Received: 10 April 2016 | Revised: 17 October 2016 | Accepted: 1 December 2016

DOI: 10.1002/ijgo.12075

REVIEW ARTICLE

Gynecology

WILEY

International Journal of Gynecology & Obstetrics

Overview of the benefits and potential issues of the nonavalent HPV vaccine

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Abstract

HPV-related diseases affect anogenital and oropharyngeal regions, heavily affecting the psychosexual dimension of both male and female individuals. HPV vaccination programs based on a bivalent or quadrivalent vaccine have opened broad perspectives for primary prevention. A nonavalent HPV vaccine (9vHPV), covering nine genotypes (HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, and HPV58), might provide further improvement in terms of direct protection. In the present report, efficacy and safety data from 9vHPV vaccine development programs are examined. Efficacy data come from a pivotal trial, which was conducted among women aged 16–26 years randomly assigned to receive either the 9vHPV or the quadrivalent HPV (4vHPV) vaccine. The 9vHPV vaccine was shown to have potential benefits as compared with 4vHPV, increasing the overall estimated rate of prevention to 90% for cervical cancer and up to 80% for precancerous cervical lesions. For all other HPV-related pre-invasive and invasive lesions, 9vHPV showed potentially greater disease reduction, depending on the anatomic region examined. Thus, the 9vHPV vaccine shows clinical potential for the prevention of HPV-related diseases in both sexes. Future adoption of 9vHPV will depend on factors including market price, cost-effectiveness data, use of a two-dose schedule, and safety and efficacy monitoring in real-life programs.

KEYWORDS

Cervical cancer; HPV; HPV nonavalent vaccine; Prevention

1 | INTRODUCTION

Approximately 5% of all human cancers are caused by HPV infection, resulting in more than 600 000 new cases per year worldwide.[1] The cervix, penis, vulva, vagina, anus, and oropharynx are among the tissues for which the International Agency for Research on Cancer has acknowledged a direct causal correlation between HPV and disease, although the strength of the correlation does vary.[2] Therefore, HPV is considered the most important oncogenic virus affecting humans and the primary cause of uterine cervical cancer.[2]

Among the high-risk genotypes for neoplastic transformation, HPV16 and HPV18 show the most biologically aggressive behavior and are the main contributors to HPV-related carcinogenesis.[3] However, other high-risk genotypes are also involved in cancer transformation, with their contribution varying with anatomic region. In the uterine cervix, the contribution of non-HPV16/HPV18 genotypes to HPV-related tumor genesis is approximately 30% (Fig. 1), whereas in the anal, vulvovaginal, penile, and oropharyngeal areas, their contribution is less relevant.[4] Two available vaccines, one of which is bivalent against HPV16 and HPV18 (2vHPV) and the other quadrivalent

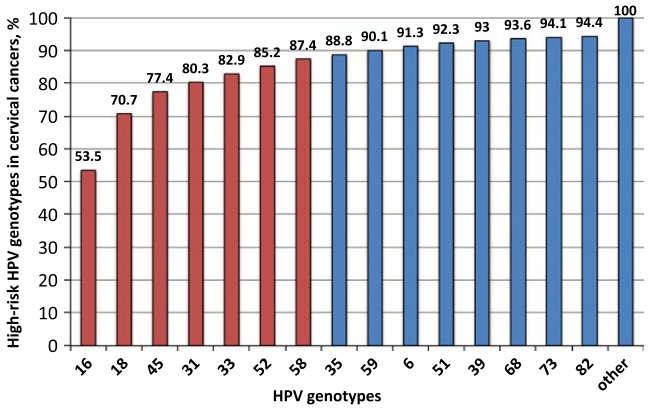

FIGURE 1 Proportion of HPV-related cervical cancers (squamous and glandular lesions) attributed to different HPV genotypes. The seven more prevalent high-risk HPV genotypes (red bars) are included in the 9vHPV vaccine;[3] the other two genotypes included in the vaccine are low risk (HPV6 and HPV11). Figure created using data from IARC monographs on the evaluation of carcinogenic risks to humans, volume 90L Human Papillomaviruses.[2] Abbreviation: 9vHPV, nonavalent HPV vaccine.

