HAVING REGARD TO the report of the Directorate General for Health Prevention, relating to: "Strategies for actively offering the vaccine against HPV infection in Italy";

SINCE, with the aforesaid report, the Higher Health Council has been called upon to make its assessments of the strategies for vaccinating against human papilloma virus (HPV) infection that are most suitable for Italy, the target population to be given preference, the organizational procedures to be established, including the possibility of the Italian National Health Service bearing the costs of vaccination and cases of co-administration of the new vaccine with other vaccines already provided in the Italian national vaccination programme;

WHEREAS, based on the scientific evidence available today:

- Cervical cancer is the first cancer to be recognized by the World Health Organization as totally attributable to an infection. In fact, it is caused by genital HPV infection of which over 120 genotypes have been identified to date, that affect humans, one third of which are associated with both benign and malignant pathologies of the anogenital tract;

- HPV type 16 is recognized as being the cause of around half the cases of cancer of the cervix, HPV type 18 20% and other types of HPV the remaining 30%;

- HPV infection is very frequent in the female population: it is estimated that around 75% of sexually active women are infected with an oncogene HPV during the course of their lives. The infection has to persist for it to develop into a carcinoma, although only a minority of high-risk HPV is actually able to produce squamous intraepithelial lesions or cervical intraepithelial neoplasias or dysplasias. Generally, the time elapsing between the infection and the onset of precancerous lesions is around five years, while the latency period for a cervical carcinoma to appear may be ten years. For this reason, secondary prevention of carcinoma is based, in particular, on screening programmes, which enable precancerous lesions to be identified and suitable treatment to be duly given;
• The vaccination programme for the primary prevention of HPV infection falls into this scenario. Two products have recently been developed, one is licensed and one is in the course of licensure in Europe. The first is a tetravalent vaccine for HPV 6, 11 (low-risk type), 16 and 18 (high-risk type), while the second is a bivalent vaccine for HPV 16 and 18. Both vaccines are administered in 3 doses (at 0, 1 and 6 months and at 0, 2 and 6 months, respectively);

• Vaccination before commencing sexual relations is particularly beneficial, because it leads to effective protection before possible infection with HPV. HPV infection is generally acquired straight after commencing sexual activity; this is supported by various studies, which have demonstrated how, at 48 months after first relations, more than 50% of girls were already infected by the virus;

• The data published to date shows that both vaccines induce an immune response in over 90% of vaccinees. The antibody titres appear to be far higher in vaccinees than in non-vaccinees. Both vaccines showed high preventive efficacy against CIN I, II and III (Cervical Intraepithelial Neoplasia);

• The use of the tetravalent vaccine has led to a 90% reduction in the incidence of persistent infections or genital pathologies associated with HPV types 6, 11, 16 and 18. The use of the bivalent vaccine has produced similar results. Both vaccines showed slight side effects; the adverse clinical events following inoculation are predominantly fever and local reactions;

• Scientific evidence shows that the optimum approach involves vaccination before commencing sexual activity. The Advisory Committee on Immunization Practice has recommended routine vaccination for girls of 11 to 12 years of age. It has also shown how vaccination may also be effected even earlier, from 9 years onwards, and in the range of 13-26 years of age;

WHEREAS, among the potential problems of vaccination:

• In vitro studies have shown how the protection provided by vaccination is limited to the HPV types contained in the vaccine product. Consequently, women vaccinated against HPV type 16 infection are still exposed to lesions caused by other oncogenic HPV types;

• The period of protection is not yet defined;

• There is no evidence in the follow-up of the experimental studies that vaccination may facilitate the segregation and expansion of other oncogenic strains (non-HPV 16/18); in particular, serological data demonstrating this is not available;

• However, HPV uses the genome of the host cell for replication and this makes it relatively stable, protecting it from rapid mutations. Inside the HPV genotype, several variants have been observed with differences of around 2%, however;

