

OVERVIEW OF VACCINATION GUIDELINES

PAPILLOMAVIRUS VACCINATION IN BOYS

December 2019

PURPOSE

At the request of the Minister for Health, the French National Authority for Health (Haute Autorité de santé - HAS) issues recommendations concerning the role of vaccines directed against papillomaviruses as part of the current prevention strategy vis-à-vis cancers induced by these viruses in boys.

Following the evaluation, HAS recommends the expansion of Gardasil 9 HPV vaccination® to all boys aged 11 to 14, with possible catch-up for all adolescents and young adults aged 15 to 19.

CURRENT PAPILLOMAVIRUS INFECTION PREVENTION STRATEGY IN FRANCE

Human papillomaviruses

The vast majority of men and women are infected with papillomaviruses during their lifetime, usually in the first few years after the onset of sexual activity. HPV infections are mostly asymptomatic, disappearing spontaneously; in some cases however, the infection persists and can lead to more serious conditions, including cancer.

There are more than 100 types of sexually transmitted papillomavirus. High-risk oncogenic papillomaviruses (mainly HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59), particularly type 16, which is responsible for most HPV-induced cancers in humans, and low-risk oncogenic papillomaviruses in humans, mainly types 6 and 11, which can lead to benign lesions such as anogenital warts or recurrent respiratory papillomatosis.

Papillomavirus infection prevention strategy

In the 2019 vaccination calendar, vaccination against papillomavirus infections is recommended in France in young girls aged 11 to 14 years, with catch-up in young girls aged 15 to 19 years. GARDASIL 9® (9HPV) vaccination is also recommended in men who have sex with men (MSM) up to the age of 26 and in immunocompromised adolescents of both sexes, at the same ages as for the general population, with catch-up until the age of 19.

Vaccination coverage that fails to meet the objectives of the 2014-2019 Cancer Plan

Vaccination coverage is far below the 60% target set for 2019 as part of the 2014-2019 cancer plan:

- In young girls: the vaccination coverage rate in 2018 was 29% for one dose and 24% for the full regimen. This rate has dropped since 2007, although it has been very gradually increasing since 2015.
- Among MSM: recent surveys estimate vaccination coverage at between 15 and 18% among those of vaccination age.

This coverage rate does not allow optimal protection of the French population against diseases induced by papillomaviruses and in particular cervical cancer.

Papillomavirus vaccines

In France, the first adjuvanted papillomavirus vaccine containing 4 genotypes, GARDASIL® (qHPV), available from 2007, has been gradually replaced since 2018 by the adjuvanted vaccine containing 9 genotypes, GARDASIL 9® (9HPV). Another bivalent vaccine containing 2 genotypes, adjuvanted CERVARIX (bHPV) has been available since 2008.

To date, all three vaccines are recommended in France for the vaccination of young girls. Any new vaccination must, however, be initiated with the GARDASIL 9® vaccine (9HPV). Only GARDASIL® and GARDASIL 9® vaccines are recommended for men who have sex with men and for immunocompromised children or adolescents of both sexes. Failing any studies using a mixed regimen with GARDASIL 9®, vaccination regimens should be continued with the same vaccine.

