

**JCVI statement on**

**Human papillomavirus vaccines to protect against cervical cancer**

This statement summarises the work of the Joint Committee on Vaccination and Immunisation (JCVI) in relation to human papillomavirus (HPV) vaccines for protection against cervical cancer. The statement reviews the considerations made by JCVI and the JCVI HPV subgroup, the evidence examined, and the conclusions and recommendations of the JCVI.

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**Executive summary**

**Recommendation**

The evidence presented on HPV vaccination led the committee to confirm that a universal HPV vaccination programme for girls aged 12 to 13 years would be cost effective. In addition to this, the committee were also able to recommend a time-limited ‘catch up vaccination of girls aged 13 to 17 years. This would be delivered most efficiently through schools.

The committee observed that a ‘catch up’ vaccination of women aged 18 to 25 years was not cost-effective at the vaccine price considered. However, the committee recognised that the vaccine could benefit some individual women aged 18 and over who were at risk of new HPV infection by the vaccine types. The committee asked that the Department to consider this further and explore mechanisms of meeting such requests.

The committee also recommended that at the time of vaccination, the opportunity should be used to explain to women the importance of cervical screening, which will remain an essential component of the cervical cancer prevention programme.

The committee considered whether either of the two licensed vaccines should be recommended in preference over the other. Both currently available vaccines protect against the HPV types that cause over 70% of all cervical cancers (16 and 18). One vaccine also protects against HPV types 6 and 11 that cause around 90% of all genital warts. HPV vaccines are sub-unit vaccines made from the major protein of the viral-coat or capsid of HPV. Virus-like particles (VLPs) are prepared as recombinant proteins from either yeast or baculovirus infected cells that are derived from a type of moth.

VLPs mimic the structure of the natural virus but do not contain any viral DNA. There are currently two different HPV vaccine products. Cervarix® contains VLPs for two HPV types (16 and 18 – bivalent vaccine) and Gardasil® contains VLPs for four HPV types (6, 11, 16 and 18 – quadrivalent vaccine).

The committee recommended that the choice of vaccine to be purchased will be primarily determined by cost effectiveness which is highly dependent on the negotiated cost of the vaccines. However, if the vaccines were offered at similar prices, then the committee recommended choosing the quadrivalent vaccine, which would prevent genital warts as well as cervical cancer. Any differential between the prices offered would need to compensate for the lack of protection against warts.

The committee considered a comprehensive plan to monitor and evaluate the introduction of the vaccine. This will be critical in determining any future modifications to cervical cancer control. The committee recommended that this plan be fully funded as an integral part of the vaccine introduction.

### ***Cervical cancer and HPV***

HPV is the most common viral sexually-transmitted infection<sup>1</sup>; it is estimated that at least half of all sexually active women acquire genital HPV in their lifetimes.<sup>2</sup> Infection is most likely to occur in late teens and early twenties. Although the majority of high-risk HPV infections are transient and cause no clinical problems, persistent infection by a high-risk HPV type is the most important causal factor for the development of cervical pre-cancerous and cancerous lesions. Persistent infection by high-risk HPV types is detectable in more than 99% of cervical cancers.<sup>3</sup> HPV infections also cause genital warts, other rarer anogenital cancers, and cancers of the head and neck. Although routine cervical screening has prevented many deaths and invasive cancers by detecting and preventing cervical changes at an early stage, in England there were still 831 deaths from cervical cancer in 2006. For more information on HPV and cervical cancer see [Appendix A](#).

### **The role of JCVI**

The Joint Committee on Vaccination and Immunisation (JCVI) is a statutory expert Standing Advisory Committee. Its purpose is to provide expert impartial advice to the Secretaries of State for Health for England, Scotland, Wales and Northern Ireland on matters relating to communicable diseases, preventable and potentially preventable through immunisation.

JCVI has submitted its advice to ministers on the use of HPV vaccines and their potential benefit based on the best evidence reflecting current good practice and/or expert opinion. The process involved a robust, transparent, and systematic appraisal of all the available evidence from a wide range of sources.

[www.advisorybodies.doh.gov.uk/jcvi/processes.htm](http://www.advisorybodies.doh.gov.uk/jcvi/processes.htm)

JCVI was notified of new HPV vaccines that were in development in a horizon scanning paper in June 2005: [www.advisorybodies.doh.gov.uk/jcvi/mins220605.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins220605.htm)

JCVI then considered HPV vaccines on seven separate occasions and the minutes of these meetings can be found at the following links:

Feb 2006: [www.advisorybodies.doh.gov.uk/jcvi/mins150206.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins150206.htm)

June 2006: [www.advisorybodies.doh.gov.uk/jcvi/mins210606.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins210606.htm)

Oct 2006: [www.advisorybodies.doh.gov.uk/jcvi/mins181006draft.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins181006draft.htm)

