

Towards the elimination of cervical cancer: HPV epidemiology, real-world experiences and the potential impact of the 9-valent HPV vaccine

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Objectives: This review aims to describe the biology of human papillomavirus (HPV), the development of the related vaccine, real-life experiences from the perspective of the WHO's call on the elimination of cervical cancer, the vaccine's use as an adjuvant to treatments for HPV-related disease, and the international scientific societies' guidelines on HPV vaccination. A systematic review was conducted, also for the specific purpose of assessing the efficacy, immunogenicity and safety of the 9-valent HPV vaccine (the latest to become available). **Data sources and study selection methods:** PubMed was the primary source of data for this review, while additional information, such as scientific society guidelines, was found by directly searching the web. Publications were eligible if they had at least one result relating to the immunogenicity, safety and efficacy or effectiveness of HPV vaccines. **Tabulation, integration and results:** The search in the database for this systematic review yielded 266 records, none of which was a duplicate. A first screening procedure excluded 228 publications. Of the remaining 38 potentially eligible publications, 26 were ultimately included in the systematic review. **Conclusion:** While progress in vaccine development has added more tools to HPV vaccination programs, real-world studies have started to show the benefits of mass vaccination campaigns using bivalent and quadrivalent vaccines. National vaccination programs have also been a testing ground for gender-neutral vaccination—a strategy on which unanimous consensus may not still be lacking, but which undeniably responds to clinical and ethical needs. Much the same can be said of post-treatment vaccination—a relatively new, but promising practice that will certainly have a role in achieving the elimination of cervical cancer.

Keywords

Human papillomavirus; Cervical cancer; Genital warts; Vaccination; 9-valent

1. Epidemiology of HPV

Papillomaviruses are small, double-stranded DNA viruses with a selective tropism for squamous epithelia [1]. More than 200 types of papillomavirus have been completely identified to date, and approximately 150 of them can infect humans, i.e., they are human papillomaviruses (HPVs) [2]. Most types of HPV are predominantly trophic for either the

dry outer skin or the moist mucosal epithelial lining of openings in the body, but some of them can infect and reproduce in both milieu [3]. HPVs are the most common cause of viral infection of the reproductive tract [4], but these infections frequently carry no symptoms and disappear spontaneously. When the virus does produce signs and symptoms, they range from benign lesions and warts to precancerous conditions and cancers. These may occur at various anatomical sites, such as the skin, cervix, vagina, vulva, penis, anus, rectum, and oropharynx [5]. HPV is also responsible for a rare but highly morbid condition, recurrent respiratory papillomatosis [6].

The incidence of new HPV-related benign lesions and warts worldwide is unknown. In the last decade, however, various authors have agreed that the number of new HPV-related cancers can be estimated at between 630,000 and 720,000 a year [7–9]. Most HPV-related cancers occur in women. Cervical cancer alone accounts for 530,000–570,000 new cases a year, followed by cancers of the vulva (12,000–27,000), vagina (12,000–13,000), anus (18,000–22,500), and head and neck (7200–18,000) [7–9]. Worldwide, the incidence of new HPV-related malignancies in males is estimated to be between 50,000 and 100,000 a year, including 30,000–74,000 oropharyngeal cancers, 13,000–22,000 penile cancers, and 4,500–17,000 anal cancers [7–9]. Considering the narrower setting of Europe, Hartwig *et al.* [10] estimated that the total number of new HPV-related cancers in 31 countries in 2015 amounted to about 62,500 cases, with cervical cancer clearly the most frequent (approximately 35,000 cases, or 56% of the total). The Authors also estimated that the number of new cases of genital warts in the same year ranged between 379,330 and 510,492 in women, and between 376,608 and 427,720 in men, while the new cases of precancerous lesions could have numbered as many as 450,000 [10]. In Italy, it was estimated that approximately 2400 new cases of cervical cancer occurred in 2020 [11], down from the approximately 2700 cases estimated in 2019 [12]. The estimated burden of

Table 1. Classification of HPV types according to the International Agency for Research on Cancer.

Classification	HPV types
(1) Carcinogenic to humans	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59
(2B) Possibly carcinogenic to humans	30, 34, 69, 85, 97, 26, 53, 66, 67, 70, 73 and 82 5 and 8, only in people with epidermodysplasia verruciformis
(3) Not classifiable as to its carcinogenicity to humans	6 and 11

HPV-related cancers in 2019 also included about 300 cases of anal cancer, 1900 of oropharyngeal cancer, 500 of penile cancer, 200 of vaginal cancer, and 1200 of vulvar cancer [12].