against HPV6, HPV11, HPV16, and HPV18 (4vHPV), have shown high efficacy against some clinical endpoints: more than 90% prevention of high-grade intraepithelial lesions in the female genital area (cervix, vagina, and vulva), and for 4vHPV only, more than 90% prevention of high-grade anal lesions in a post hoc case-assignment analysis and close to 100% prevention of genital warts.[5,6]

Although indirect immune cross-reactivity has been detected—including protection against HPV31 with 4vHPV[7] and against HPV31, HPV33, and HPV45 with 2vHPV[8]—the strength and duration of these evoked antibody responses are lower than those of the targeted vaccine genotypes, thereby challenging the clinical efficacy. Indeed, recent real-life data gathered in England on the 2vHPV vaccine found evidence of a reduction in the prevalence of HPV31 only, and no relevant clinical impact on HPV33 and HPV45.[9] Therefore, a direct multivalent approach, arising from the inclusion of single viral genotypes, has become an advanced objective to broaden perspectives in the primary prevention of HPV infection. This is the rationale behind Merck's nonavalent vaccine (9vHPV), which includes five high-risk genotypes (HPV31, HPV33, HPV45, HPV52, and HPV58), in addition to those in the quadrivalent vaccine (HPV6, HPV11, HPV16, and HPV18).

In December 2014, 9vHPV was approved by the US Food and Drug Administration and recommended by the Advisory Committee on Immunization Practices (ACIP).[10] On March 27, 2015, 9vHPV also received a positive review from the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP), and on June 10, 2015, the European Commission approved it. Furthermore, the CHMP also gave a positive response to the two-dose schedule. The aim of the present review was to examine, with a focus on Italian data, the potential clinical benefits and critical issues of the nonavalent vaccine on the basis of currently available information.

2 | BACKGROUND CONSIDERATIONS ON HPV-RELATED DISEASES

The estimated global prevalence of cervical HPV infection among cytologically normal women is approximately 10% (range 8%–22%), with significant regional differences and increased rates in the Sub-Saharan area and Eastern European countries.[11] In Italy, the prevalence of positive high-risk HPV in the general population is 9.2%.[12]

The direct correlation between HPV prevalence and women's age is well described, with rates being highest in younger women and then gradually decreasing. Both global and Italian data indicate that the prevalence of HPV DNA increases with the grade of cervical abnormality, from mild to severe dysplasia to invasive carcinoma. In high-grade cervical intraepithelial neoplasia (CIN2+), HPV16 is by far the most prevalent genotype (>60%), followed by HPV18 (10%–15%), HPV31 (15%), and HPV33 (12%). With regard to invasive cervical carcinoma, global data show that HPV16 and HPV18 account for up to 70% of cases, followed by HPV45, HPV31, and HPV33 (Fig. 1).[2] Italian data are consistent with these values.[13–15]

In men, the prevalence and natural history of HPV seems to be different, varying greatly by tissue or organ (shaft, glans, scrotum, and urethra) and method of sample collection. Nevertheless, HPV prevalence is higher in men than in women, and is constant over time among different age groups, thereby representing a "reservoir" of infection.[16] Moreover, in selected male groups (e.g. men who have sex with men, especially those with HIV infection), HPV prevalence can be extremely high (>70%) and is frequently associated with anal carcinoma.[17]

The prevalence of oral HPV infection varies with study and method of collection. In healthy populations in low-income countries, the oral HPV prevalence varies between 4.5% and 6.9%, with threefold higher rates in men and in smokers than in women and in non-smokers, respectively.[18]

Epidemiologic evaluations are more difficult for HPV-related extracervical cancers, in most of which only HPV16 and HPV18 are present; however, a steady increase in anal and oropharyngeal neoplasms has been reported in low-income countries.[19] The interaction between oropharyngeal HPV infection and other carcinogenetic agents (e.g. smoke and alcohol), along with a lack of clear precancerous lesions, makes it difficult to properly analyze the contribution of HPV. Nevertheless, it should be noted that, at present, there is no approved screening for non-cervical HPV-related cancers, thus supporting the importance of vaccination.

The prevalence of HPV-related cancers in Italy has been recently updated:[20] new cases of cervical cancer have been estimated at 2600 per year, cervical precancerous lesions at 29 603–55 625 per year, vulvovaginal cancer cases at approximately 390 per year, and anal cancer cases at 366 in men and 526 in women.