Feb 2007: [www.advisorybodies.doh.gov.uk/jcvi/mins140207.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins140207.htm)

June 2007: [www.advisorybodies.doh.gov.uk/jcvi/mins20jun07.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins20jun07.htm)

Oct 2007: [www.advisorybodies.doh.gov.uk/jcvi/mins17Oct07.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins17Oct07.htm)

Feb 2008: [www.advisorybodies.doh.gov.uk/jcvi/mins13Feb08.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins13Feb08.htm)

In 2006, JCVI asked that a subgroup be set up to examine the available evidence on which JCVI might base a recommendation. The HPV subgroup met on three separate occasions and the minutes of these meetings can be found at the following links:

May 2006: [www.advisorybodies.doh.gov.uk/jcvi/mins-hpv-230506.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins-hpv-230506.htm)

Sep 2006: [www.advisorybodies.doh.gov.uk/jcvi/mins-hpv-220906.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins-hpv-220906.htm)

Feb 2007: [www.advisorybodies.doh.gov.uk/jcvi/mins-hpv-280207.htm](http://www.advisorybodies.doh.gov.uk/jcvi/mins-hpv-280207.htm)

## Evidence examined by JCVI

JCVI examined both published and unpublished research and considered the limitations and gaps in the available evidence during the process. This section details several areas of work that JCVI considered before eventually reaching a recommendation for the introduction of an HPV vaccination programme in the UK.

The areas of work included:

- vaccine efficacy studies
- burden of disease resulting from HPV infection (epidemiology)
- the expected health benefits of introducing an HPV vaccination programme
- whether the programme would be cost effective
- attitudinal work, and
- the suitability of a routine immunisation programme.

### *Vaccine composition, efficacy and safety studies*

JCVI has considered vaccine efficacy data presented from published papers and as provided by the manufacturers. JCVI also considered conference abstracts and posters and other published work when assessing the efficacy of the HPV vaccines (see [Appendix B](#) for a full list of all papers).

### **Vaccine composition**

The vaccine made by GSK (Cervarix®) is a bivalent vaccine and contains virus-like particles (VLPs) for two HPV types (16 and 18 – bivalent vaccine). The VLPs for Cervarix® are produced by recombinant DNA technology using a baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni* (a type of moth). The VLPs used in Cervarix® are adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on aluminium hydroxide.

The vaccine made by Sanofi Pasteur MSD (Gardasil®) is a quadrivalent vaccine and protects against four HPV types (6, 11, 16 and 18). The VLPs for Gardasil® are produced by recombinant DNA technology using yeast cells (*Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895)). The VLPs used in Gardasil® are adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant.

### **Vaccine efficacy and safety**

JCVI considered the evidence on vaccine efficacy and safety for both vaccines based on clinical trial data and post-marketing surveillance reports; this data is summarised in the specific product characteristics for both vaccines.<sup>6,7</sup>

JCVI also considered the vaccine effectiveness in individuals infected with one or more of the HPV types but naïve for the remaining types in the vaccine prior to or during the vaccination course.

In addition, JCVI considered a document outlining the safety of Cervarix® and Gardasil® from clinical trials; the document detailed a presentation to the EMEA from the Global Advisory Committee on Vaccine Safety.

After considering data provided by GSK and Sanofi Pasteur MSD, JCVI asked the manufacturers to provide additional information regarding the cross-reactive protection against other HPV types.

## **Conclusions**

JCVI concluded that both vaccines have a good safety record, and they are highly effective in protecting against the precursors of cervical cancer. Individuals who received the vaccines have been followed for at least six years in clinical trials so far, and the level of antibodies remains at a high level and appears not to decline. Based on these high levels, the opinion of the JCVI was that the duration of immunity is expected to be at least ten years. Furthermore, the vaccines produce higher antibody titres in individuals aged 10 to 14 years compared with those who are 15 to 24 years old. JCVI also noted that the data on the quadrivalent vaccine Gardasil® demonstrated effective protection against genital warts.

The vaccine studies also demonstrated that if an individual is infected by one HPV type at the time of vaccination, such individuals still gained a high level of protection from the other HPV types that are included in the vaccine.