Not all types of HPV have the same carcinogenic potential and there are fortunately just a few responsible for most cases of disease. The World Health Organization's International Agency for Research on Cancer (IARC) lists (Table 1): HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 in group 1, "Carcinogenic to humans"; types 30, 34, 69, 85, 97, 26, 53, 66, 67, 70, 73 and 82 in group 2B, "Possibly carcinogenic to humans"; and types 6 and 11 in group 3, "Not classifiable as to its carcinogenicity to humans" [13]. Although HPV types 5 and 8 are listed in group 2B, their carcinogenic effect is related to a rare autosomal recessive hereditary skin disorder, epidermodysplasia verruciformis [14]. Among the types in group 1, HPV types 16 and 18 are by far the most common, accounting for 70% of cervical cancers and precancerous lesions [4]. Almost all the remaining cancers (30%) are caused by HPV types 31, 33, 45, 52 and 58 [15]. Types 16 and 18 are also the most often responsible for all the other forms of cancer too, in both men and women [16]. The non-carcinogenic HPV types 6 and 11 cause about 80–95% of cases of genital warts [17, 18], although some studies found infection with low-risk types of HPV 1 (including types 6 and 11) associated with certain low-grade cervical, vaginal and vulvar intraepithelial neoplasms [19, 20].

HPV-related cancers are still associated with high mortality rates, despite important advances in screening and treatment. Cervical cancer alone, for instance, caused approximately 311,000 deaths worldwide in 2018, 90% of which occurred in lower- to middle-income countries [4]. In high-income countries, the introduction of organized screening programs has reduced the mortality rates for cervical cancer [21], but there are no such programs for less frequent but more aggressive HPV-related cancers, such as those involving the penis, anus and oropharyngeal region, which are still associated with high mortality rates [12]. Since 2006, however, HPV-related cancer prevention has also been able to count on vaccines against HPV [22].

2. HPV vaccine development

The first vaccine against HPV-related disease was a quadrivalent vaccine (4-valent) approved in 2006 by the Food and Drug Administration (FDA) [23], and by the European Medicines Agency [24]. It contained genotypes 6, 11, 16 and 18. In 2007 and 2009, the EMA and FDA respectively also approved a bivalent vaccine (2-valent) containing types 16

and 18 [25, 26]. The two formulations relied on the same approach—both vaccines contained noninfectious human papillomavirus L1 self-assembling virus-like particles produced using a recombinant DNA technology—but they differed in the cell culture used to produce the particles, the adjuvants, and the therapeutic indications [27, 28]. The bivalent vaccine was indicated for the prevention of premalignant cervical, vulvar, vaginal and anal lesions, and cervical and anal cancers from vaccine HPV types. The quadrivalent was also indicated for preventing genital warts from vaccine HPV types [23, 24]. A nine-valent (9-valent) HPV vaccine was then approved, in 2014 in the US [29] and in 2015 in the European Union [30]. It was developed on the same platform as the quadrivalent vaccine, but with addition of five HPV types—31, 33, 45, 52, and 58—making the vaccine indicated for the prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina, and anus, as well as for genital warts caused by vaccine HPV types [31]. Characteristics of HPV vaccines are detailed in Table 2.

3. Immunogenicity, safety, and efficacy of the 9-valent HPV vaccine: a systematic review

We conducted a systematic review to assess the immunogenicity, safety and efficacy of the 9-valent HPV vaccine, and pool the currently-available evidence. The review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), PRISMA 2020 Update [32].

We searched the PubMed/MEDLINE and EMBASE databases without applying any restrictions as concerns time, language, study design or participants' characteristics. The search was performed on March 17th 2021. The search strategy for one of the databases (PubMed/MEDLINE) is shown in Table 3. Manual searches in the reference lists of the studies selected, and in related reviews were also performed. Two authors (GMP and SC) independently screened the titles and abstracts to identify potentially eligible studies. Disagreements between the two authors were solved by a third author (VB). Full texts of all potentially eligible studies were independently screened by the two authors and earmarked for further consideration. As before, discrepancies between the two authors (GMP and SC) were solved by a third author (VB). Two authors (GMP and SC) independently collected data from each study included in the review using a structured and standardized table. The data extracted concerned: the study design; the geographical location; the sample size; the participants' characteristics; the 9-valent vaccine admin-

Table 2. Characteristics of HPV vaccines.