Table 1. Characteristics of the various HPV vaccines available in France

	Quadrivalent (qHPV) Gardasil®	Bivalent (bHPV) Cervarix®	Nonavalent (9HPV) Gardasil® 9
Manufacturer	MSD vaccines	GSK	MSD vaccines
Type of vaccine	protein L1 VLP	protein L1 VLP	protein L1 VLP
Eukaryotic vector for VLP production	<i>Saccharomyces cerevisiae</i> yeast cells	<i>Trichoplusia ni</i> Hi-5 insect cells	<i>Saccharomyces cerevisiae</i> yeast cells
Members	HPV 6: 20 µg HPV 11: 40 µg HPV 16: 40 µg HPV 18: 20 µg	HPV 16: 20 µg HPV 18: 20 µg	HPV 6: 30 µg HPV 11: 40 µg HPV 16: 60 µg HPV 18: 40 µg HPV 31: 20 µg HPV 33: 20 µg HPV 45: 20 µg HPV 52: 20 µg HPV 58: 20 µg
Adjuvant	Aluminium hydrophosphate sulphate: 225 µg	ASO4 (aluminium hydroxide: 500 µg + purified lipid derivative A of <i>Salmonella minnesota</i>: 50 µg)	Aluminium hydrophosphate sulphate: 500 µg
Date of 1st European MA	20/09/2006	20/09/2007	10/06/2015
Indications (MA)	Prevention of: - precancerous genital lesions (of the cervix, vulva and vagina), precancerous anal lesions, cancer of the cervix and anal cancer due to certain oncogenic types of HPV; - genital warts (condyloma acuminata) caused by specific HPV types	Prevention of precancerous anogenital lesions (of the cervix, vulva, vagina and anus) and cancers of the cervix and anus caused by certain oncogenic types of HPV	Prevention of: - precancerous genital lesions (of the cervix, vulva and vagina), precancerous anal lesions, cancer of the cervix, vulva, vagina and anus caused by certain oncogenic types of HPV; - genital warts (condyloma acuminata) caused by specific HPV types
Reimbursement	Yes, 65%	Yes, 65%	Yes, 65%
Public Price Including VAT	€ 105.12	€ 94.77	€ 131.58

The recommended vaccination regimen is, for vaccinations initiated:

- between 11 and 13 years of age for qHPV or 9HPV (or 14 for bHPV): 2 doses 6 months apart (M0, M6);

- between 14 and 19 years of age for qHPV or 9HPV (or 15 for bHPV): 3 doses administered according to a 0, 2 and 6-month regimen (M0, M2, M6);
- for MSM up to the age of 26: 3 doses according to a 0, 2 and 6 month regimen (M0, M2, M6) for qHPV or 9HPV.

EPIDEMIOLOGY OF PAPILLOMAVIRUS INFECTIONS

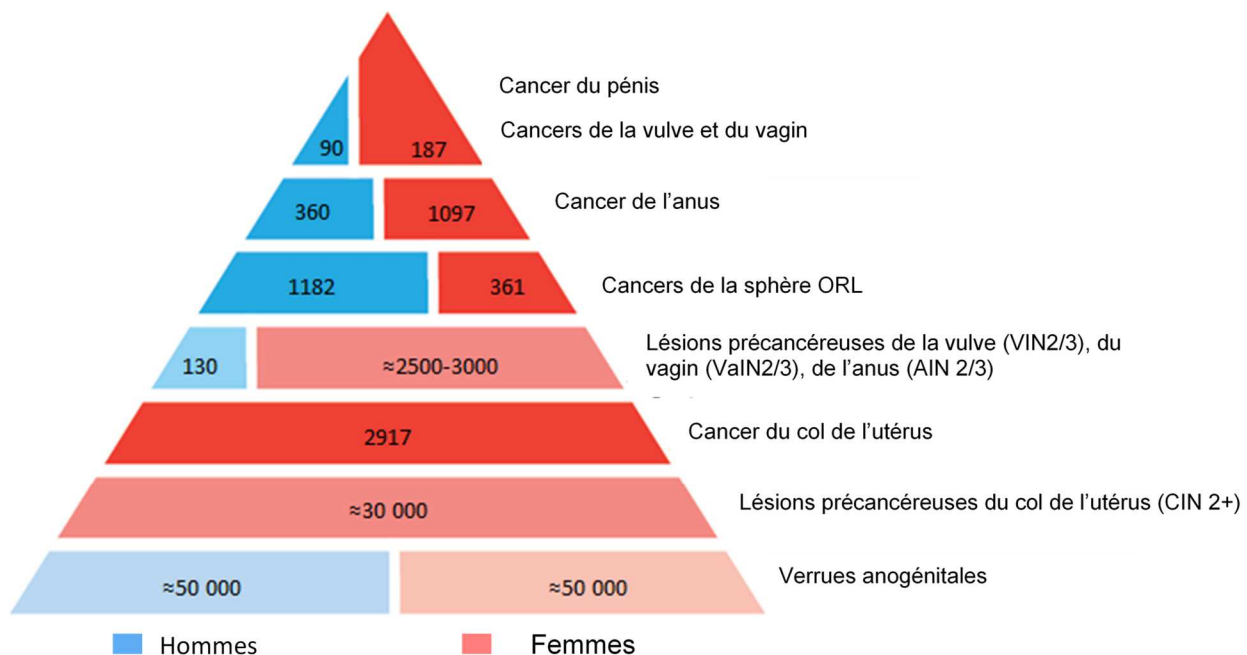
Each year in France, more than 6000 new cases of cancer are caused by papillomaviruses.

