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TRANSPARENCY COMMITTEE

Opinion
20 March 2013

GARDASIL suspension for injection, Human Papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – vial (glass) – 0.5 ml

B/1 (CIP: 34009 377 143 6 5)

GARDASIL suspension for injection in a pre-filled syringe, Human Papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) pre-filled syringe (glass) – 0.5 ml

B/1 (CIP: 34009 377 130 1 6)

Applicant: SANOFI PASTEUR MSD

INN	Papillomavirus (type 6, 11, 16, 18) recombinant
ATC Code (2012)	J07BM01
Reason for the review	- Change of the conditions for inclusion on the list of medicines reimbursed by National Health Insurance following the 28 September 2012 opinion of the High Council for Public Health (HCSP) on the revision of the age for vaccination against human papillomavirus (HPV) infections in girls: <u>Estimate of the size of the new target population</u> - Request by the Directorate-General for Health and the Social Security Directorate dated 8 March 2013 for a reassessment of the target population.
List(s) concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indication(s) concerned	“Prevention of: - premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. - genital warts (condyloma acuminata) causally related to specific HPV types. The use of GARDASIL should be in accordance with official recommendations.”

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date: 29 September 2006 (Centralised procedure)
Prescribing and dispensing conditions / special status	List I
ATC Classification	2012 J: Antiinfectives for systemic use J07: Vaccines J07B: Viral vaccines J07BM: Papillomavirus vaccines J07BM01: Papillomavirus (type 6, 11, 16, 18) recombinant

02 BACKGROUND

Following the HCSP Opinion of 28 September 2012 (published on 15 January 2013) concerning the revision of the age of vaccination of young girls against Human Papillomavirus (HPV) infections,¹ the applicant SANOFI PASTEUR MSD is requesting the modification of the inclusion conditions for the GARDASIL vaccine.

The Directorate-General for Health and the Directorate for Social Security have also requested that the Committee examine the possibility of changing the inclusion conditions for HPV vaccines (CERVARIX and GARDASIL).

The development of data regarding the vaccines and their Marketing Authorisations, awareness of insufficient vaccine coverage in France and opinions on the development of a vaccine schedule has led the HCSP to revise the guidelines for vaccination against HPV infections.

The change in the data on vaccines and their Marketing Authorisations, the finding that vaccination coverage in France is inadequate and the prospects for a change in the vaccination schedule have led the HCSP to revise the recommendations on vaccination against HPV infections.

In its opinion of 28 September 2012, the HCSP recommends that:

- ***“The vaccination of girls against papillomavirus can be done between the ages of 11 and 14 years;***
- ***any opportunity, including the vaccination appointment at 11-14 years, should be used:***
 - ***to initiate the vaccination of those for whom there has not yet been an opportunity for co-administration with another vaccine: tetravalent diphtheria-tetanus-pertussis-polio vaccine, hepatitis B vaccine;***
 - ***or to complete an incomplete schedule and in particular to administer the 3rd dose of vaccine to those who have not yet received it”***

This takes the place of the recommendation of 2007 on offering vaccination from the age of 14 years only.

- ***“The age for catch-up vaccination should be limited to the 20th birthday years (i.e., 19 years of age). This vaccination is no longer based on the concept of the age at which***

¹ Haut Conseil de la santé publique. Avis relatif à la révision de l'âge de vaccination contre les infections à papillomavirus humains des jeunes filles. 28 September 2012.

girls become sexually active, even though the vaccine will be all the more effective if girls have not yet been infected with the papillomaviruses targeted by the vaccination.”

This replaces the 2007 recommendation to vaccinate girls and young women aged 15 to 23 years who are not yet sexually active, or at the latest, who have been sexually active for less than one year.

The HCSP opinion setting out the arguments on which these recommendations are based can be found in Appendix 1.

03 THERAPEUTIC INDICATION(S)

“GARDASIL is a vaccine for use from the age of 9 years for the prevention of:

- premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types.
- genital warts (condyloma acuminata) causally related to specific HPV types.

See sections 4.4 and 5.1 of SPC for important information on the data that support these indications.

The use of GARDASIL should be in accordance with official recommendations”.