WHEREAS, furthermore, with regard to the consequences of vaccination on the health of the embryo and the foetus, the preliminary information currently available seems to indicate a potential risk of malformations, if vaccination is carried out during
the early stages of pregnancy, or in the weeks or months immediately preceding conception;

**AFTER HEARING** the observations and assessments made by the members of Sections II and III and by the representatives of the Directorate General for the Prevention of Health, the AIFA *[Italian Medicinal Products Agency]* and the ISS *[Higher Health Institute]*;

**In the light** of the in-depth and full discussion involving all those present;

Unanimously

**CONSIDERS**

that it needs to state the following on the questions raised by the competent Directorate General for the assessment of the Council.

- The vaccination strategy that is most likely to prevent HPV infections is that adopted in the pre-adolescent stage (9-12 years), in view of the almost total absence of occasions of sexual transmission of the infection.

  Obviously, the effect of immunization of a cohort of pre-adolescents may be observed over an estimated period of 30-40 years. In the desire to reduce the period of such latency, it becomes necessary to increase the number of cohorts, selecting other older cohorts, in a similar manner to that already adopted for other vaccination strategies, such as hepatitis B (HBV), a disease that presents several analogies in terms of method of transmission.

- With regard to pre-adolescent vaccination, the **12th year of life** is considered to be the *ideal* age owing to several considerations:

  - Almost total absence of previous infections;
  - Better immunological response documented in subjects of that age, as shown by international literature;
  - Attendance at first two years of secondary school, in which context girls and parents can easily obtain adequate information on the infection and vaccination;
  - Possibility of catching up the missing doses of the vaccination cycle during the third year of secondary school and offering immunization again if it is not accepted;
  - Existence of parental influence at that age, which is later lost;
  - Possibility of including this vaccination during the same stage of life as that in which all other vaccinations laid down by the national programme are provided. This would also enable anti-HPV vaccination to be seen as normal immune prevention;
Recent positive experience of the anti-hepatitis B vaccination programme in pre-adolescence, with the possibility of using the network of relations and organizational procedures already used by the vaccination services between 1991 and 2003.

The cohort of 12-year-olds should therefore be considered to be the cohort on which to act as a priority from a strategic point of view.

The subsequent development of the vaccination strategy should provide for modular development, extending to a second cohort of women of 25 or 26 years of age, already being called for screening. For this second cohort, the screening and vaccination programme would co-exist, thus emphasizing the complementarity of the two means of effective prevention from carcinoma of the neck of the womb.

Finally, if the available resources allow, one might also consider involving a third cohort, to be identified at an age between the two defined above.

In this connection,

**CONSIDERING IT ADVISABLE**

prior to identifying the cohorts of women of childbearing age to undergo vaccination, in the light of the data becoming available and in accordance with the indications of the EMEA “Post-marketing commitment”, to acquire useful information to consolidate the profile of safety of vaccination, with reference to the commencement of pregnancy during the vaccination cycle and/or in the immediately following months;

**CONSIDERS**

further that

- Any strategy should, however, be accompanied by active enrolment measures, also including widespread information and communication aimed at target subjects and their families on topics relating to vaccination, prevention of carcinoma of the neck of the womb, related screening programmes and sexual activity;

- For the cohorts being actively recruited, the vaccine should be offered **with the full cost borne by the Italian National Health Service**. For the remaining population not actively offered the vaccine within the age range for which it is marketed, it is thought that methods of supply by the Public Health Services with mechanisms for tracing the prescription/supply would be useful for containing the cost borne by the community, at the same time favouring the monitoring of circulation of the vaccination and its results, even outside the aforesaid programmes. The planning and organization of these activities shall fall within the competence of the region, in view of the different bodies of the Regional Health Services and their methods of operation;
Monitoring vaccination is fundamental in order to assess the impact of the immunization programme, not only on the cervical neoplastic pathologies, but also on precancerous lesions and on benign neoplasias. It is also essential to estimate the economic impact of the programme and to establish, in the medium term, the changes in sickness profiles in relation to the prevaccination period, allowing possible adaptations and additions of primary and secondary prevention measures.