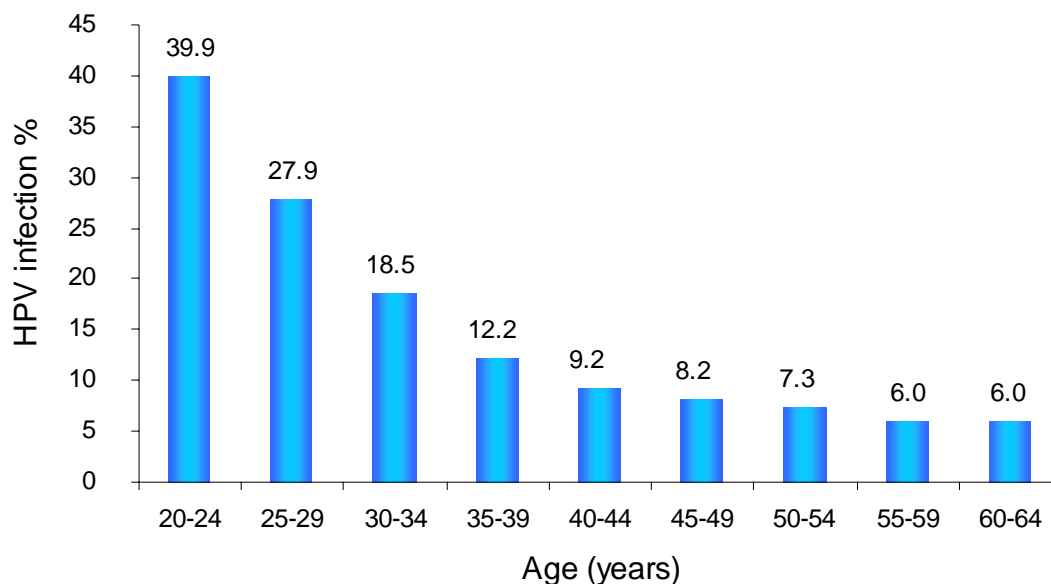
JCVI agreed that there was, so far, no evidence of any difference in the duration of protection between the two vaccines. Some other high-risk HPV types are closely related to those contained in the vaccines, and vaccination has been shown to provide some cross-protection against infection by these types. In terms of cross-protection offered by the vaccines, JCVI agreed that there was not yet any evidence of greater cross-protection against the non-vaccine HPV types 31 and 45 by one vaccine compared with another. In addition, JCVI noted that there was insufficient evidence that the vaccine provides protection against anal cancer: the committee would look at this again when more evidence becomes available.

## ***Burden of disease and expected cost-benefits from a vaccination programme***

Before commissioning detailed cost-effective modelling on the benefits of an HPV vaccination programme, JCVI were presented with a critical review<sup>8</sup> of four published cost-effectiveness studies.<sup>9</sup> This review detailed the most influential assumptions and<sup>10;11</sup> where gaps in information lay. Three of the models used static Markov models and one<sup>12</sup> used a transmission dynamic model in addition to a progression model. JCVI considered that the full range of vaccine effects can only be estimated in a dynamic transmission model. For example, only such a model could investigate whether vaccination of boys would be cost effective if there were high vaccine take-up in girls. JCVI concluded that the models discussed in the review paper were not able to provide sufficient basis for a recommendation on the cost effectiveness of an HPV vaccination programme, partly because the models were not specific to the UK.

JCVI then considered modelling work from Imperial College and the HPA that was specific to the UK and addressed the previously identified concerns. JCVI looked at

three aspects of the modelling, namely natural history of HPV disease, sexual transmission, and economic models. The HPA model was used primarily as the Imperial model did not cover all oncogenic types (only HPV16 was modelled), did not consider genital warts, and did not include any economic analysis.



**Figure 1 Prevalence of high-risk HPV according to age quinquennia.**

Data from (Kitchener *et al.*, 2006<sup>13</sup>) demonstrates that HPV infection is greater in 20 to 24 year olds and decreases rapidly after age 30.

### **Modelling the natural history of HPV**

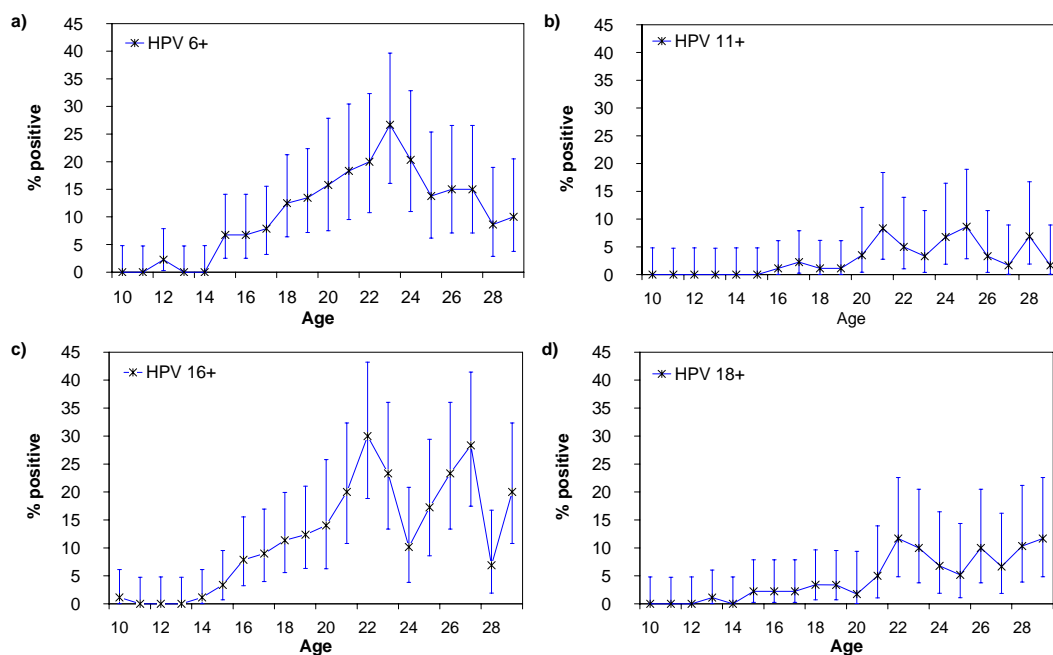
JCVI considered data on the epidemiology of HPV disease that was used to develop a model for HPV disease in the UK. The natural history model was then used in the sexual transmission model that was, in turn, applied to the cost-effectiveness model (see figure 3).