04 CLINICAL DATA

Data regarding the evaluation of the GARDASIL vaccine in support of the HCSP guidelines of 2012 are those already submitted and assessed by HAS during the assessment of the dossier for inclusion (Transparency Committee Opinion of 18 April 2007) and during the re-assessment in 2012 (CT Opinion of 1st February 2012), as well as epidemiological data analysed by VTC. This data is as follows:

- **vaccination coverage:** follow-up data on coverage with papillomavirus vaccines, whereas such data demonstrates that coverage is inadequate and fell between 2010 and 2011;
- **immunogenicity in girls aged 9 to 15:** antibody titres in the 7th month after vaccination observed in studies carried out in girls aged 10 to 14 years were higher than those observed in girls aged 15 to 25 years; the titres are also higher in girls aged 9 years than in those aged 10 to 14 years. Vaccine efficacy in girls aged 9 to 15 years was extrapolated from these immunogenicity data.
- **persistence of antibodies to the 101st month,** is greater than that of natural immunity in women aged 15 to 25 years at the time of vaccination. This stability was confirmed at 113 months.
- **protection after four years** of 94.9% in terms of preventing high-grade cervical lesions (CIN 2+) related to HPV 16 and 18, of (95% CI: [87.7 -98.4]).
- possible **co-administration** with a combined diphtheria (d), tetanus, acellular pertussis and poliomyelitis booster, a hepatitis B vaccine, a combined hepatitis A and B vaccine.
- **the results of vaccination in women over 25 years of age,** which show that the vaccine will be all the more effective if girls have not yet been infected with the papillomaviruses targeted by the vaccination. In fact, in women not infected with the HPV type(s) contained in the vaccine (per protocol population), the efficacy of CERVARIX after six months against persistent infection related to HPV-16/18 (relevant surrogate marker for cervical cancer) was 82.9% [53.8; 95.1], whereas in women with or without infection (TVC population), it was only 47% [25.4; 62.7].
- **changes in sexual practices,** which shows an increase in the percentage of girls who are sexually active before the age of 15 years between 2005 and 2010.
- **studies concerning the acceptability of vaccination according to age,** which show opinions are divided between the supporters of late vaccination linked to information about sexuality and STIs and the supporters of early vaccination, which avoids raising this issue.

In addition, in view of the reported cases of narcolepsy with cataplexy attributed to the lipid adjuvant AS03 (composition: vitamin E and squalene in an oil-in-water emulsion) used in the influenza vaccination, the National Medicines and Health Products Safety Agency (ANSM) was consulted and confirmed that no similar cases were observed with any of the anti-HPV vaccines with a different adjuvant.

In addition, within the scope of this request to amend the conditions of inclusion based on the HCSP Opinion of 28 September 2012 concerning the revision of the age of the vaccination, no new clinical data likely to change the conclusions of the previous Transparency Committee opinions on the efficacy and safety of the GARDASIL vaccine have been included in the dossier.

The Transparency Committee reiterates that, given the current state of the dossier, the following have not been established:

- the efficacy in terms of preventing cervical cancer (even though additional data have been presented regarding premalignant CIN 3 and AIS lesions, immediate precursors of cervical cancer),
- the duration of cross-protection beyond 48 months is not known,
- immunogenicity in immunocompromised populations (study in progress in South Africa),
- the assessment of a possible change in viral ecology associated with the introduction of the vaccination.

The new HCSP recommendations broaden the target population for anti-HPV vaccination to girls aged 11 to 14 years and restrict the target population in older young women by setting an age limit of 20 years.

The HCSP believes that earlier vaccination must not allow any departure from the provision of detailed information for girls who are candidates for anti-HPV vaccination, particularly about exposure to sexually transmissible diseases.

05 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all of the above information, and following the debate and vote, the Committee's opinion is as follows:

05.1 Actual benefit

GARDASIL is a vaccine against Human Papillomavirus 6, 11, 16 and 18 for:

- the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain potentially life-threatening types of oncogenic Human Papillomavirus (HPV).
- the prevention of genital warts (condyloma acuminata), which are recurring non-life threatening non-malignant tumours.

This proprietary medicinal product is intended as a preventive therapy (primary prevention).

The vaccine efficacy/adverse effects ratio of this proprietary medicinal product in the new population is high.

Public health benefit:

The incidence of invasive cervical cancer in France is estimated to be 2,810 new cases a year (InVS projections 2011²). It is therefore the 10th most common cancer in women. The number of deaths from cancer was estimated at 998 in 2011, which puts cervical cancer in 13th place as the cause of cancer deaths among women in 2011.

The public health burden of cervical cancer (corresponding to about 135,000 DALYs³) is therefore considered to be moderate.