One quarter of all HPV-induced cancers occur in males (around 1753 new cases), the most frequent of which are cancers of the ENT sphere (around 1182 new cases), mainly represented by cancers of the oropharynx (around 1059 new cases), followed by anal cancer (around 360 new cases) and penile cancer (around 90 new cases). In males, the incidence rates of anal cancer are higher among MSM, especially those who are HIV-positive, who are at 100 times higher risk than men in the general population.

However, the burden of HPV-induced diseases remains primarily borne by women, with approximately 4,580 new cases of cancer per year (cervix, vulva, vagina, anus and ENT sphere).

HPV viruses are also the causative agents of anogenital warts that are very common both in women and in men (around 100,000 individuals impacted each year) and that can negatively affect their quality of life, especially their sex life, and promote social exclusion. These warts are benign, but recurrent and their treatment is particularly painful. HPV viruses also cause recurrent respiratory papillomatosis, a rare disease that can cause dysphonia and respiratory problems, especially in children.

Graphical representation of the burden of papillomavirus-induced disease in France in men and women * (according to Shield et al., 2018, Hartwig et al., 2015)



* La représentation graphique ci-dessus n'est pas à l'échelle

Approximately 90% of cases of HPV-induced disease are linked to types of HPV targeted by the GAR-DASIL 9® vaccine.

More limited clinical development in men

Efficacy on precancerous lesions and proven safety in men

Efficacy on precancerous lesions demonstrated in boys for certain types of cancer

- The 3 vaccines induce a similar immune response in girls and boys;
- Given the slow progression of HPV infection-related cervical and anogenital cancers, there is still no evidence of clinical efficacy on cancers, but only on high-grade precancerous lesions, which are the precursors of cancer.
- In men, the GARDASIL® vaccine (qHPV) has demonstrated its clinical efficacy in preventing anogenital warts caused by vaccine genotypes (89.9% [67.3%; 98.0%]).
- In the MSM subgroup, its clinical efficacy with regard to precancerous lesions of the anus due to vaccine genotypes is 77.5% [39.6% -93.3%] in subjects not previously infected HPV viruses and 50.3% [25.7% -67.2%] in subjects infected or not before vaccination and/or who did not receive all three doses. These analyses confirm that vaccine effectiveness is at its maximum before the onset of sexual activity.
- To date, the efficacy in the prevention of other cancers (penile cancers or cancers of the ENT sphere) has not been demonstrated, but initial data (vaccine efficacy observed against carriage in the ENT sphere, impact of vaccination observed on the prevalence of HPV viruses in oral samples), though they do not constitute evidence, are in favour of potential vaccine efficacy in the prevention of HPV-related infections of the ENT sphere.

A similar safety profile in boys

- The vaccine safety profile in men is similar to that seen in women.
- Numerous studies now support the absence of a link between vaccination and the onset of autoimmune diseases. Other events reported after vaccination (CRPS, POTS)¹, or the increased risk of Guillain-Barré syndrome observed in one French epidemiological study, have not been confirmed by other international studies.