Vaccine Types included	HPV	Authorization year	Posology	Indications	
2-valent 16 and 18		EMA - 2007	9 to 14 years of age included ^I	2 doses, at 0 and at 5–13 months	Prevention of premalignant cervical, vulvar, vaginal and anal lesions, and cervical and anal cancers causally related to certain oncogenic HPV types
		FDA - 2009	15 years of age or more ^{II}	3 doses, at 0, 1 and 6 months	
4-valent 6, 11, 16 and 18		FDA - 2006	9 to 13 years of age included ^{III}	2 doses, at 0 and at 6 months	Prevention of premalignant cervical, vulvar, vaginal, and anal lesions, cervical and anal cancers causally related to certain oncogenic HPV types, and genital warts causally related to specific HPV types
		EMA - 2006	14 years of age or more ^{IV}	3 doses, at 0, 2 and 6 months	
9-valent 6, 11, 16, 18, 31, 33, 45, 52 and 58		FDA - 2014	9 to 14 years of age included ^V	2 doses, at 6 and 12 months	Active immunization against premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types, and genital warts caused by specific HPV types
		EMA - 2015	15 years of age or more ^{VI}	3 doses at 0, 2 and 6 months	

(I) If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.

(II) If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 and 2.5 months after the first, and the third dose between 5 and 12 months after the first.

(III) If the second vaccine dose is administered earlier than 6 months after the first, a third dose should always be administered. Alternatively, a quadrivalent vaccine can be administered according to a 3-dose schedule (0.5 mL at 0, 2, 6 months). The second dose should be administered at least one month after the first, and the third dose should be administered at least 3 months after the second. All three doses should be given within a 1-year period.

(IV) The second dose should be administered at least one month after the first, and the third dose should be administered at least 3 months after the second. All three doses should be given within a 1-year period.

(V) The second dose should be administered between 5 and 13 months after the first. If the second dose is administered earlier than 5 months after the first, a third dose should always be administered. Nine-valent vaccine can be administered according to a 3-dose schedule (0, 2, 6 months). The second dose should be administered at least one month after the first, and the third dose should be administered at least 3 months after the second. All three doses should be given within a 1-year period.

(VI) The second dose should be administered at least one month after the first, and the third dose should be administered at least 3 months after the second. All three doses should be given within a 1-year period.

istration schedule; comparator details; and outcomes. Any discrepancies between the data collected by the two authors were discussed and a consensus was reached between the two.

Eligible studies compared the 9-valent vaccine with either placebo or any other previously-existing vaccine, whatever the number of doses administered, the vaccination schedule used, and the site of vaccine administration. To be eligible, studies had to report at least one of our three outcomes of interest, i.e., immunogenicity (measured as the percentage of participants who seroconverted or in terms of mean antibody levels); safety (in terms of frequency and severity of adverse reactions/events observed after HPV vaccine administration); efficacy (in terms of a reduction in either incident and persistent infections with both vaccine and non-vaccine HPV types or in the rates of cervical intraepithelial neoplasia and invasive cervical cancer).

The search yielded 266 records, and no duplicates were found, so 266 titles and abstracts were screened, and 228 records were excluded. The full texts of 38 potentially eligible publications were considered, and 26 were ultimately

included in the review. Fig. 1 shows the study search and selection process. **Supplementary Table 1** (Ref. [33–52]) lists the articles in chronological order and summarizes their characteristics and findings.

Seventeen clinical trials and three database studies were ultimately obtained from the PubMed search. These publications explored the immunogenicity, safety/tolerability, and efficacy/effectiveness profiles of the 9-valent in various combinations of the different variables (age at vaccination, sex, dosage schedules, previous vaccination with 4-valent vaccine, coadministrations, and national/ international groups). The main results of these clinical trials and database studies are reported below.

Immunogenicity: the clinical trials showed that the 9-valent vaccine consistently elicited immunological responses to all the vaccine types in immunocompetent subjects. Notably, percentages nearing 100% seroconversion were seen in all immunocompetent subjects in the age groups vaccinated, of both sexes and whatever their nationality [33–44, 46–48, 50, 52]. The studies focused on three age/sex segments:

Table 3. PubMed search strategy.

Search	Query
#1	Search (HPV OR papillomavirus*) AND vaccine* AND (9-valent OR nonavalent OR ninevalent OR 9vHPV OR Gardasil 9 OR Gardasil-9)
#2	Search ("Immunogenicity, Vaccine" [Mesh] OR efficacy OR effectiveness OR safety OR tolerability)
#3	Search (#1 AND #2)