Reducing the incidence of cervical cancer is an established public health priority (objective 48 of the Law of 9 August 2004 relating to public health policy "to continue reducing the incidence of cervical cancer by 2.5% a year, and in particular by hitting the target of 80% screening coverage among women aged from 25 to 69 years", 2009-2013 Cancer Plan "Measure 15: To improve the structuring of the action plan for national cancer screening programmes").

Vaccination against oncogenic human papillomavirus (HPV) types could constitute a response to this need, and could optimise nationwide cervical cancer screening. Even though improvements in screening coverage have continued to be made since 1995, coverage was only 58.5% in 2007-2009,⁴ which is still far from the target of 80%, especially in certain more disadvantaged social and occupational categories.^{5,6}

In France, the vaccination coverage rate (full vaccination schedule) was estimated on the basis of the national health insurance system's general sample of beneficiaries

² Hospices civils de Lyon / National Health Monitoring Institute / National Cancer Institute / Francim / National Institute of Health and Medical Research. Projections of the incidence and mortality from cancer in France in 2011. Technical report. June 2011. <http://www.invs.sante.fr/surveillance/cancers> [retrieved 21.10.2011].

³ Regional burden of disease estimates for 2004. Standard DALYs for Zone EURO A. World Health Organization. http://www.who.int/healthinfo/global_burden_disease/DALY14_2004.xls [retrieved 25.02.2013]

⁴ DRESS. L'état de santé de la population en France – State of health of the population in France – Follow-up of objectives related to the Public Health Law - 2011 Report http://www.sante.gouv.fr/IMG/pdf/Etat_sante-population_2011.pdf [retrieved 26 02 2013].

⁵ Public health objectives. Assessment of the objectives of the Law of 9 August 2004. Proposals. High Council for Public Health (HCSP). April 2010

⁶ Recommendations in public health: "Situation and recommendations for cervix cancer screening in France". Haute Autorité de santé. July 2010.

(CNAM-TS/InVS) on 31 December 2011.⁷ It was on average 36.9% in girls born in 1993 (18 years), 39.0% in girls born in 1994 (17 years), 31.2% in girls born in 1995 (16 years) and 20.2% in girls born in 1996 (15 years).

Follow-up of the coverage rates according age indicates a downward trend in the vaccination coverage rate for one dose between 2010 and 2011 in cohorts of girls who were 16 years of age in the year in question (49.9% versus 46.8% respectively), 15 years of age in the year in question (39.4% versus 35.8% respectively) and 14 years of age in the year in question (22.5% versus 15.8% respectively).

The majority of girls start vaccination at age 15 years or later. The vaccination coverage of girls aged 14 years is therefore still insufficient today.

In view of the low rate of vaccination coverage achieved in France, especially in girls aged 14 years, as well as the inadequate level of individual screening, the public health need remains.

Considering the only immunogenicity data available for young girls between 11-14 years and in the absence of new data enabling the impact of the vaccine on morbidity to be documented for other age ranges, the impact of GARDASIL is still considered as being significant in the reduction in short-term morbidity (CIN2+), especially for young girls who have yet to be infected by oncogenic HPV, independent of the age of vaccination.

However, given the development of the natural history of HPV infections, 3.6 years is insufficient time to be able to assess the impact of GARDASIL in terms of morbidity and mortality (CIN 3 and *in situ* carcinoma) in young girls aged 15 to 25 years.

Furthermore, the uncertainties raised previously remain (cross protection not demonstrated in each of the oncogenic HPV types, unknown duration of vaccine protection, consequences of the vaccination on the distribution and viral ecology of HPV and consequences of the vaccination on screening practices).

Consequently, with the inadequate vaccination coverage rate as it is at present in France likely to not guarantee immunity of the group, and despite the expected considerable potential public health interest in vaccination against Papillomavirus, the public health benefit for GARDASIL with the scant retrospective information at our disposal, remains regarded as low.

In order to optimise the public health impact of this vaccine and to meet the public health needs, the Committee in its Opinion of 2 February 2012 considered it necessary to put in place measures designed to:

- stimulate the vaccination programme and increase the vaccination coverage rate especially among HPV-naïve girls, amongst whom vaccination efficacy is greatest,
- and improve access to, information about and interest in cervical smear screening, particularly among young women in disadvantaged neighbourhoods.