Cross sectional data from the ARTISTIC trial (that measured HPV during routine cervical screening<sup>13</sup>) was considered by JCVI. No UK data was available on HPV prevalence rates for females under 15 years old. Therefore, the HPA had estimated the prevalence of human papillomavirus antibodies in young female subjects in England using sera from 1483 females in England aged 10 to 29 years old.<sup>14</sup>

The data from both of the above studies demonstrated that infection by HPV is most likely to occur in the late teens and early twenties. Forty per cent of the cervical smears from 20- to 24-year-old women were positive for HPV DNA that indicated a current infection<sup>13</sup>; 15 per cent of these women had recently been infected by HPV types 16 or 18. In addition, the incidence of disease caused by HPV 45 (another HPV type that causes cancer) was low. As individuals get older the likelihood of infection by HPV decreases (see figure 1).<sup>13;15</sup> The study carried out by the HPA showed that the proportion of females who have been infected by HPV increases rapidly from age 14 years to around age 24 years<sup>14</sup> (see figure 2).

The data was used to fit a range of models of HPV progression from infection to disease. These models allowed predictions to be made on the development of different

classes of cervical cancer and pre-cancerous lesions by age and HPV type. The models reflected different assumptions about progression, cervical cancer screening and HPV epidemiology. The resulting best-fitting natural history of disease models were then incorporated into the transmission model.



**Figure 2 The percentage of females aged 10 to 29 years who have antibodies to (a) HPV 6, (b) HPV 11, (c) HPV 16 and (d) HPV 18.**

The error bars indicate the upper and lower confidence intervals. The presence of antibodies is evidence of past HPV infection. The graphs show that over the age of 14 years, infection by HPV has already occurred in some girls. Data taken from (Jit *et al.*, 2007<sup>14</sup>).