Genital warts deserve a specific mention, because they represent the most widespread sexually transmitted infection worldwide, with a peak incidence in young individuals aged 15–24 years. In more than 90% of cases, they are related to HPV6 and HPV11 infection. In Italy, epidemiologic data on genital warts have been gathered from the sentinel

surveillance system for sexually transmitted infections, coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità), and which have been further confirmed by a gynecologic network study,[21] showing a high incidence of genital warts among individuals younger than 25 years, with an increasing trend in both sexes since 2004.

The relationship between HPV and human reproduction is currently the focus of scientific research. One of the first retrospective studies of the potential association between HPV and infertility was conducted by a North American group,[22] who correlated cervical HPV infection with reproductive outcomes of in vitro fertilization techniques among infertile patients. The study showed a sharp decrease in pregnancy among HPV-positive women relative to HPV-negative women (pregnancy rate 23.5% vs 57%, respectively). Similarly, a prospective study by Perino and colleagues[23,24] among infertile couples undergoing assisted reproductive technology found a higher incidence of spontaneous abortion among women with partners whose seminal fluid tested positive for HPV DNA than among women with HPV-negative partners (66.7% vs 15%, respectively).

A debated point concerns the association between HPV infection and male infertility. One study has reported a relationship between viral infection and reduced motility of spermatozoa, supporting a role for the virus as a cause of idiopathic asthenozoospermia.[25] Another study by Golob et al.[26] among 340 male members in couples experiencing infertility in Slovenia did not find that HPV infection influenced the quality of semen. This result was consistent with that of Schillaci et al.,[27] who in turn demonstrated that the virus interacted with the equatorial region of the spermatozoon head.

Therefore, while a scientific consensus on if and/or how to perform HPV screening among men and women eligible to undergo in vitro fertilization techniques is awaited, an extension of vaccination practices to the male population would be welcome.

3 | CURRENT STATUS OF HPV VACCINATION

Since 2007, HPV vaccination programs have been organized nationwide in almost all high-resource countries.[28] In low- and middle-income countries, many pilot studies are being conducted under the guidance and support of the Global Alliance for Vaccines and Immunization (GAVI). Conversely, in countries representing the poorest regions of the world and subject to the highest risk of HPV infection, preventive programs are almost absent. In fact, in the poorest regions, cervical cancer has the highest incidence and mortality rate among HPV-related cancers, whereas other forms (anal and oropharyngeal) are mainly increasing in high-income countries. Therefore, the objectives of HPV vaccination should be continually updated and redesigned consistent with the geographic area, reframing the aim of HPV vaccination in high-resource countries from control of cervical cancer to control of all HPV-related diseases.

Italian National Institute of Health data published in April 2015[29] indicate that vaccination coverage reached approximately 71% in over 7 years since the beginning of the organized program, although there are some local differences. Although these data are a long way from the original target of 95%, they are compliant with subsequent changes included in the 2012–2014 National Prevention Plan and following agreements.[30] Forthcoming logistic efforts must focus on gradually increasing coverage and compliance to reach 95% of the target population with the cohort born in 2003.

Real-life HPV vaccination programs have shown relevant clinical benefits in reducing the prevalence of genital warts,[31] HPV infections,[32,33] positive cervical smear results,[34] and high-grade CIN.[34–36] However, some methodologic aspects of HPV vaccination, such as the magnitude and duration of cross-protection vaccine efficacy, are still debated. Even though the preregistration studies of the two current vaccines (2vHPV and 4vHPV)[37,38] were not designed with the aim of investigating cross-protection efficacy, a certain amount of cross-protection was proven. Given methodologic differences between the trials (e.g. inclusion criteria, baseline prevalence of HPV, demographics, and antibody determination method), it is difficult to compare the data in terms of cross-protection. Additionally, such cross-reactivity has been shown to have a lower intensity and shorter duration as compared with the direct evocation of vaccine genotypes.[7,39] As a result, the "direct protection" provided by adding new genotypes to the vaccine will probably overtake the debate on cross-protection.