The new recommendations of the HCSP on lowering the age of vaccination to 11-14 years are intended to promote an increase in vaccination coverage by making it possible:

- to promote the vaccination of girls who have not yet been exposed to the risk of HPV infection and in whom vaccination efficacy is maximal;
- to use the vaccination appointment for 11-14 year-olds (booster of tetravalent vaccine against diphtheria-tetanus-pertussis-polio or vaccine against hepatitis B) to start vaccination or to complete an incomplete vaccination schedule.

In addition, the withdrawal of the concept of the age at which sexual activity starts in the catch-up vaccination population aged 15-19 years could also limit the obstacles to vaccination. However, in terms of public health, the greatest benefit of vaccination is in girls or young women who have not yet been exposed to papillomaviruses.

⁷ Opinion on the revision of the age for vaccination against human papillomavirus infections in girls. High Council for Public Health (HCSP). 28 September 2012.

Even though it does not specifically pertain to HPV vaccination, the national programme for the 2012-2017⁸ vaccination policy improvement programme implemented by the Directorate-General for Health in October 2012 will, in coming years, also aim to facilitate access to vaccines and encourage preventive actions using vaccination.

Finally, since the vaccination does not protect against all oncogenic HPV types, it cannot be a substitute for screening for premalignant and malignant lesions of the cervix. Rather, it should be a complement. Thus, improving access, information and the benefit of screening by means of cervical smears recommended every three years (after two normal cervical smears carried out one year apart) in all women aged 25 to 65 years remains necessary, particularly in young women from disadvantaged neighbourhoods who may not enjoy the optimal conditions of regular screening.

To this end, the organisation of screening by means of nationwide cervical smears is still essential.

There is an alternative vaccination for the prevention of premalignant cervical lesions and cervical cancer.

Screening, which relies on a cytological test – cervical smear – is an effective secondary means of preventing cervical cancer.

There is no way to screen for vulvar or vaginal lesions.

There is no means of preventing external genital warts.

Taking account of these points, the actual benefit of this vaccine is substantial in the new population recommended by HCSP in the current vaccination schedule.

05.2 Target population

To reiterate, in 2007 the vaccination was recommended for:

- the population of girls aged 14 years, i.e., about 370,000 girls every year (INSEE data as of 1 January 2007: 350,769 girls)
- the population of girls and young women aged 15 to 23 years (catch-up vaccination population) who have not yet had sexual relations or, at the latest, in the year after becoming sexually active i.e., about 1,570,000 young women in 2007.

New target population (replaces the previous estimate):

The target population eligible for vaccination against with human papillomavirus (HPV) infections as defined by the HCSP (Opinion of 28 September 2012) is made up of:

- girls aged 11 to 14 years,
- girls and young women aged 15 to 19 years who have not yet received an HPV vaccination. The recommendation for a catch-up vaccination is no longer supported by the concept of the age at which sexual activity starts.

The estimate of the target population is made on the basis of the demographic profile⁹ as of 1 January 2013 and data on vaccination coverage against HPV infections.¹

The estimate of this population must take into account:

1-Every year

- a birth cohort of girls who can receive the vaccination from their 11th birthday or at the age of 12, 13 or 14 years if they have not already received it.

The population of girls aged 11 years was 404,653 individuals as of 1 January 2013.

⁸ 2012-2017 vaccination policy improvement programme 2012 – 2017.
http://www.sante.gouv.fr/IMG/pdf/Programme_national_damelioration_de_la_politique_vaccinale.pdf retrieved 25.02.2013.

⁹ Insee: Demographic profile 2012. Total population on 1 January 2013. <http://www.insee.fr>

On the basis of these data, **the target population likely to be vaccinated every year between the ages of 11 and 14 years is of the order of 400,000 patients.**

2. During a transitional period

- Girls aged 12 to 14 years eligible for vaccination in 2013

This corresponds to the cohorts of girls who will have their 12th, 13th or 14th birthday between 1 January and 31 December 2013. Given the ages defined by the previous recommendation (vaccination starting at age 14 years), this population can be regarded as vaccination naïve on 1 January 2013.

The population of adolescents aged 12 to 14 years is 1,197,298 individuals in 2013.

- Continuation of catch-up vaccination in girls and young women of 15 to 19 years of age:

Part of this population has already received vaccination in accordance with the previous recommendation. The new target population therefore consists of girls and young women who have not been vaccinated, regardless of their sexual history.

The population of girls and young women 15 to 19 years of age is 1,941,561 individuals in 2013. If an average vaccination coverage of about 50% for one dose is applied to this population, the target population of girls and young women aged 15 to 19 years who have not been vaccinated could be estimated at about 970,000 patients in 2013.