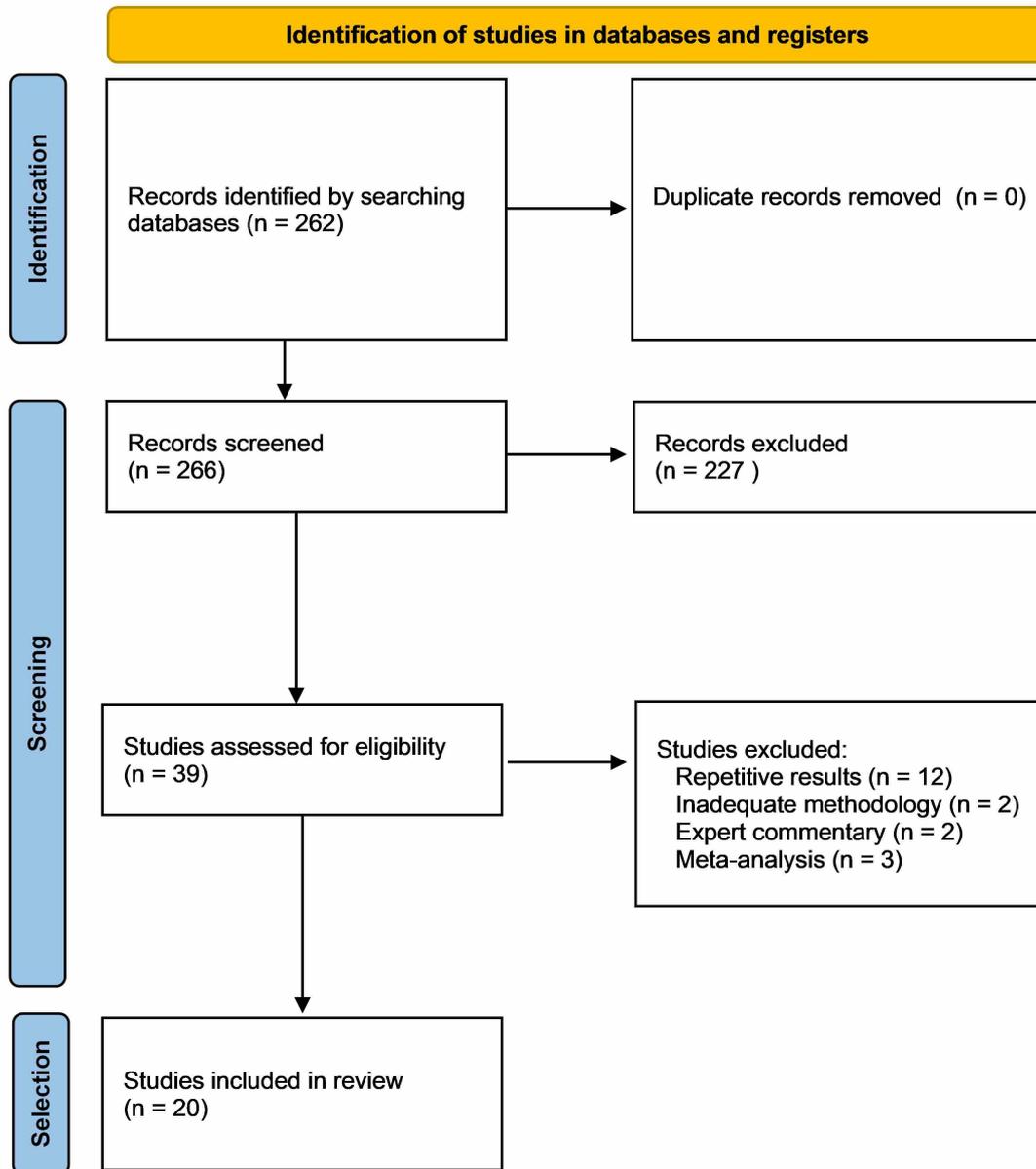


Fig. 1. PRISMA flow diagram showing the study search and selection process.

females and males aged 9 to 15 years [35, 37, 39–41, 50]; females and males aged 16 to 26 years [33, 37, 39–41, 50]; and females aged 27 to 45 years [52]. Four clinical trials also specifically examined whether or not the new 9-valent vaccine was inferior in terms of immunogenicity to the 4-valent vaccine, in both the short term (1 month after the 3rd dose) [33, 35, 40] and the long term (42 months after the 3rd dose) [44], concluding for a non-inferiority of the new vac-

cine for the 4 shared HPV types. Immunogenicity was also assessed in case of co-administration with other vaccines. An open-label, randomized study examined the administration of 9-valent HPV vaccine concomitantly with combined vaccine against diphtheria, tetanus and acellular pertussis, and inactivated poliomyelitis in healthy 11- to 15-year-olds [34]. Another trial tested the concomitant administration of 9-valent HPV vaccine with the meningococcal 4-valent vaccine,