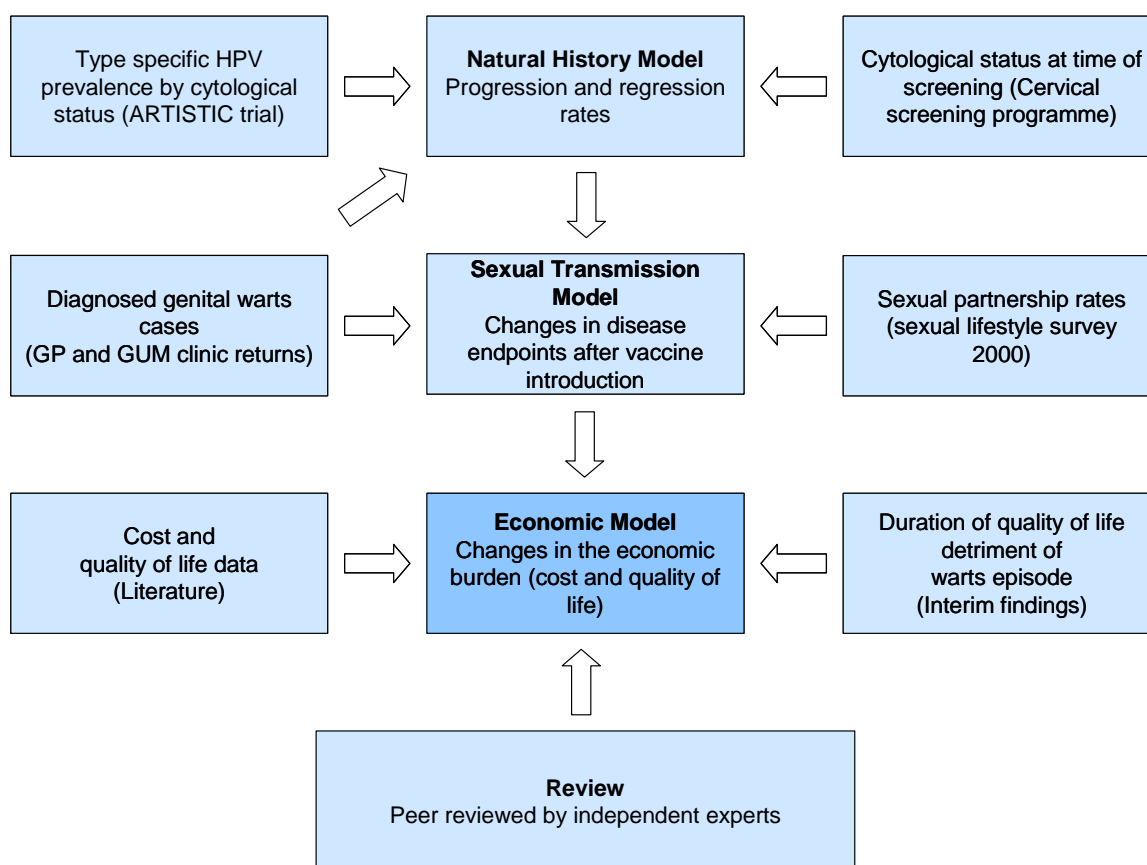
### Modelling sexual transmission

JCVI also considered a sexual transmission model that assessed the changes in disease endpoints after the introduction of the HPV vaccine (see figure 3). In order to inform the modelling and note where gaps in the knowledge lay, JCVI examined the following papers.<sup>16-20</sup> Although models had already been published for the UK, USA and Australia they had assumed a fixed structure for epidemiology and progression.<sup>21</sup> Because there were significant gaps in knowledge about HPV epidemiology and natural history<sup>16,18</sup> rather than developing a single model, the HPA considered multiple scenarios that each contained different assumptions on parameter values and model structure. Further refinement of model selection was based on using the models that gave the best overall predictions as compared with estimates of prevalence. The models included parameters such as demography, sexual behaviour, screening and treatment, and disease progression. Sexual behaviour data was taken from the national survey of sexual attitudes and lifestyles II, 2000-1.<sup>22</sup> The models also used coverage data from the Cervical Screening Programme for England 2005-6. For disease progression, the model generated from the natural history of HPV was used (see previous section).

### Modelling the cost effectiveness of HPV vaccination in the UK

The natural history and sexual transmission models were then used in the economic model with cost and quality of life (QoL) data and duration of quality of life detriment. The model also took into account:

- whether or not the vaccine protects against genital warts
- the duration of vaccine-induced protection, and
- whether or not a catch-up campaign conducted at the start of the programme should include 12- to 14-year-olds, 12- to 16-year-olds, 12- to 18-year-olds or 12- to 25-year-olds.



**Figure 3 Diagram showing the data used in generating a cost-effectiveness model for the use of HPV vaccine in the UK.**

The analytical framework adopted followed NICE guidelines. Quality-adjusted life years (QALYs) were the preferred outcome measure, the health care perspective was adopted and the discount rate used for costs as well as benefits was 3.5%. Adoption of this framework meant that the results could be compared with other health care programmes in terms of cost-effectiveness.

### **Peer review**

JCVI recommended that the models be peer reviewed by independent mathematical modellers (not working directly in the HPV field), HPV biologists (both in the UK and abroad) who would examine the plausibility of the assumptions about the natural history of HPV made in the model, and health-economists who included economists at NICE. All potential reviewers were asked to declare any conflicts of interest and those with conflicts were not consulted further. The reviews concluded that the modelling paper did provide an appropriate basis for making a decision based on the current state of knowledge. The reviewers agreed that there were several areas where further research would be useful but that current uncertainties were well reflected in the modelling.

Following the peer review process, the HPA made changes to the model that provided a better fit with regard to the high-risk HPV types. The administration costs were also

altered to reflect that a nurse would administer the majority of vaccinations, if the programme were carried out in a school-based setting. The contributions of adenocarcinomas were included in the models.

## **Results**

The results showed that routine vaccination of girls aged 12 to 14 years with an HPV vaccine could reasonably be expected to be cost-effective at 80% vaccine coverage, assuming the average duration of vaccine protection is at least 10 years. On the basis of these results and the observations that routine vaccination of girls aged 12 is likely to produce greater antibody titres than vaccination in girls aged 15 years, the committee concluded that age 12 to 13 years was an appropriate age for routine vaccination. The analysis also indicated that, if girls were vaccinated at 12 years old, it was also reasonable to expect a catch-up programme up to the age of 18 years to be cost effective. Vaccination of girls above this age was not cost-effective given the assumed cost of vaccine and administration, and the increase in prevalence of previous infection in this age group. Vaccination of boys in addition to girls was unlikely to be cost-effective.