Areas to be given preference in the monitoring field will be as follows:

1. Monitoring vaccination as such, from the extent and coverage (with particular reference to those not responding or not accepting) and adverse effects. This area also includes monitoring the efficacy of the information and communication measures and the development of screening;

2. Monitoring the development of infection (cervical carcinomas, precancerous lesions, condylomas) and the relative mortalities and survivals;

3. Monitoring the effects and results of vaccination on other sexually transmitted infections and on other possible HPV-related neoplastic pathologies.

The monitoring activities may relate to all subjects undergoing vaccination, using ad hoc sources of information and/or information already known or available, but could also include suitable studies on population samples and specific research on the consequences of vaccination in subjects undergoing vaccination and in the entire population;

• A preliminary condition for achieving high vaccination coverage of the target populations is adequate information for the population, at the same time as training the personnel involved in the educational processes and, obviously, health personnel. Access at the moment of prevention may be guaranteed by accurate control by the health units, through their own divisions. Times of awareness and immunization proposals should be organized in the scholastic, work and consultancy environments, and access to vaccination should be planned in the regional services.

INDICATES

that specific studies on the possibility of associating vaccination for HPV infection with vaccination against tetanus are in progress. At the moment, it is known to be impossible to associate anti-HPV vaccination with anti-hepatitis vaccination. In the uncertainty of the scientific knowledge available, it is not recommended that strategies of co-administration of the vaccination including anti-HPV vaccination be followed for the time being.

Finally,

IT CONSIDERS IT NECESSARY
• For the strategy of vaccination against infection, identified at the moment, to be remodelled in view of the possible development of multivalent vaccines that extend primary prevention to other types of HPV and/or provide for the administration of a lower number of doses;

• In subsequent studies conducted over a longer observation period, for the possibility of segregation and expansion of other oncogenic strains facilitated by vaccination to be assessed;

• In view of the composition of the vaccine that only includes some of the oncogenic strains and the lack of definitive data on the duration of immunity, for the information campaigns accompanying vaccination to emphasize the efficacy of the combined vaccination-screening strategy and to recommend that vaccinated women undergo screening, following the reference guidelines for non-vaccinees. Cytological screening and the relative measures have, in fact, reduced the incidence of cervical cancer to 60% in some populations in which screening is intensely practised. Studies conducted on the cost-efficacy ratio seem to indicate that the most beneficial approach in that connection is represented by vaccination at 12 years of age and by three-year cytological screening as from 25 years of age.

SECRETARY GENERAL
[signature]

CHAIRMAN OF THE
HIGHER HEALTH COUNCIL
[signature]
Opinion of Combined Sections II and III – Meeting on 11th January 2007

Errata

On the opinion in question, two typographical errors were noted (relating to the vaccination programme and the co-administration with other vaccines), to be attributed to a mere physical error, which is corrected as follows:

- On page 2 line 13 [of the Italian original], instead of "Both vaccines are administered in 3 doses (at 0, 1 and 6 months and at 0, 2 and 6 months, respectively)", should read "Both vaccines are administered in 3 doses (at 0, 2 and 6 months and at 0, 1 and 6 months, respectively)";

- On page 6 line 22 [of the Italian original], instead of "At the moment, it is known to be impossible to associate anti-HPV vaccination with anti-hepatitis vaccination", should read "At the moment, it is known to be possible to associate anti-HPV vaccination with anti-hepatitis vaccination".

These corrections, attached to the original opinion, form an integral part thereof.

Rome, 2nd February 2007

Secretary General
Dr Daniela Rodorigo [signature]

Chairman of the Higher Health Council
Prof. Franco Cuccurullo [signature]

MINISTRY OF HEALTH
HIGHER EDUCATION COUNCIL