and the combined diphtheria, tetanus and acellular pertussis vaccines, and inactivated poliomyelitis vaccine [38]. In both cases, the immune response elicited in the case of co-administration was not inferior for any of the vaccine components, and no immunological interference issues emerged [34, 38]. Using immune-bridging outcomes, clinical trials also played a pivotal part in testing for any sex-related differences in immunological response. None came to light, and this paved the way to gender-neutral HPV vaccination programs for preadolescents, adolescents and adults [36, 37]. The immunogenicity of 9-valent HPV vaccine was initially investigated using a 3-dose schedule in all age groups. Then the 2-dose schedule was examined in two clinical trials on younger people (9 to 14 years of age), and seroconversion occurred in >98% of the vaccinated subjects, a percentage statistically not inferior to the one elicited by the 3-dose schedule [41]. This led to the authorization of a 2-dose schedule for boys and girls aged 9 to 14 years [31]. A follow-up study then confirmed that, as seen for the 3-dose schedule [44], so too for the 2-dose schedule, the immune response persisted for at least 36 months after the last dose of vaccine [50]. One clinical trial investigated immune response to the 9-valent HPV vaccine in HIV-positive subjects aged 18 to 45 years, and in solid organ transplant recipients aged 18 to 55 years: the seroconversion rates were 100% in the former group and ranged between 46% and 72% in the latter [49].

Safety and tolerability: the safety and tolerability of the 9-valent HPV vaccine were been investigated not only in all the clinical trials, but also in the database studies. All the trials were consistent in indicating that, irrespective of the recipients' age, sex or nationality, the vaccine schedule, the concomitant administration of other vaccines, and concomitant clinical conditions, the 9-valent HPV vaccine was well tolerated and safe, and there were no reported vaccine-related deaths [33–44, 46–50, 52]. The most common adverse events related to the injection site, reported in percentages varying from 57.6% [49] to 90.7% [33]. Systemic adverse events occurred in percentages varying from 20.6% [49] to 55.8% [33]. Four studies compared the safety and tolerability profile of the 9-valent vaccine with that of the 4-valent vaccine, and it generally emerged that the rates of adverse events were much the same or slightly higher for the 9-valent vaccine [33, 35, 40, 44]. The two retrospective database studies [45, 51], and single prospective one [46] were all conducted in the United States, and collected data from three different systems. Analyzing data from the Vaccine Adverse Event Reporting System (VAERS), Landazabal and colleagues found that no unexpected adverse events had been observed in a population of pregnant women for whom the vaccine was contraindicated, but in whom it had accidentally been administered [45]. The other two studies—one with data from six Vaccine Safety Datalink sites [46], and one with data from the MarketScan database [51]—found no evidence of any specific clusters or patterns of unexpected serious adverse events.

4. Real-world data

Real-world data concerning the impact of the 9-valent HPV vaccine are still limited as its approval and use in vaccination programs are too recent. On the other hand, there are plenty of publications on the abundant usage of its predecessors in several countries in Europe, North America and Oceania.

4.1 Australia

Australia was the first country in the world to introduce a nationally funded HPV vaccination campaign in April 2007. By means of school-based HPV vaccination programs first for 12- and 13-year-old girls, and later for boys of the same age, along with targeted catch-up programs, the country has been able to protect a vast proportion of its population [53]. The combination of screening and vaccination programs generated remarkable results, justifying by 2019 the unprecedented and bold claim that cervical cancer could be eliminated as a public health problem in less than 20 years [54]. While awaiting this historic goal, there has been an abundance of real-world evidence to support the country's great disease prevention success story. An ecological study analyzed the incidence of cervical abnormalities in young women during the years 2001–2009 to compare the measure of the first 3 years of the national vaccination program in the state of Victoria. A comparison with data regarding the 4 years before the vaccination program was implemented showed a significant decrease in high-grade cervical abnormalities (0.38%; 95% CI 0.16–0.61; $p = 0.003$) among young women afterwards [55]. A second study measured the effectiveness against cervical abnormalities of the 4-valent HPV vaccine four years after a state-funded vaccination program had been started in Queensland. The vaccine's effectiveness was found to be 46% for cases of high-grade cervical disease, and 34% for cases of cytological or histological abnormalities. The Authors also made the point that the drop in the population prevalence of cervical abnormalities thanks to vaccination would have affected the predictive power of cytological testing, which therefore needed adjusting in screening programs [56]. A third finding came from the analysis of national data on histological diagnoses of cervical dysplasia and excisional treatments in the years 2004–2013. Robertson and colleagues found a significant drop in the incidence of low-grade squamous dysplasia in the female population. After stratifying the results by age group, it emerged that this decline only involved women 20 to 24 years old, while the incidence was slightly higher for older age groups. Similarly, the number of excisional treatments declined, but only in women under 35, not in those aged 35 years or older [57]. Finally, Cornall and colleagues [58] examined the prevalence rates of CIN3/AIS due to HPV-types 16 and 18 over a period of 4 years by genotyping consecutive biopsies with histologically-confirmed CIN3/AIS from vaccine-eligible women. Comparing 213 cases from the pre-vaccine era with 529 from the post-vaccine era, they found that in women aged 18 to 25 the positivity rates for HPV