Although the number of HPV-related cancers in men is approximately half that in women, the reduction in vaccine price has made male vaccination economically possible in some countries. Gender-neutral vaccination (ongoing in Australia, the USA, Canada, Austria, Switzerland, and eight Italian regions) prevents male HPV-related diseases[5] and improves public health interventions, lowers the rate of transmission, and confirms the principle of equal access to prevention.[39,40] As decided by the Ministry of Health, universal HPV vaccination of all individuals aged 12 years will be undertaken in Italy from 2017.

4 | STUDY DESIGNS AND AVAILABLE RESULTS FOR 9vHPV

The 9vHPV is an evolution of the 4vHPV. To facilitate the inclusion of five more virus-like particles (VLPs) from high-risk genotypes (HPV31, HPV33, HPV45, HPV52, and HPV58), some adjustments were made to the original formulation (Table 1): the amount of VLPs of the four initial genotypes was increased, and the quantity of adjuvant was doubled.

The clinical development program of 9vHPV has been organized into many studies (Table S1), some of which have been published.[41–44] The main objectives of such trials were: first, to investigate whether 9vHPV has a level of immunogenicity similar to that of the 4vHPV vaccine against infections caused by HPV6, HPV11, HPV16, and HPV18 (on the basis of the principle of non-inferiority of immune response); second, to prove clinical efficacy toward infections or diseases caused by the added genotypes (HPV31, HPV33, HPV45, HPV52, and HPV58); third, to demonstrate non-inferior immunogenicity among teenagers as compared with young women, a population in which clinical protection has already been proven (immunobridging); and last, to establish whether the safety and tolerability profile is acceptable.

TABLE 1 Composition of HPV vaccines.[a]

Vaccine	Adjuvant	HPV genotype, µg								
		6	11	16	18	31	33	45	52	58
2vHPV	50 µg AS04	–	–	20	20	–	–	–	–	–
4vHPV	225 µg AAHS	20	40	40	20	–	–	–	–	–
9vHPV	500 µg AAHS	30	40	60	40	20	20	20	20	20

Abbreviations: 2vHPV, bivalent HPV vaccine; AS04, 3-O-desacyl-4′-monophosphoryl lipid A; 4vHPV, quadrivalent HPV vaccine; AAHS, amorphous aluminum hydroxyphosphate sulfate; 9vHPV, nonavalent HPV vaccine.
[a]Data obtained from http://www.ema.europa.eu/ema/ (accessed November 26, 2016).

The pivotal study on 9vHPV (Study 001[41]) was a randomized, multicenter, double-blind, phase 2–3 study that began in 2009 in 19 countries on four continents. The trial enrolled more than 14 000 women aged 16–26 years, who were randomly assigned to receive 9vHPV or 4vHPV vaccine. A direct clinical comparison of the new vaccine with placebo was not possible because of both ethical reasons and the need to enroll more than 45 000 women with more than 30 months of follow-up. The reported efficacy results refer to the per-protocol population, defined as women who were seronegative, PCR-negative, and cytologically normal at baseline, and who completed three doses within 1 year with no protocol violations. Additionally, data from the modified intention-to-treat (ITT) group, including women who received at least one vaccine dose and at least one evaluation of efficacy, were analyzed.

In study 001,[41] non-inferiority of the 9vHPV immune response was demonstrated for the four genotypes in common with the 4vHPV vaccine. Seroconversion close to 100% (for new and previous vaccine genotypes) was documented for all women enrolled (Table 2). In the per-protocol population, clinical protection was demonstrated against the new genotypes (HPV31, HPV33, HPV45, HPV52, and HPV58) as follows: 96.7% for CIN of grade 2 or worse (CIN2+), vaginal intraepithelial neoplasia of grade 2 or worse (VaIN2+), and vulval intraepithelial neoplasia of grade 2 or worse (VIN2+); and 96% for persistent infection over 6 months (Table 3). Protection in the ITT group was similar between 4vHPV and 9vHPV, resulting in an overall nonsignificant reduction of cervical, vulvar, and vaginal high-grade disease for the 9vHPV vaccine. There was an increase in the rate of adverse events (swelling, erythema, and pruritus) at the site of 9vHPV injection as compared with 4vHPV (90.7% vs 84.9%). Similar data on systemic events were reported.