In total, the target population eligible for vaccination on 1 January 2013 according to the new HCSP recommendations is about 2,500,000 patients aged 11 to 19 years who can receive the vaccination in the next few years.

Ultimately, after a transition period (estimated at 3-5 years), this population will be represented by a birth cohort of girls eligible for the vaccination from their 11th birthday or at the age of 12, 13 or 14 years if they have not previously received the vaccination, i.e., about 400,000 patients every year.

06 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance in the new population recommended by the HCSP in the current vaccine schedule.

►Proposed reimbursement rate: 65%

► Packaging:

Appropriate for the prescription conditions.

► Other requests

In addition to the recommendations already given in its Opinion of 1 February 2012, the Committee stresses that the effectiveness of this strategy of prevention by vaccination against HPV depends on achieving the highest possible vaccination coverage rate.

It finds that, since the implementation of vaccination in 2007, only a small proportion of the eligible population is currently vaccinated against HPV, and that there was even a slight drop in the vaccination rate between 2010 and 2011.

Consequently, if this coverage did not achieve the objective despite the new recommendations issued, the Committee might have cause to reconsider, in the medium term (in a period of three years), the assessment of the actual benefit of anti-HPV vaccines.

In addition, the Committee points out that the prevention of cancers of the cervix and uterus, regardless of the type of HPV is involved, has for decades been based on screening for premalignant/malignant lesions using the cervical smear test, which has largely proved its efficacy when correctly organised, and that vaccines for preventing infection with oncogenic HPV 16 and 18 complement screening and cannot replace it.

In any event, the Committee confirms its previous opinion and believes that it remains vital for cervical smear screening for premalignant and malignant cervical lesions to be organised nationwide.



High Council for Public Health

OPINION

on the revision of the age of vaccination against human papillomaviruses for girls

28 September 2012

On 9 March 2007, the French Higher Council on Public Hygiene (CSHPF) recommended the quadrivalent papillomavirus vaccine GARDASIL® for the **vaccination of girls aged 14 years** in order to protect them before they are exposed to the risk of HPV infection [1]. It also recommended **that the vaccine should also be offered to girls and young women aged 15 to 23 years** who have not yet had sexual relations or, at the latest, in the year after they become sexually active.

On 17 December 2010, the High Council for Public Health (HCSP) considered that the quadrivalent GARDASIL® and bivalent CERVARIX® vaccines were equivalent as regards protection against premalignant lesions of the cervix [2].

The choice of the vaccination target, i.e., girls aged 14 years, was determined in 2007 with consideration for [3]:

- The age of first sexual relations

This age was on average 17.5 years in girls. About 3% of women say that they had sexual relations before the age of 14 years.

- Doubts about the duration of protection

At that time, there was only five years' experience with the vaccine and the fear was that, by recommending vaccination at the age authorised by the Marketing Authorisation (MA) – currently 9 years for both vaccines – there would later be a need to recommend boosters for persons who had not yet been exposed to the risk.

- The lack of studies authorising co-administration

The only data available at the time concerned the co-administration of GARDASIL® and vaccines against hepatitis B. Thus, the vaccination appointment at 11-13 years for the DTCaP (diphtheria, tetanus, acellular pertussis and polio) booster could not be used to administer one of the doses of vaccine against the papillomavirus.

The change in the data concerning vaccines and their MAs, the finding that vaccination coverage in France was very inadequate and the prospects of a change in the vaccination schedule justify the HCSP's initiative to revise its own recommendations.

The High Council for Public Health took into consideration:

➤ **The follow-up of human papillomavirus vaccination coverage**

This follow-up shows that the levels of vaccination coverage as of 31 December 2011, calculated using the national health insurance system's general sample of beneficiaries (EGB) (Cnam-TS/InVS), for girls born in 1993 (18 years), 1994 (17 years), 1995 (16 years) and 1996 (15 years) are, for one dose, 53.0%, 53.8%, 46.8% and 35.8% respectively (Fig.1) and for three doses 36.9%, 39.0%, 31.2% and 20.2% respectively.