types 16 and 18 went from 69% in 2001–2005 to 62% in 2011–2012, to 47% in 2013–2014. In women 26 to 32 years old, there were no such changes in the rates of types 16 and 18 positivity. Nearly all study participants had been vaccinated beyond the average age of sexual debut—a finding that would seem to support the value of catch-up programs for young women, and might suggest that vaccination against HPV is much more effective when scheduled before sexual debut [58].

The impact of HPV vaccination on genital warts has also been investigated. Ali and colleagues found that, using data collated from 2004 to 2011, the proportions of genital warts declined from 11.5% to 0.85% in girls <17 years old, and from 11.3% to 3.1% and in women aged 21 to 30 [59]. There was a corresponding decline from 12.1% to 2.2% in boys <20 years old, and from 18.2% to 8.9% in men aged 21 to 30. Consistent results emerged from two other analyses [60, 61], suggesting that vaccination programs have rapid and substantial effects on the prevalence of genital warts in the age group primarily targeted for vaccination. Among these effects, vaccinating females seems to indirectly benefit males [61].

4.2 Costa Rica

The Costa Rica Vaccine Trial included data on more than 3700 women given the bivalent HPV vaccine and followed up for over 11 years [62, 63]. Vaccine efficacy against incident HPV 16 or 18-associated CIN2+ was 100%, and the cumulative vaccine efficacy against HPV 16 or 18-associated CIN2+ was 97.4%. Similarly high levels of protection were seen against HPV 16 or 18-associated CIN3 [63].

4.3 Denmark

One cohort study in Denmark was conducted to assess the effect of the quadrivalent vaccine in terms of the association between individual HPV vaccination status and subsequent risk of cervical lesions [64]. A second population-based cohort study using the national health register data expanded the analysis to vaccinated and unvaccinated women [65]. A third then assessed the real-life impact of HPV vaccination in the first birth cohort of vaccinated Danish women [66]. The three analyses produced consistent results that all pointed to a reduced risk of cervical abnormalities in vaccinated women [65, 66].

4.4 Italy

In Italy, HPV vaccination programs started for girls in the 13th year of age in 2007, and in 2015 they were extended in some regions to boys of the same age [67]. In 2017, the National Immunization Plan introduced a gender-neutral approach to HPV vaccination, also advocating for the vaccination of women 25 years of age at the time of their first HPV screening exam, and of men who have sex with men [68]. Finally, starting in 2018, the 21 Italian regions also gradually introduced vaccination programs for women with a history of cervical disease. A study on hospitalizations for HPV-related disease, conducted in the Veneto region in the years 2008–2011, showed an average hospitalization rate of 49.4

per 100,000 population per year. This analysis also showed a declining trend: from 57.2 hospitalizations per 100,000 in 2008 to 39.7 per 100,000 in 2011. The same downward trend was seen for the rate of genital cancer hospitalizations too: from 11.86 per 100,000 in 2008 to 7.92 per 100,000 in 2011 [69]. A second study conducted in Veneto showed that HPV vaccination coverage rates of around 70% in girls were associated with a significant decrease in hospitalization rates for anogenital warts (AAPC: –6.1%; 95% CI: –8.4; –3.7) in women 17 to 46 years old in the years from 2007 to 2018. Interestingly, hospitalization rates for anogenital warts in men increased during the same period (AAPC: 3.8%; 95% CI: 1.2; 6.4), a change driven only by rising numbers of cases of anal warts [70].

4.5 Sweden

A national cohort study on data in the Swedish Cancer Registry examined the effectiveness of HPV vaccination in preventing invasive cervical cancer. The study included details of more than 1.7 million women 15 to 30 years old, and found that the risk of cervical cancer for those who had received a first dose of vaccine before the age of 17 was 88% lower than for those who had never been vaccinated [71].