Among the other published protocols, study 002[42] was designed to evaluate immunogenicity and immunobridging in boys and girls aged 9–15 years as compared with young women aged 16–26 years for whom clinical efficacy data were available. Non-inferiority was demonstrated for all new genotypes, with a seroconversion rate of

TABLE 2 Immunogenicity of the nonavalent HPV vaccine.[a]

Assay (cLIA)	4vHPV vaccine		9vHPV vaccine	
	Seroconversion, %	GMT, mMU/mL	Seroconversion, %	GMT, mMU/mL
Anti-HPV6	99.8	875	99.8	893
Anti-HPV11	99.9	830	100	666
Anti-HPV16	100	3156	100	3131
Anti-HPV18	99.7	679	99.8	805

Abbreviations: cLIA, competitive Luminex; GMT, geometric mean titer; mMU, milli-Merck units.
[a]Data obtained from Joura et al.[41]

TABLE 3 Clinical endpoints of 9vHPV versus 4vHPV, by endpoint-related HPV genotypes.[a]

Endpoint	4vHPV vaccine	9vHPV vaccine	
	Cases/participants	Cases/participants	Vaccine efficacy, %
HPV31, HPV33, HPV45, HPV52, HPV58			
CIN2+, VIN2+, VaIN2+	30/6017	1/6016	96.7
CIN2+	27/5943	1/5948	96.3
HPV6, HPV11, HPV16, HPV18			
CIN2+	1/5832	1/5823	–
Anogenital warts	1/5893	5/5876	–

Abbreviations: 9vHPV, nonavalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; CIN2, cervical intraepithelial neoplasia grade 2; VIN2+, vulval intraepithelial neoplasia grade 2 or worse; VaIN2+, vaginal intraepithelial neoplasia grade 2 or worse.
[a]Data obtained from Petrosky et al.[10]

99% across individuals of both sexes. These data support the bridging of efficacy results from adult women to boys and girls aged 9–15 years. Among male individuals aged 16–26 years, the administration of 9vHPV was highly immunogenic, showing a seroconversion rate of more than 99.5%.[43]

Last, safety results are available for all female individuals aged 12–26 years who received a 9vHPV dose.[42] The new vaccine was generally well tolerated, although there was a higher incidence of local reactions (e.g. pain, fever, and itch) as compared with 4vHPV. Because 9vHPV has a higher content of proteins and adjuvant, these data are consistent with what would be expected.

5 | POTENTIAL BENEFITS OF 9vHPV

The extension of primary protection is related to the number of VLPs included in the vaccine formulation, in addition to the pathogenic role of each single genotype in specific organs and tissues. Taking into account the contribution of HPV genotypes, the female genital area—and the uterine cervix particularly—probably has the highest potential to benefit from 9vHPV protection. Conversely, genotypic HPV variability in other anatomic areas is lower, because HPV16 and to a lesser extent HPV18 account for almost all oncologic contribution to disease in these regions.

Given the contribution of the single genotypes,[45] the new nonavalent vaccine formulation substantially expands, by 75% or more,[20] the potential to prevent high-grade pre-neoplastic genital lesions as compared with 4vHPV. Specifically, the estimated prevention of HPV-related disease is extended by 9vHPV from 45.5% to 82.3% for CIN2+ lesions, from 82.2% to 94.4% for VIN2+, from 64.1% to 77.7% for VaIN2+, and from 75.4% to 81.5% for anal intraepithelial neoplasia grade 2 or worse (AIN2+) in both sexes (Figs 2 and 3).

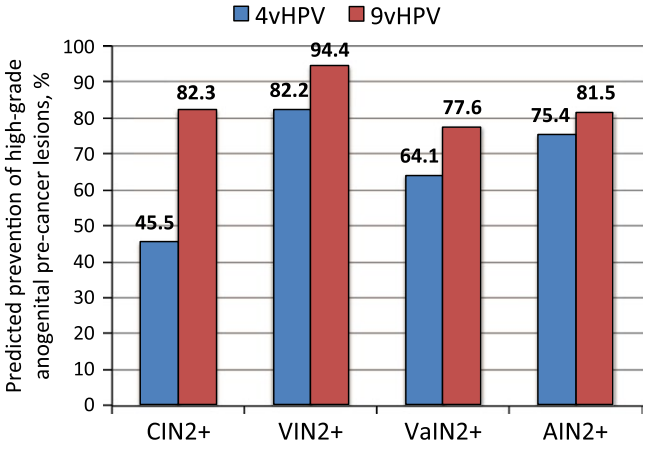

FIGURE 2 Proportion of HPV-related anogenital pre-cancer lesions attributed to viral genotypes included in 4vHPV and 9vHPV. Abbreviations: 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; VIN2+, vulval intraepithelial neoplasia grade 2 or higher; VaIN2+, vaginal intraepithelial neoplasia grade 2 or higher; AIN2+, anal intraepithelial neoplasia grade 2 or higher. Figure created using data from Hartwig et al.[20]