## **Attitudinal work**

The Department of Health had commissioned work on knowledge and public attitudes about cervical cancer, HPV and vaccination in 2005 and this was considered by JCVI. The study had looked at the parental responses to the introduction of a vaccine against human papillomavirus.<sup>4</sup> The work demonstrated that, in general, parents were very positive about a vaccination to prevent cervical cancer. Many parents were aware of cervical cancer but knowledge about HPV was limited. In addition to the paper presented by the Department of Health, the committee also considered a paper concerning the psychosocial aspects of vaccine acceptability. The attitudinal work raised concerns from some parents about introducing the vaccine in primary school and opinions tended towards offering it in early adolescence at secondary school. Previous experience with provision of rubella vaccine in the last year of primary school had shown that coverage was highest when provided at this age. With each successive year of secondary school, vaccine coverage declines in school-based campaigns (MR vaccine campaign 1994, meningococcal C campaign 1999-2000). The Department of Health commissioned further qualitative work into the views of older children, their parents, teachers, and school nurses on the introduction of the HPV vaccination programme.<sup>5</sup> In considering at what age the vaccine should be given, JCVI took into account the opinions of parents in addition to the vaccine efficacy studies and cost-effective analysis.

## **Conclusion**

The committee accepted the results of the modelling; including the underlying assumptions used in the model and acknowledged the appropriateness of the processes that had been used for peer review. The evidence presented led the committee to confirm that a universal vaccination programme for girls aged 12 to 13 years would be expected to be cost effective. In addition to this, based on the new analysis presented, the committee was able to recommend a 'catch up' vaccination of girls aged 13 years to under 18 years old. The committee suggested that this would be delivered most efficiently through schools.



## Recommendations

### *The choice of vaccine*

JCVI recommended that the choice of vaccine purchased would be primarily determined by cost effectiveness, which is highly dependent on the negotiated cost of the vaccines. However, if the vaccines were offered at similar prices, then the committee recommended choosing the quadrivalent vaccine, which would prevent genital warts as well as cervical cancer. Any differential between the prices offered would need to compensate for the lack of protection against warts. The committee also recommended that Gardasil® and Cervarix® should not be used interchangeably – unless further evidence becomes available in order to reconsider this position.

### *Routine vaccination of girls*

JCVI recommended to the Secretary of State for Health that a universal vaccination programme against HPV for girls aged 12 to 13 years (school year 8) would be cost effective. Furthermore, JCVI also recommended a time-limited ‘catch up’ vaccination of girls aged 13 to under 18 years.

### *Vaccination of women over 18 years old*

The committee observed that a ‘catch up’ vaccination of women aged 18 to 25 years was not cost-effective at the price considered. However, the committee recognised that the vaccine could benefit some individual women aged 18 and over who were at risk of new HPV infection by one of the types covered by the vaccine.

### *Vaccination of pregnant women*

Based on the evidence, the committee recommended that the vaccination of females known to be pregnant should be deferred until after their pregnancy, and that breastfeeding is not a contraindication for vaccination.

### *Vaccination of boys*

JCVI did not recommend vaccinating boys, as it was not cost-effective. Since vaccine efficacy is high, if there were a high coverage in girls then vaccinating boys would not provide any additional benefit since vaccination causes a decrease in the prevalence of disease, generated by herd immunity. Moreover, if there is high coverage in women, the vaccination of boys does not add any additional benefit to the prevention of cervical cancer.

### *Vaccination of people in other risk groups*

At the time of recommendation, JCVI considered that there was insufficient evidence on the protective effects of the vaccine against cancers affecting males such as anal, and head and neck cancers. When more data becomes available, high-risk groups such as men who have sex with men would be considered.

### *Surveillance*

After considering a comprehensive plan to monitor and evaluate the introduction of the vaccine, JCVI recommended that if possible the plan should be fully funded as an integral part of the vaccine introduction. This plan will be critical in determining any future modification to cervical cancer control.

### ***Cervical screening***

JCVI recommended that at the time of vaccination the opportunity should be used to explain to women the importance of cervical screening, which will remain an essential component of cervical cancer prevention.

### ***Administration with other vaccines***

The committee further advised that HPV vaccine and the Td/IPV school leaver booster can be co-administered, and noted in so recommending that this might reduce the time gap between the pre-school booster and the teenage booster.