Effectiveness of papillomavirus vaccination in boys

While no medico-economic model could not be developed for France as part of this work, few models with coverage rates comparable to that of France are available.

The main lessons learnt from the international medico-economic literature are that the gender-neutral vaccination strategy does not appear to be cost-effective in countries with high vaccination coverage, but that the low vaccination coverage rate for girls, as observed in France, promotes the cost-effectiveness ratio of vaccination of girls and boys. This essentially depends on the cost of the vaccine, the duration of protection and the number of HPV-related diseases considered.

In the French context however, increasing vaccination coverage among girls remains the most cost-effective strategy.

Vaccination of boys seen as a lever by professionals

In acceptability surveys, HPV vaccination in boys is viewed very favourably by healthcare professionals (84% of general practitioners in the HAS/InCa survey). Thus, in this same survey, 68% considered it as the main lever for increasing vaccination coverage.

Vaccination against HPV in boys is also viewed rather favourably by parents, adolescents and young adults. Thus, according to the French HAS/InCa survey, 38% of parents with at least one boy aged 11 to 14

¹CRPS: Complex Regional Pain Syndrome; POTS Postural Orthostatic Tachycardia Syndrome

in their household would intend to have them vaccinated if vaccination against HPV infections was recommended in France for boys, 42% would be hesitant and 20% would refuse. A greater majority of parents (72%) would intend to have their son(s) vaccinated once they have already agreed to have their sister(s) vaccinated.

Vaccination intentions are, however, marked by a high proportion of undecided parents (42% in the HAS/InCa survey). This vaccination hesitation appears associated with the lack of information concerning HPV viruses, but also with the fear of adverse effects perceived as associated with this vaccination. The currently identified main obstacles to HPV vaccination are the lack of proposal by a doctor and doubts concerning the safety of the vaccine.

Significant ethical issues

The current policy targeting young girls may appear to be discriminatory since it does not offer the same rights of access to vaccination to young boys and young men, while they participate equally in the transmission of infection through the population. and that they are also affected by HPV infections and their consequences. Moreover, the vaccination policy targeting people at risk of infection such as MSM, also raises questions of stigma linked to sexual orientation, invasion of privacy and difficulties of implementation that do not guarantee not equal access to the vaccine at an age when sexual orientation may not be known or stated.

From an ethical standpoint, vaccination of boys is an element that contributes to reducing the inequalities between men and women in terms of health prevention, by enabling young boys to participate in the overall decrease in HPV transmission. Furthermore, MSM cannot benefit from group immunity resulting from the vaccination of young girls alone and are to date insufficiently vaccinated.

Now a significant decline in women confirming the impact of vaccination on the incidence of precancerous lesions abroad

In countries that have introduced vaccination with high coverage rates, a significant reduction in genital HPV infections, genital warts and precancerous lesions due to vaccine serotypes is seen in vaccinated girls. A recent meta-analysis of girls' vaccination programmes abroad has shown an 83% [75% -89%] reduction in genital warts in girls aged 15 to 19. The same analysis reported a 51% reduction [42% -58%] in precancerous lesions of the cervix in girls aged 15 to 19 years and a 31% reduction [16% -43%] in women aged 20-24.

In these countries, vaccination of girls has also benefited boys. A reduction in the prevalence of genital HPV-related infections and of genital warts has also been observed in boys, thanks simply to the vaccination of girls. In Australia, for example, a 78% [53% -90%] reduction in the prevalence of HPV type 6, 11, 16 and 18 infections has been reported in men who are too old to be vaccinated, after girls have been vaccinated. Vaccination of girls has resulted in a 48% [25% -63%] reduction in genital warts in boys aged 15 to 19, with reductions also being reported in older boys and men. The protection conferred by group immunity is greater in countries where vaccination coverage is higher.