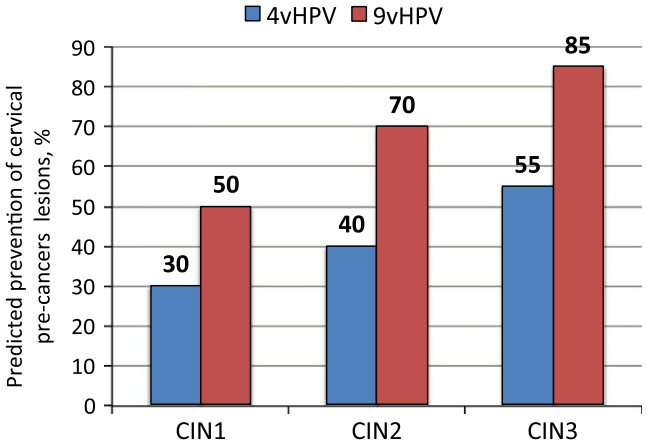

FIGURE 3 Proportion of HPV-related cervical pre-cancer lesions attributed to viral genotypes included in 4vHPV and 9vHPV as reported in literature.[20,45,46] Abbreviations: 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; CIN, cervical intraepithelial neoplasia.

Regarding HPV-related cancers (Fig. 4), the expected prevention achieved by 9vHPV as compared with 4vHPV ranges from +2% to +20%, depending on the affected organ.[20,46] On the basis of contributions of the vaccine genotypes, it has been calculated that 9vHPV has the power to prevent more than 490 000 cases of HPV-related cancer affecting the female genital area,[47] which would account for 87.4% of all cases. Similar to pre-neoplastic lesions, the highest potential benefit of 9vHPV is observed for cervical cancer, in which the estimated additional prevention over the quadrivalent vaccine ranges from +14.7%[46] to +20%.[20] Another marked observation is the improved prevention of anal cancer: the overall expected prevention achieved by 9vHPV equals 90%.[45]

The potential benefits of 9vHPV for other HPV-related neoplasms—theoretically including oropharyngeal cancers, although no

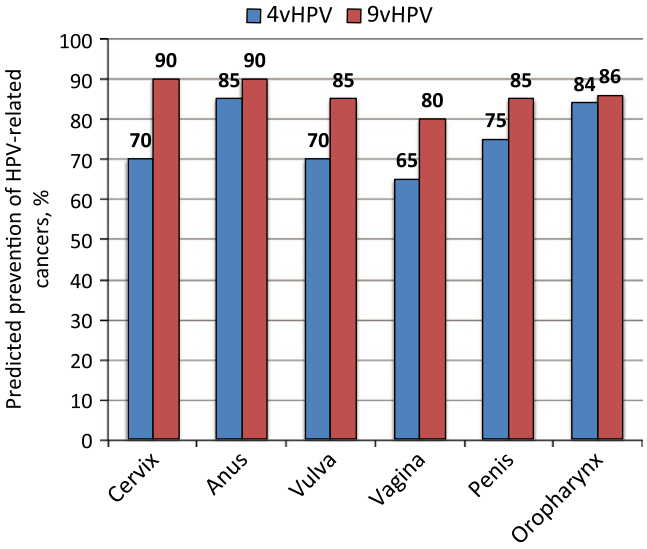

FIGURE 4 Proportion of all HPV-related cancers attributed to viral genotypes included in 4vHPV and 9vHPV as reported in the literature.[20,46,47] Abbreviations: 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine.

vaccine has been approved as yet—are lower. In fact, vaccine efficacy remains clinically unproven in the oropharyngeal tract, although a reduced prevalence of vaccine genotypes after administration of 2vHPV has been reported in a Costa Rican trial.[48] However, it seems reasonable that the biomolecular mechanisms underlying HPV vaccination will result in high clinical protection also in the head and neck area, as they do in the anogenital tract.