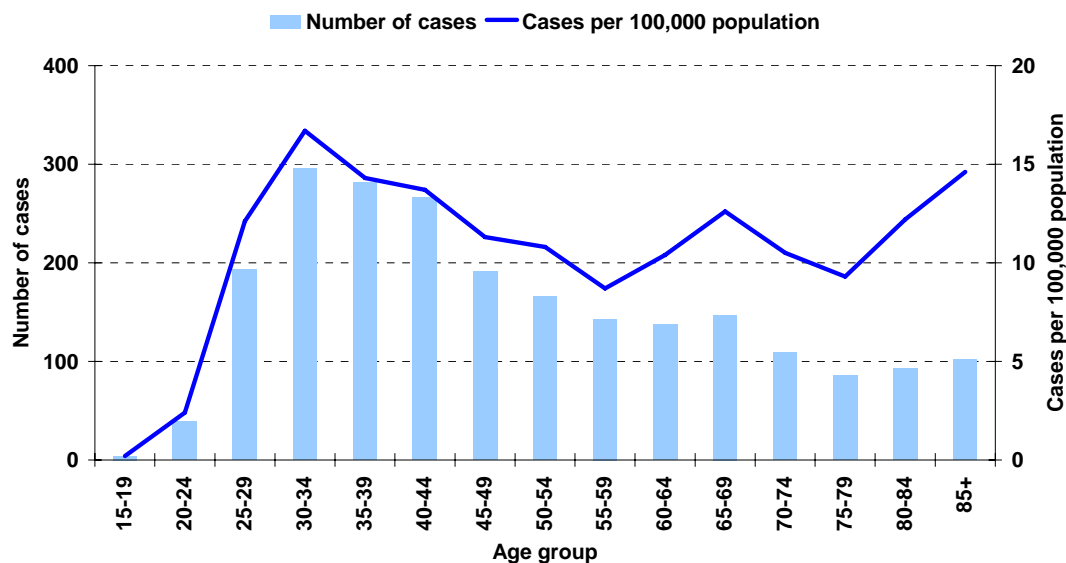
## Appendix A Background to cervical cancer and the human papillomavirus (HPV)

### Cervical cancer

Cervical cancer is the second commonest cancer of women worldwide, with approximately 500,000 new cases and 270,000 deaths annually.<sup>3;23</sup> Persistent infection by high-risk HPV types is detectable in more than 99% of cervical cancers.<sup>3</sup>

The introduction of the UK national cervical screening programme has made a major contribution to the fall in the incidence and death rate from cervical cancer. Due to cervical screening in the UK, mortality rates fell approximately 60% between 1974 and 2004.<sup>24</sup>

A total of 2253 new cases of invasive cervical cancer were diagnosed in England in 2005.<sup>25</sup> The peak incidence occurred in women in their 30s with a second peak in women in their 60s to 80s (women less likely to have benefited from cervical screening during their lifetimes; figure 4). In the UK, the lifetime risk of developing cervical cancer is estimated as 1 in 116.<sup>26</sup> Of those women diagnosed with invasive cervical cancer in the UK, approximately one-third die within five years of the diagnosis.<sup>26</sup>



**Figure 4 Number of cases of newly diagnosed cervical cancer in England, 2005.<sup>25</sup>**

There are certain groups of women who are reported to have low cervical screening rates, e.g. ethnic minority groups and women born in foreign countries.<sup>27;28</sup> More recently, there has been a fall in the number of young women taking up invitations for cervical screening.<sup>29</sup>

Persistent infection by HPV is also a contributory factor to other anogenital cancers. In the UK, anal cancer is diagnosed in around 800 individuals annually.<sup>26</sup> Overall, anal cancer is more common in women than in men, but relatively high rates are found

among men who have sex with men. There are around 1200 UK cases of vulvar and vaginal cancers per year.

## HPV

Human papillomavirus (HPV) is a double-stranded DNA virus that infects squamous epithelia including the skin and mucosae of the upper respiratory and anogenital tracts. There are approximately 100 types of HPV, of which about 40 infect the genital tract.<sup>30</sup> Although most infections are asymptomatic and self-limiting, genital infection by HPV is associated with genital warts and anogenital cancers in both men and women. HPV viruses are classified as either 'high-risk' or 'low-risk' types depending on their association with the development of cancer.

Genital HPVs are transmitted by sexual contact with an infected individual, primarily through sexual intercourse. The risk therefore, generally increases after the introduction of a new sexual partner, and will depend upon the sexual history of the partner and the number of sexual partners. Studies of incident HPV infection based on HPV DNA detection demonstrate that acquisition of at least one type of HPV infection occurs soon after sexual debut with around 30% of women being infected within two years after sexual debut.<sup>31;32</sup>

The use of condoms reduces but does not eliminate the risk of sexual transmission. Non-sexual routes of HPV transmission include vertical transmission from mother to newborn baby.