4.6 United Kingdom

In the United Kingdom, a national HPV prevention program introduced in 2008 envisaged routine vaccination for girls aged 12–13, and catch-up vaccination for girls up to 18 years old. The program started with the 2-valent vaccine, which was replaced in 2012 with the 4-valent vaccine [72, 73]. The success of vaccination in preventing HPV type 16 and 18 infections in sexually-active young women has been confirmed by several studies. Mesher and colleagues [72–74] conducted three consecutive analyses on genital specimens from women aged 16–24 years, obtaining consistent results that all pointed to a decrease in the prevalence of HPV types 16 and 18 in the period after vaccination was introduced. Notably, the rate of this decrease was strongly associated with the estimated increase in vaccination coverage [75]. Similar results emerged from studies performed in Scotland, where coverage rates have consistently been above 90% in the routinely-vaccinated cohort. This country's introduction of vaccination with the bivalent HPV vaccine achieved a reduction in the prevalence of HPV infection, and of low- and high-grade cervical abnormalities [74, 76].

4.7 United States of America

In the United States, vaccination with the quadrivalent HPV vaccine was first recommended in 2006 for girls aged 11–12 years. In 2011 it was also recommended for boys of the same age. In 2016 the 9-valent vaccine replaced the 4-valent version as the recommended vaccine [77]. The HPV-IMPACT Project stemmed from a collaboration between the Centers for Disease Control and Prevention (CDC) and catchment areas in five states. The aim was to establish a population-based approach to monitoring the impact of HPV vaccination on cervical cancer precursors and the associated

HPV genotypes. From 2008 to 2012, the CDC performed HPV DNA typing on 4678 diagnostic specimens from females aged 18 years or older who had been diagnosed with CIN2+. By stratifying the data by vaccination status, the authors concluded that there was compelling evidence of the real-world impact and effectiveness of HPV vaccination in reducing cervical disease associated with targeted HPV types [78, 79]. In a case-control study, its impact on precancerous cervical lesions and cervical cancers was established in relation to age at first dose and number of doses. Silverberg and colleagues found higher levels of protection associated with full vaccination schedules and a younger age of vaccination, while no significant protection was achieved in women aged 21 years or older at the time of their first dose [80]. This result is consistent with the findings of a study by Mix and colleagues, who reported that the decrease in the rates of cervical squamous cell carcinoma and adenocarcinoma was greater for women aged 15 to 20 than for those aged 21 to 29 [81].

5. Towards the elimination of cervical cancer

In 2009, the World Health Organization recognized the prevention of cervical cancer and other HPV-related diseases as a public health priority. Its first position paper on HPV included a recommendation that HPV vaccination be routinely included in national immunization programs. The primary target population for immunization programs should be girls in early adolescence, while vaccination for older adolescent girls and young women was recommended providing it was feasible, affordable and cost-effective, and did not divert resources, and only if a significant proportion of the secondary target population was likely to be naive to vaccine-related HPV types. HPV vaccination for males was not recommended [82]. The same recommendations were reiterated (with slight modifications) in 2014 [83], and again in 2017. In its 2017 document, the WHO moved forward and recommended not only vaccinating multiple cohorts of 9- to 14-year-old girls (primary goal), but also targeting multiple cohorts of girls aged 9 to 18 years at the time of an HPV vaccination program's introduction, as this would have a faster and greater impact at population level than the vaccination of single age cohorts. The WHO document of 2017 also recognized, for the first time, the value of vaccinating males as a secondary target population [84]. A further step was made in 2018, when the WHO Director-General called on all countries to take action against cervical cancer by ensuring that all girls everywhere are vaccinated against HPV, and that every woman over 30 years old is screened and treated for precancerous lesions [85]. Finally, in 2020, the WHO declared its first global commitment to eradicating a form of cancer—cervical cancer. The WHO identified three key steps: vaccination (90% of girls fully vaccinated with the HPV vaccine by 15 years of age); screening (70% of women screened using a high-performance test by age 35 and again by 45); and treatment (90% of women identified with cervical disease given treatment). If implemented globally by 2030, this will lead

to a more than 40% reduction in new cases of cervical cancer [86]. In its 2019 Resolution on the elimination of HPV-related cancer, the European Cancer Organization identified even more ambitious goals for all countries to reach by 2030: the adoption of gender-neutral vaccination programs (target vaccination rate $\geq 90\%$); enhanced screening ($\geq 70\%$ of women for cervical cancer with high-precision HPV tests every 5 years); improved treatment rates (90% of women with grade 3 CIN treated within 3 months, and 90% of all invasive cancer cases detected and managed) [87].

The number of countries implementing HPV vaccination has increased year after year, and there are now 106 countries around the world with immunization programs underway, 33 of which also include males in their vaccination programs [88].