6 | CRITICAL ISSUES

Given the clinical background outlined above, 9vHPV raises some potential issues. The similar clinical efficacy observed between 9vHPV and 4vHPV in the ITT group requires a comment. Women with prevalent cervical disease or infection are not excluded from ITT groups, and might thereby contribute to the decreased efficacy of the vaccine. This was the case in study 001, in which many of the young participants (aged 16–26 years) were found to be already infected with the additional five HPV types in the new vaccine at baseline. Although the efficacy of a prophylactic vaccine must be evaluated among women who have not been exposed to HPV (per protocol), in the context of organized real-life vaccination a non-negligible number of individuals could already be infected with HPV.

Additionally, a methodologic issue arises from the lack of a placebo group in study 001. However, this unusual hybrid approach, using a different method of evaluation for the original genotypes (immunogenic endpoint) and the added ones (clinical endpoint), was necessary for ethical reasons.

Other critical issues of 9vHPV vaccine include the cost and dose schedule, both important considerations in light of funding programs established by single regions of some countries where, as in Italy, organized vaccination programs are regionalized. A recent study in the USA[49] suggests that the switch from 4vHPV to 9vHPV within a universal gender-neutral program would remain cost-effective as long as the price increase for one dose does not exceed US$13.

Concerning the dose number, in February 2016, the European CHMP gave a preliminary positive opinion on the two-dose schedule (as opposed to the three-dose schedule) for girls younger than 15 years. This reduced dosage is an unavoidable prerequisite of a national vaccination program, owing to the health cost savings and to higher compliance by the target population.

The management of the switch from one generation of vaccines to another raises some matters of debate during the ongoing organized national programs. Individuals vaccinated with 2vHPV or 4vHPV might request either to have the 9vHPV vaccination or to complete an incomplete schedule with it. As stated recently by the ACIP, it will be important to have national or regional recommendations on what to do in the case of revaccination or an incomplete vaccination schedule to be able to transition to the 9vHPV vaccine.[10] From this perspective, it is important to clarify that the administration of 9vHPV to women already vaccinated with 4vHPV, as approved by the ACIP, has already demonstrated high safety and immunogenicity.[44]

7 | FUTURE PERSPECTIVES AND CLOSING REMARKS

The disease caused by HPV infection represents a major social health problem for male and female individuals in both low- and high-income countries. The clinical outcomes of benign, preneoplastic, and invasive HPV-related disease play an important part in health expenditure, requiring huge economic resources and heavily affecting the psychosexual dimension of the population.

Beyond the implementation and efficacy of organized screening programs, the possibility of primary prevention through vaccination has widened perspectives. Through the 2vHPV and 4vHPV vaccines, important clinical benefits have been achieved in the vaccinated population. The 9vHPV vaccine might represent a true turning point in terms of direct prevention of a higher number of HPV-related cancers. As compared with 4vHPV, the nonavalent vaccine has the potential to further reduce the prevalence of both pre-invasive and invasive anogenital lesions from 6% to 20%, depending on the anatomic region. Major benefits are expected against cervical cancer and, to a lesser level, against vulvovaginal and anal cancers.

The adoption and implementation of 9vHPV will depend on market price, cost-effectiveness data, and the use of a two-dose schedule among teenagers. Moreover, as in the case of 2vHPV and 4vHPV, safety and efficacy monitoring in real-life population programs will be needed for this vaccine. On the basis of the data reviewed herein and the analysis of pre-registration studies, 9vHPV has important clinical potential and might represent an innovation for the prevention of HPV-related diseases for both men and women.

ACKNOWLEDGMENTS

The review was supported by an unrestricted grant from Sanofi Pasteur SMD.

CONFLICT OF INTEREST

All authors have been involved in scientific meetings or congress with companies related to gynecologic prevention activities. LM has received speaker's fees and honoraria from Sanofi Pasteur, GlaxoSmithKline, and Roche. AP has received speaker's fees and honoraria from Sanofi Pasteur and GlaxoSmithKline.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Summary of studies and numerical dimension on the 9vHPV vaccine.