Persistent infection by high-risk HPV types is detectable in more than 99% of cervical cancers.<sup>3</sup> Of these high-risk types, HPV16 is responsible for more than 50% and HPV18 for more than 15% of all cervical cancers in Europe.<sup>33</sup> A further 11 high-risk types have been described.<sup>34\*</sup> In addition to cervical cancer, HPV is causally associated with other less common cancers, which include cancer of the vulva, vagina, penis and anus, and some cancers of the head and neck.<sup>23;35</sup>

The majority of high-risk HPV infections are transient and cause no clinical problems. Within one year, around 70% of new infections will clear and approximately 90% of new infections will clear within two years.<sup>36;37</sup> The median duration of a new infection is eight months. Infection by multiple types is common. Persistent infection by a high-risk HPV type is the most important causal factor for the development of cervical pre-cancerous and cancerous lesions. Persistence and disease is more common for infections by HPV types 16 and 18 than for other high risk types. The time span between infection by HPV and the development of CIN3 or cervical cancer varies from between one and ten years.<sup>38</sup>

HPV infection is associated with 80-90% of all anal squamous cell cancers. HPV types 16 and 18 are found in most anal cancers.<sup>3</sup> The natural history of vaginal and vulval cancers is not completely understood. Although HPV infection is a risk factor for the development of vaginal or vulval lesions, unlike cervical cancer, only approximately 50% are associated with HPV infection.<sup>3</sup> Around 40% of cases of penile cancer are attributable to HPV infection.<sup>39</sup> For all sites of infection, the evidence for a causal association and the percentage attributable to HPV infection, is greatest for HPV types 16 and 18 than for other HPV types. HPV infection has also been associated with

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\* Including types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66.

cancerous and non-cancerous lesions outside the ano-genital area including laryngeal papillomas,<sup>40</sup> and some head and neck cancers.<sup>41</sup>

Low-risk HPV types are responsible for genital warts, which is the most common viral sexually transmitted infection in the UK.1 HPV types 6 and 11 cause over 90% of all genital warts.<sup>42</sup> Genital warts appear between three weeks to eight months after primary infection (most commonly 2-3 months).<sup>43</sup> In the absence of treatment, up to 30% of affected individuals may clear the infection in the short term.<sup>44;45</sup> The rate of spontaneous regression in the long term is not known. Treatments focus on removal of the warts, but do not necessarily eliminate infection, which may persist sub-clinically, and be a source of recurrence and continuing viral transmission. Genital warts are not life threatening, but they can cause significant morbidity.

Surveillance of HPV is complex due to the high proportion of asymptomatic infections, the variable presentation of the different viral types and the long period between infection and disease.

A UK seroprevalence study in an unselected population showed that HPV prevalence is extremely low in girls aged 14 years but HPV infections rise sharply in the mid teens.<sup>14</sup>

Information on the prevalence of high-risk HPV infection is available from a large cross-sectional study of women having routine cervical screening in the UK.<sup>13</sup> This study found evidence of current high-risk HPV infection (indicated by the presence of HPV DNA) in 40% of women at 20 to 24 years of age, declining with increasing age. Prevalence of any HPV type, and particularly of HPV 16 or 18 was higher in women who had abnormal cytology.

Information on incidence of genital warts comes primarily from people attending genitourinary medicine (GUM) clinics. Over 80,000 new cases of genital warts were diagnosed in GUM clinics throughout the UK in 2006.<sup>46</sup> Rates of diagnoses are highest in young men and women under 24 years.

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## Appendix B

### Published papers considered by JCVI†

#### **Attitudinal work**

Reference numbers:  
4, 5, 47, 48, 49

#### **Vaccine efficacy and safety**

Reference numbers:  
50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75

Specific product characteristics (SPC) for Cervarix® and Gardasil® can be accessed via the electronic medicines compendium [www.emc.medicines.org.uk/](http://www.emc.medicines.org.uk/)

#### **Cervical screening**

Reference numbers:  
24, 76, 77

#### **HPV epidemiology including sexual behaviour and cancer**

Reference numbers:  
13, 14, 15, 23, 38, 42, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 98

#### **Modelling**

Reference numbers:  
8, 9, 10, 11, 12, 16, 17, 18, 19, 20, 89, 90, 91, 92, 93, 94, 95

#### **Other programmes**

Reference numbers:  
96, 97

Slides from the Advisory Committee on Immunization Practices (ACIP) vaccination workshop on 21 February 2006 were also presented:  
[www.cdc.gov/vaccines/recs/acip/meetings.htm](http://www.cdc.gov/vaccines/recs/acip/meetings.htm)

Papers included:

Giltsdorf J. ACIP HPV vaccination workgroup  
Lawson HW. Cancer of the cervix and other HPV-related cancers  
Liddon N. Possible sexual behavioral issues associated with HPV vaccine  
Chesson H. The cost-effectiveness of HPV vaccination in the United States  
Dunne E. Epidemiology of HPV infection  
Barr E. Gardasil® (Merck & Co., Inc.) Presentation to the ACIP  
Lowy DR. HPV infection and humoral immunity

[Return to Vaccine composition, efficacy and safety.](#)

† Data that was presented as unpublished work that is now published is referenced as the published work.

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