, it is more cost-effective - if all else is equal - to vaccinate at a later age (14 years of age compared to 12 years) as the prevention of cancer is closer to the time of vaccination.

With high vaccine coverage, the vaccination of boys does not add any additional benefit to either the prevention of cervical cancer or genital warts.

It was agreed by the group, that the models examined by JCVI should be peer reviewed by 1. independent modellers not working directly in the HPV field] 2. HPV biologists (both in the UK and abroad) who could examine the plausibility of the assumptions of the natural history of HPV made in the model and 3. health-economists. Reviewers may be sought from abroad as/if necessary.

This Peer review should be carried out prior to the main JCVI meeting in June.

9. Public attitudes to HPV vaccination

In September 2005 research was conducted by DH to explore the response of parents to the introduction of HPV vaccine to 8-10 year old girls and boys and this work has since been published. Parents were of the opinion that vaccination should be carried out in older children at secondary school, in conjunction with a sexual education programme (through Personal and Social Education (PSE). Other research groups have published similar findings. A new qualitative research study is to be carried out by DH in spring 2007 reflecting possible changes to the programme should it be introduced.

The target groups will comprise:

- parents of 11 - 12 year old girls and boys (weighted towards girls)
- girls aged 11 - 15
- young adult women aged 16 - 18 yrs
- secondary school teachers, especially those involved with personal health and social education (PHSE)
- GPs and practice nurses (for 'mop-up' only)

Work with religious groups will be undertaken as a separate piece of work.

The findings from these studies will provide the Department with useful intelligence on how attitudes have changed since 2005 given the possible raising of the age when the vaccine will be given. The results will also help to inform and shape the communications planning.

Papers for information

An extract from Scottish Parliament Official Report 1 February 2007 detailing a debate held on cervical cancer and HPV vaccine was included for information. The group thought the debate was balanced and raised many interesting points already considered in today's meeting. The Chair of JCVI would write to Kenneth Macintosh who raised the issue for debate.

8. Any other business

The group agreed that a further sub group meeting was probably not necessary and that with some further work on the current models including further work on catch-up element of the programme and further work to understand the serology data the results could be considered by main JCVI. The subgroup committee felt that further analyses on the impact of genital warts prevention was necessary to make an informed decision on the choice of vaccine (bivalent vs. quadrivalent),The subgroup would attach their proposed advice on a recommended HPV vaccination schedule and include this with the models that will be peer-reviewed. This advice would be circulated as an executive summary to the minutes shortly following this meeting.

The Committee also noted that there were important areas for research raised during the meeting which could be informative to research funding organizations. In particular the issue of cross protection and cross reactivity between serotypes, the use of 2 doses of vaccine rather than 3, and the issue of vaccination in males.