Having read the report of the ad hoc working committee;

Whereas on the one hand:

♦ The advice on vaccination against papillomavirus types 16 and 18 issued by the French Council for Public Health during its session of 5th December 2006 has been taken into consideration;

Whereas on the other hand:

♦ Certain strains of human papillomavirus (HPV) are found in 99.7% of cancers of the cervix;

♦ It is now recognised that cervical cancers are caused by certain HPV strains;

♦ In France, cervical cancer is the 8th most common type of cancer in women and the 15th most common cause of deaths from cancer;

♦ The peak in incidence of cervical cancer occurs at the age of 40;

♦ The average age at which the cancer appears is 51 in France;

♦ The number of deaths per year from this type of cancer dropped between 1980 and 2000, from 1,941 deaths in 1980 to 1,004 deaths in 2000, according to the statistics of the cancer registries; in 2002 the figure was estimated to be 904 deaths;

♦ There has been a comparable drop in the incidence of cervical cancer;
Squamous cell cancers are preceded by precancerous lesions; the estimated incidence of CIN\textsuperscript{a} 2 and 3 in mainland France was between 20 and 30,000\textsuperscript{d} in 2004.

These lesions do not develop systematically into cancer;

Invasive cancer develops approximately 15 to 25 years after the HPV infection is acquired;

HPVs are also responsible for genital condylomas;

The incidence of genital condylomas has been estimated at 10 per year for every 100,000 inhabitants in France, with women representing 40\% of these cases;

These condylomas have major repercussions on patients' psychological wellbeing;

HPVs are transmitted by skin-to-skin contact and body fluids, most often during sexual intercourse and the use of barrier contraceptives gives only partial protection against HPV infection;

The majority of infections are acquired when subjects first become sexually active;

Approximately 3\% of adolescent girls have sexual intercourse for the first time before the age of 15 and 9\% before the age of 16;

There are around 120 strains of HPV, 40 of which cause infections of the genital epithelium, certain HPVs being oncogenic (notably HPV 16 and HPV 18) and potential causes of cancers of the cervix, the vulva and the anus, others being non-oncogenic but potential causes of genital condylomas or warts (notably HPV 6 and HPV 11);

In Western Europe, strains 16 and 18 are responsible for around 73\% of cervical cancers, 57\% of high-grade lesions and 24\% of low-grade lesions;

Whereas furthermore:

There is a test for screening lesions which may develop into cervical cancer: the cervical smear test;

Organised screening programmes implemented in some Northern European countries have helped reduce cervical cancer incidence and mortality by 80\%;

In mainland France, cervical screening is currently a matter for the individual; the smear test being recommended for women aged between 25 and 65 every 3 years after 2 initial normal smear tests one year apart (ANAES – French national health accreditation and evaluation agency);

Treatments applied to CIN 2 and 3 have a success rate of almost 100\%;

Treatment of genital condylomas, whether chemical, physical or surgical, does not always succeed in eradicating them and they recur in 20 to 30\% of cases;

There is a vaccine, Gardasil\textregistered, against strains 6, 11, 16 and 18;

The success rate of the vaccine over 2 years in relation to high-grade cervical lesions (CIN 2/3) and to carcinoma in situ of the cervix linked to infections by HPV 16 and 18 is about 95\%; two phase III studies of the vaccine have been carried out in Asia, Oceania, the Americas and Europe, in women aged between 16 and 23\textsuperscript{b}:

\textsuperscript{a} Cervical Intra-epithelial Neoplasia
\textsuperscript{b} Fewer than 100 women aged between 24 and 26 were included in one of the studies.
• the women received either an injection of the vaccine at month 0, month 2 and month 6, or 3 injections of placebo at the same intervals,
• around 17,000 women received at least one injection, either of the vaccine or of placebo,
• among the 16,000 women approximately who received three injections of vaccine or placebo, who had not been infected and were not infected up to the 3rd injection, the success of the vaccine in preventing CIN 2/3 and carcinoma in situ linked to infection by HPVs 16 and 18, diagnosed from the month following the 3rd injection, was 100%,
• among the 17,000 women approximately who received at least one injection of vaccine or placebo and who had not been infected on the day of the first injection, the success rate of the vaccine in preventing CIN 2/3 and carcinoma in situ linked to infection by HPVs 16 and 18, diagnosed from the month following the first injection, was about **95%**, which is the figure that can be taken to represent the success rate of the vaccine in the conditions in which it would actually be used,
• among the 17,000 women approximately who received at least one injection of vaccine or placebo, and who were either infected or not infected, the success rate of the vaccine in preventing CIN 2/3 and carcinoma in situ linked to infection by HPVs 16 and 18, diagnosed from the month following the first injection, was about **95%**, which is the figure that can be taken to represent the success rate of the vaccine in the conditions in which it would actually be used,

♦ In these same studies, the success rate of the vaccine in relation to vulvar condylomas linked to infection by HPVs 6, 11, 16 and 18 was about **95%**:

• among the 16,000 women approximately who received three injections of vaccine or placebo, who had not been infected and were not infected up to the 3rd injection, the success rate of the vaccine in preventing vulvar condylomas linked to infection by HPVs 6, 11, 16 and 18, diagnosed from the month following the 3rd injection, was about **99%**,
• among the 17,000 women approximately who received at least one injection of vaccine or placebo and who had not been infected on the day of the first injection, the success rate of the vaccine in preventing vulvar condylomas linked to infection by HPVs 6, 11, 16 and 18, diagnosed from the month following the 1st injection, was about **95%**, which is the figure that can be taken to represent the success rate of the vaccine in the actual conditions in which it would be used,
• among the 17,000 women approximately who received at least one injection of vaccine or placebo, and who were either infected or not infected, the success rate of the vaccine in preventing vulvar condylomas linked to infection by HPVs 6, 11, 16 and 18, diagnosed from the month following the 1st injection, was about **70%**;

♦ The average number of sexual partners was 2, and was fewer than or equal to 4 for 99% of the women who took part in the study;

♦ Tolerance of the vaccine was satisfactory, but the numbers participating were not high enough to detect any undesirable effect whose incidence would be less than 1/4,000;

♦ Among the women who were pregnant in the month following the vaccination, 5 cases of congenital malformation were noted, as opposed to 0 in the placebo group; whilst the difference is not significant, information regarding this point has been included in the summary of product characteristics;

---

5 Who were seronegative and PCR negative for HPVs 6, 11, 16 and 18

14, avenue Duquesne, 75350 PARIS 07 SP – Tel: 01 40 56 60 00 – Fax: 01 40 56 78 00

www.sante.gouv.fr
The immunological data gathered during the course of the trials show a higher level of antibodies than that observed after natural infection, which indicates that strong and lasting protection can be anticipated;

A study carried out to compare the epidemiological and financial impact at the population level of systematic screening and vaccination of girls at 14 years shows:

- that priority should be given to systematic screening,
- that vaccination would nevertheless have a significant additional epidemiological impact: over the first 70 years, systematic screening and systematic screening in conjunction with vaccination would cause the number of cancers diagnosed to drop by 16% and 34% respectively,
- an estimate, based on the current cost of the vaccine, of the cost/success ratio of vaccination in conjunction with systematic screening is placed between €17,500 and €35,000 in terms of Healthcare insurance per year of life saved, depending on the discount rate used to calculate the future benefits, and not taking into account the impact of vaccination on condylomas;

Whereas finally:

- The percentage of women who have not had a cervical smear test for 6 years was about 34% in France in 2000, with regional disparities;
- Based on the trial screening programme in the Bas-Rhin département, coverage reaches 72% in 3 years and 82% in 5 years;
- Screening is a secondary prevention measure against cervical cancer;
- The vaccine is a primary prevention measure against pre-cancerous and cancerous lesions of the cervix, as well as against genital condylomas;
- Treating lesions that may occur can have physical and psychological consequences;
- The impact of the vaccine on the cervical cancer incidence and mortality will only become apparent in the long term, in 15 to 25 years' time;
- The short and medium term advantage of the vaccine is its ability to reduce the number of potentially traumatic situations caused by the discovery and treatment of cervical lesions and the discovery and treatment of vulvar condylomas;
- It could happen that if women who had been vaccinated were less inclined to attend screening tests, the incidence of and more importantly the mortality from cervical cancer could increase, since the vaccine is only effective against approximately 30% of cancers;
- It cannot be ruled out that the effect of the vaccine may only be short-lived due to the emergence of other oncogenic HPV strains which may take over from strains 16 and 18;
- The duration of the protection afforded by the vaccine, evaluated across a restricted population of around 100 women and on immunological data is at least 5 years, but the long-term duration of the protection cannot yet be determined;
- If repeat vaccination proved to be necessary and some women failed to take it up, there would be a risk of a shift towards the incidence of cervical cancer at a more advanced age;

The Technical Committee on vaccinations and the French Council for Public Health, communicable diseases section:
Reiterate their recommendation to carry out screening programmes for precancerous and cancerous lesions of the cervix throughout the territory, by means of cervical smear tests, as vaccination against papillomaviruses 16 and 18 is not an adequate substitute for this;

Reiterate their recommendation that information and training activities aimed at health professionals be developed concerning the complementary nature of vaccination and screening, as well as on ways in which to approach the subject of sexuality with their young female patients;

Reiterate their recommendation that the health authorities should initiate a publicity campaign aiming to promote cervical cancer screening and draw attention to its benefits, both to women who have been vaccinated and those who have not;

Recommend, with a view to prevention of precancerous and cancerous lesions of the cervix and the prevention of vulvar condylomas, vaccination of girls at 14 years, in order to protect them before they are exposed to the risk of HPV infection;

Recommend that the vaccine should also be offered to girls and women between the ages of 15 and 23 who may not have had sexual intercourse, or at the latest in the year after they first become sexually active, which could be done on the occasion of a first prescription for contraceptives or the morning after pill, or consultation for any other reason;

Recommend a widening of the current arrangements so that any adolescents wishing to be vaccinated without parental involvement can be catered for financially;

Recommend that doctors should explain, before vaccination takes place, the need for screening and how it is done, the vaccination schedule, the fact that pregnancy is not advisable during the month following each injection, the fact that the vaccine is not effective in preventing around 30% of cancers, that a repeat vaccine may prove to be necessary; a written document should be given to the patient indicating the date on which the first screening is to take place;

Recommend that the companies which produce or may in the future produce an HPV vaccine should be obliged to promote the use of the vaccine alongside screening for cervical lesions at the same time in their publicity and to mention the fact that it is not effective in preventing 30% of cancers;

Request that public health impact studies be carried out into the following areas: tolerance; monitoring congenital malformations in children of women who may have been accidentally vaccinated during pregnancy or may have begun a pregnancy immediately after vaccination; duration of protection, incidence of cancerous and precancerous lesions, emergence of new oncogenic strains of HPV and ecology of HPV strains; cross protection against strains other than 16 and 18; impact of vaccination on screening and impact of vaccination on action to prevent sexually transmitted diseases;
♦ **Recommend the creation of a national resource centre** devoted to papillomavirus;

♦ **Request** that studies be carried out specifically on vaccination of immunodeficient girls and young women;

♦ **Reiterate** that use of barrier contraceptives contributes to the prevention of other sexually transmitted infections; it is therefore important to ensure that campaigns promoting the use of these contraceptives should be ongoing.

**THIS OPINION MAY ONLY BE PUBLISHED IN ITS ENTIRETY, WITH NO PART REMOVED OR ADDED.**

**References** (as in source text).