6. Vaccination in women treated for precancerous cervical lesions

In the gynecology literature, several authors have reported that a significant percentage of patients treated for precancerous cervical lesions subsequently experienced recurrences of the same disease or, worse still, cervical cancer [89, 90]. In parallel, women vaccinated before being treated surgically for HPV-related diseases reportedly had a significant reduction in the incidence of recurrences [91]. These findings paved the way to a new field of research on the usage of vaccination as an adjuvant treatment for HPV-related disease. In 2013, the first evidence to support a role for vaccination in reducing the frequency of recurrent CIN2–3 was published by Kang and colleagues: they offered HPV vaccination to a group of more than 700 women after treating them for high-grade cervical intraepithelial neoplasia. In the subgroup of women who were vaccinated, the recurrence rate was 2.5%, while in the unvaccinated group it was 8.5% ($p < 0.05$) [92]. Five years later, similar results came from the SPERANZA study. Ghelardi and colleagues [93] performed a case-control study involving 350 women aged 18–45 years treated for CIN2+ disease. Participants were offered a first dose of vaccine 30 days after their treatment, and were then followed up for 4 years. There were 11 cases of recurrence in the unvaccinated group (n.172), and only 2 in the vaccinated group (n.172), a result consistent with an 81.2% reduction in the clinical disease relapse rate. Notably, none of the vaccine HPV types were detected in the women in the vaccinated group whose disease recurred, whereas types 16, 11 and 18—alone or, more frequently, in association with others—were detected in 9 women in the unvaccinated group [93]. Further data on the significance and relevance of HPV vaccination as an adjuvant therapy for gynecological diseases came recently from a retrospective study conducted by Sand and colleagues in Denmark [94], from the works of Petrillo and colleagues [95], and Bogani and colleagues [96] in Italy, from the research done by Del Pino and colleagues in Spain [97], and from two systematic reviews and meta-analyses [98, 99].

7. Scientific society guidelines

The importance and value of HPV vaccination have been acknowledged by scientific societies around the world, with a general consensus on recommending the vaccine in females and males before sexual debut. Guidelines differ slightly in two aspects, however, concerning the age at which the vaccine should be administered in adolescents, and whether or not it should be offered to adults. The American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the American Cancer Society all recommend starting a series of HPV vaccinations at between 9 and 12 years of age [100–102]. The International Federation of Gynecology and Obstetrics recommends starting between 10 and 14 years old, and focusing on girls [103]. The American Society of Clinical Oncology suggests vaccination at an age between 9 and 14 years [104]. The European Board and College of Obstetrics and Gynaecology (a representative body of 37 national scientific societies) recommends vaccinating females and males before the age of 15 years [105]. On the vaccination of adults, the American College of Obstetricians and Gynecologists suggest that, for unvaccinated women between 27 and 45 years old, a shared clinical decision should be made on the basis of a given woman's risk of acquiring a new HPV infection and the potential benefit deriving from vaccinating her against HPV [104]. On the other hand, the American Cancer Society does not recommend vaccinating this category of subjects [101]. Finally, it is worth mentioning the position of the Gruppo Italiano Screening del Carcinoma (Italian Group on Carcinoma Screening), which recommends vaccinating women who have been treated for grade two or worse cervical intraepithelial lesions [106].

8. Conclusions

Once only a remote hope, now the elimination of cervical cancer seems to be a public health outcome within reach. Three actions are needed to achieve this goal: screening; treatment; and vaccination. This review focused on the last aspect, considering two important aspects: the development of vaccines with ever-higher valences; and the real-world assessment of their usage. Although reports on the use of the nine-valent vaccine, and data from low- and middle-income countries are still limited, there is already compelling evidence of vaccination with the bivalent and quadrivalent HPV vaccines having a substantial impact on cervical cancer in high-income countries. The clinical impact of vaccination programs reaching high vaccination coverage rates and targeting multiple cohorts is undeniable. Strategies for targeting multiple cohorts are essential, in terms of both offering vaccination to females of different ages and including males in HPV vaccination programs. Although such an approach is bound to be associated with higher costs for healthcare systems, it has nevertheless been adopted by increasing numbers of countries around the world. The rationale behind gender-neutral programs has solid scientific and ethical grounds: vaccinating females and males enables positive

herd-immunity effects on the circulation of the virus to be achieved more quickly. It also has the clinical advantage of preventing HPV-related diseases in males (for which the lack of any specific screening programs often translates into a late diagnosis). From an ethical standpoint, gender-neutral vaccination is a duty because the protective effect on heterosexual males of sufficiently high vaccination rates ($\geq 80\%$) in females does not extend to males who have sex with males. Finally, vaccination policies will need to consider recent developments in cancer treatments, a field in which the adjuvant use of vaccination to help prevent recurrences is gaining consensus.

Author contributions

GMP, SC and VB performed the literature research and analysis. GMP, SC and VB wrote the manuscript. MF, PF and MN provided help and advice. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://ejgo.imrpress.com/EN/10.31083/j.ejgo4205156>.

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