Cumulative HPV (1 dose) vaccination rate as a function of age and birth cohort

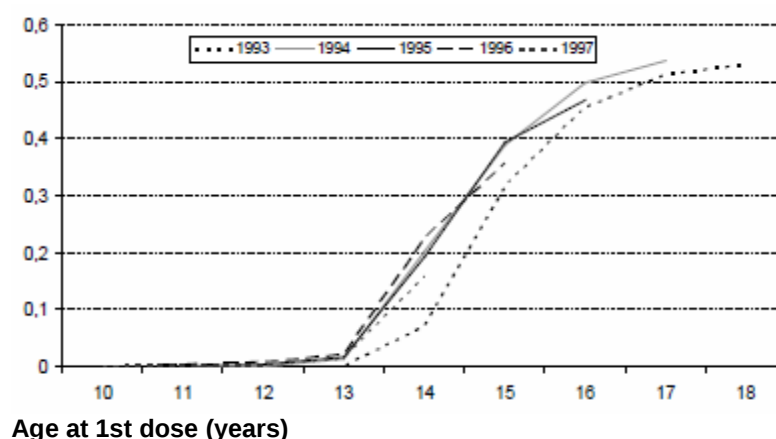


Fig. 1: Cumulative HPV (1 dose) vaccination rate as a function of age and birth cohort

Follow-up of the coverage rates according to age shows that vaccination coverage for one dose fell. It was 49.9% in 2010 in girls who were 16 years old that year and 46.8% in 2011 in those who were 16 years old that year. Vaccination coverage for one dose at age 15 years also fell. It was 39.4% in 2010 in girls who were 15 years old that year and 35.8% in 2011 in those who were 15 years old that year, as it was for girls aged 14 years (22.5% in 2010 and 15.8% in 2011). "Vaccination coverage for three doses at age 15 years, on the other hand, remained stable between 2010 (20.3%) and 2011 (20.2%)."

These data suggest a drop in vaccination compliance between 2010 and 2011.

This low vaccination coverage rate could mean that that it is no longer possible to guarantee the achievement of group immunity.

In Australia, thanks to vaccination in schools, the vaccination of girls with the quadrivalent vaccine and a vaccination coverage rate of the order of 80% was accompanied by a reduction in the incidence of condylomas in unvaccinated heterosexual young men, which suggests the existence of group immunity (level 2) [4-5].

In addition, as suggested in two studies conducted in Belgium [6] and in California [7], it is possible that girls who get vaccinated are those who will later comply with cervical cancer screening in the form of a cervical smear test (level 2). Thus, vaccination would not benefit those most in need of it. These data on vaccination coverage may also reflect the difficulty of being able to vaccinate only from the age of 14 years. Most countries offer vaccination at an earlier age. The French data also show that there is some difficulty in completing the vaccination schedule and in particular in administering the 3rd dose. The compliance rate on 31 December 2011 (number of girls who received three doses compared with the number of girls who received a first dose before 1 January 2011) was 76.7%, 72.8% and 72.1% in girls born in 1994, 1995 and 1996 respectively.

In addition, most catch-vaccination up work is done before the age of 19 years. The French vaccination coverage data show a low level of catch-up vaccination after the age of 18 years. Three-dose vaccination coverage in 2009, for girls aged 19 to 23 years in 2007, did not exceed 10% [8].

Vaccination against papillomavirus was included in the vaccination schedule for 2008, with a policy of catch-up vaccination up to the age of 23 years. After five years of experience, it is found that in most cases vaccination starts before the age of 16 years. In addition, the policy of catch-up vaccination necessarily based on the date on which sexual activity starts proves difficult to apply in practice. The continuation of catch-up vaccination beyond 18 years is therefore no longer justified. The option of giving girls access to vaccination until their 20th birthday is still justified by the fact that, from 18 years of age, parental authorisation is no longer required.

➤ Scientific data on the assessment of vaccines

Immunogenicity

The antibody titres in the 7th month after vaccination are:

- for GARDASIL®, higher in girls aged 9 to 15 years compared with those observed in young women aged 16 to 26 years;
- for CERVARIX®, higher in girls aged 9 years compared with those observed in girls aged 10 to 14 years and in young women aged 15 to 25 years; they are also higher in girls aged 10 to 14 years compared with those observed in young women aged 15 to 25 years.

Thus, vaccination response is better the earlier vaccination is started. In addition, in these studies, administration of the vaccine between 9 and 15 years of age reveals a safety profile comparable to that of later administration.

This better immunogenicity has, moreover, led the Swiss authorities [9] to recommend (off-label) a vaccination schedule of two doses, given six months apart, for girls who start vaccination between the ages of 11 and 14 years, whereas the classic three-dose vaccination schedule is retained for girls who start vaccination from the age of 15 years.