In France, there is insufficient perspective to estimate the impact of vaccination on precancerous lesions and it is uncertain whether such an impact can be detected given the low vaccination coverage. Moreover, no data are available to assess the impact of vaccination on genital warts.

Evolving guidelines

To date, some fifteen European countries have included the vaccination of boys in their vaccination schedule. Several countries have developed school vaccination programmes, enabling them to achieve much higher vaccine coverage than in France. Moreover, in the United States, where universal vaccination was implemented in 2011, the extension of vaccination to boys did not have a significant impact on the vaccination coverage of girls and the vaccination coverage of boys has remained to date lower than that of girls.

Furthermore, WHO recognizes, from a public health point of view, the excellent safety profile of the 3 vaccines that offer comparable immunogenicity, along with potential and true efficacy in the prevention of cervical cancer, mainly caused by HPV types 16 and 18. WHO is, however, very concerned that the current shortage of HPV vaccines may lead to the failure to introduce or maintain HPV vaccination programmes in some countries, particularly in countries where the burden of cervical cancer is high.

CHANGING THE CURRENT PAPILLOMAVIRUS VACCINE STRATEGY

HAS is in favour of expanding vaccination against papillomaviruses to boys in the French vaccination calendar

HAS thus recommends:

- **1) Expanding HPV vaccination with GARDASIL 9® (9HPV) to all boys aged 11 to 14 years old according to a 2-dose schedule (M0, M6).**
- **2) Possible catch-up for all adolescents and young adults from 15 to 19 years old according to a 3-dose scheme (M0, M2, M6).**
- **3) Maintaining a specific vaccine recommendation with Gardasil 9 for men who have sex with men up to the age of 26 according to a 3-dose schedule (M0, M2, M6).**

Only the GARDASIL 9® vaccine (9HPV) is recommended to start any new vaccination in men as it confers protection both against HPV 16 and against genotypes 6 and 11 responsible, in men, for as many genital warts as in women on the one hand, and, on the other hand, that it will eventually definitively replace GARDASIL® (qHPV) whose marketing discontinuation is near.

Moreover, the CERVARIX vaccine (bHPV) is not recommended in men, given the vaccine's lower genotype coverage (lack of protection against genotypes 11 and 6) and the lack of data concerning its efficacy on precancerous lesions in humans (immunogenicity data only).

HAS advocates more systematic vaccination of all adolescents to curb transmission of HPV

This broadening, beyond the protection conferred on vaccinated boys, would also better protect unvaccinated girls and women, and better protect boys and men regardless of their sexual orientation, by reaching future MSM more easily and avoiding any stigma, at an age when their sexual preference is either not known (by the individual and his entourage), or unasserted.

HAS considers that the mere extension of vaccination to boys will not make it possible to achieve the objective of protecting the population (expected vaccination coverage for boys at best similar to that for girls) and that increasing the vaccination coverage for girls (most cost-effective strategy) should therefore remain the priority.

HAS thus calls for a more committed vaccination policy and recommends:

- **A more systematic vaccine proposal by health professionals** through the implementation of true vaccination programmes, like organised screening programs, and a sexual health consultation with each adolescent including vaccination against HPV.
- The implementation of **actions aimed at restoring confidence in this vaccination among the public and healthcare professionals** through the dissemination of public information campaigns, including among healthcare professionals, aimed at providing parents, adolescents and vulnerable groups with the best possible information on the expected benefits and safety of vaccination, relieving fears about the side effects of vaccination and reducing vaccine hesitation.
- **Easier access to vaccination, along with full vaccination coverage to offset the socio-economic inequalities noted.** For this purpose, vaccination must be offered in multiple places, in particular in places frequented by the most disadvantaged populations and under conditions allowing no advance payment. Vaccination experiences in schools are also likely to increase adolescent vaccination coverage and reduce socio-economic inequalities.
- Specific measures to strengthen the vaccination coverage of MSM, to allow better information for MSM and to provide easier access to vaccination.