Antibody persistence

The data available to date show:

- for GARDASIL®, antibody persistence at a level higher than that of natural immunity until at least the 60th month in women aged 16 to 26 years at the time of vaccination;
- for CERVARIX®, antibody persistence at a level higher than that of natural immunity until at least the 113th month in women aged 15 to 25 years at the time of vaccination.

Protection after 4 years

Efficacy in the prevention of high-grade cervical lesions (CIN 2+) related to HPV 16 and 18 in per protocol use after four years is:

- for GARDASIL® 98.2% (95% CI: 93.5-99.8);
- for CERVARIX® 94.9% (95% CI: 87.7-98.4).

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Co-administration data

Co-administration is possible for both vaccines with a combined booster diphtheria (d), tetanus, acellular pertussis and poliomyelitis vaccine, a hepatitis B vaccine, and, for CERVARIX®, with the combined hepatitis A and B vaccine.

Vaccination after the age of 25 years

o GARDASIL®

In women not infected with the HPV type(s) contained in the vaccine, the efficacy of GARDASIL® in preventing the combined incidence of persistent infections, genital warts, lesions of the vulva and vagina, CIN of any grade, AIS and cervical cancers related to HPV types 16 or 18, was 84.7% (95% CI: 67.5-93.7).

In women with or without pre-existing infection or disease related to HPV types 6, 11, 16 or 18, the efficacy of GARDASIL® in preventing the combined incidence of persistent infections, genital warts, lesions of the vulva and vagina, CIN of any grade, AIS and cervical cancers related to HPV types 16 or 18, was 41.6% (95% CI: 24.3-55.2).

o CERVARIX®

The efficacy of CERVARIX® against persistent infection related to HPV-16/18 (relevant surrogate marker for cervical cancer) after six months was 82.9% (53.8; 95.1) in the per protocol population.

In women with or without infection (TVC population), the efficacy of CERVARIX® against persistent infection related to HPV-16/18 after six months was 47% (95% CI: 25.4; 62.7).

Several studies show that the cumulative incidence of HPV infection in girls under 20 years of age exceeded 30% in a two-year follow-up after the start of sexual activity and 40% in a three-year follow-up [10, 11]. In terms of public health, the greatest benefit of vaccination is therefore girls or young women who have not yet been infected with oncogenic HPVs.

➤ Change in sexual activity

French data for the international “Health Behaviour in School-aged Children” survey (The health of school-aged children in France, 2010, INPES) show that 3.6% of girls questioned in the survey in 2010 said they had had sexual relations before the age of 13 years and 14.1% before the age of 15 compared with 1.6% before 14 years and 6.3% before 15 years in the 2005 INPES health barometer survey, which also reported that 79% of young women aged 20 years had become sexually active [12]. In a survey on the context of sexuality in France, only 12.8% of young women aged 20-24 years stated they had never had sexual relations [13].

➤ Studies on the acceptability of vaccination according by age

Vaccination against papillomavirus is strongly related to sexuality and raises issues that concern young adolescents, their parents and society. Surveys regarding the optimal age for HPV vaccination are mixed and therefore difficult to interpret.

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International data: surveys of parents

In a study conducted in England, where 75% of the 684 mothers of girls aged 8 to 14 years were in favour of vaccination, the fact that the subject of sexuality has to be addressed is a barrier and an argument in favour of early vaccination [14]. In another study conducted in the United Kingdom, in a focus group of 24 mothers, there was consensus about mentioning sexually transmissible infections (STIs) after the age of 11 years and not before the age of 9 years [15]. In a survey conducted in California of 522 parents of girls under 18 years of age, 75% of them thought that the ideal age of vaccination was before 13 years [16]. In another study conducted in the United States of parents of children aged 8 to 12 years, vaccination was more acceptable for teens than for preteens [17]. In a Swedish survey conducted

amongst 13,946 parents of children aged 12 to 15 years, 35% of the parents thought that the optimal age for vaccination was between 12 and 14 years and 53% of parents thought it was 15 to 17 years [18]. In Belgium, in a survey of women seen at a hospital gynaecology office, most of the women thought that the optimal age for vaccination was between 12 and 16 years [19, 20]. Finally, in New Zealand, in a survey conducted amongst the parents of school-age children before vaccinations were initiated in schools, 50% stated they would prefer vaccination to take place at the age of 13 years or older and 28% stated they would prefer it take place between the ages of 10 and 12 [21].

French data: surveys of doctors

In France, we have only surveys conducted amongst doctors. In a survey of 545 general practitioners in the Pays de la Loire region, 64.4% of them agreed with the recommendations to vaccinate at 14 years [22]. However, in a survey conducted in the PACA region amongst 359 general practitioners, while 89.6% were in favour of HPV vaccination, 34.4% of them thought the ideal age for vaccination was between 11 and 13 years, and 53.9% thought it was between 14 and 15 years [23]. Finally, in a study performed in the Rhône-Alpes region amongst 279 general practitioners, 80.8% were in favour of vaccination but 28.9% thought that the currently recommended age was a barrier. They thought it was difficult to talk to adolescents about sexually transmissible infections (STIs) and 50% of doctors who were in favour of vaccination thought that vaccination at an earlier age would prevent the need for such discussions [24].

Overall, opinions are divided between the advocates of late vaccination combined with information about sexuality and STIs and the supporters of early vaccination to avoid broaching these issues. Recommendations with a broader age range and an earlier lower limit would allow greater flexibility. Doctors could thus suggest vaccination at the age that seems most appropriate to given their knowledge of the child and family and, where appropriate, take the opportunity to discuss any problems related to sexuality.

➤ Special points about the two-vaccine vaccination schedule

When a vaccination schedule is interrupted, it is not necessary to redo the complete schedule. It is possible to administer missing doses outside the interval recommended by the Marketing Authorisation of 12 months after the 1st dose. In fact, as a general rule in immunology, the spacing of vaccine doses helps improve of immune response rather than cause non-response.

The three-dose vaccination schedule must be followed even if the 3rd dose is administered more than 12 months after the 1st dose. Data that could justify a two-dose vaccination schedule are limited. A study performed in Costa Rica [25] suggests that people vaccinated with fewer than three doses of bivalent vaccine have a level of protection comparable to that of people who received the complete schedule. These data are based on a limited number of people with a maximum follow-up period of four years, which means that at present, a vaccination schedule of less than three doses cannot be recommended.

The High Council for Public Health reiterates that HPV vaccination is more effective if girls have not yet been exposed to the risk of HPV infection.

The High Council for Public Health recommends, in accordance with the latest data from the ECDC [26], that:

- **the vaccination of girls against papillomavirus can be carried out between the ages of 11 and 14 years;**
- **any opportunity, including the vaccination appointment at 11-14 years, should be used:**

- o to initiate the vaccination of those for whom there has not yet been an opportunity with the possibility of co-administration with another vaccine: tetravalent diphtheria-tetanus-pertussis-polio vaccine, hepatitis B vaccine;
 - o or to complete an incomplete schedule and in particular to administer the 3rd vaccine dose to those who have not yet received it;
- the age for a catch-up vaccine should be limited to 20 years (i.e. 19 years inclusive). This vaccination is no longer based on the idea of the age at which sexual activity starts, even though the vaccine will be all the more effective if girls have not yet been infected with the papillomaviruses targeted by the vaccination.

The High Council for Public Health reiterates that achieving a high vaccination coverage rate is a priority objective both for the protection of girls and for the induction of group immunity. It also stresses that these high vaccination coverage rates are achieved in countries (United Kingdom, Australia) that vaccinate in schools.

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- Le CTV a tenu séance le 21 septembre 2012 : 14 membres qualifiés sur 17 membres qualifiés votant étaient présents, 0 conflit d'intérêt, le texte a été approuvé par 14 votants, 0 abstention, 0 vote contre.

Un vote partiel a porté sur le problème des limites d'âge du rattrapage :

- 2 personnes ont voté pour 18 ans révolus (proposé par le groupe de travail) ;
- 12 personnes ont voté pour 19 ans révolus.

Daniel Floret a voté pour 18 ans révolus argumentant sur le fait que les filles âgées de 19 ans sont celles qui étaient âgées de 14 ans en 2007 (qu'elles ont donc eu 5 ans pour se décider). Cet âge ménage un délai de 1 an après la majorité. En outre, tous les autres pays ont des périodes de rattrapage plus courtes.

Le texte final a été approuvé par 14 votants, 0 abstention, 0 vote contre.

- La CSMT a tenu séance le 28 septembre 2012 : 9 membres qualifiés sur 15 membres qualifiés votant étaient présents, 0 conflit d'intérêt, le texte a été approuvé par 9 votants, 0 abstention, 0 vote contre.

Avis produit par la Commission spécialisée Maladies transmissibles, sur proposition du Comité technique des vaccinations

Le 28 septembre 2012

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