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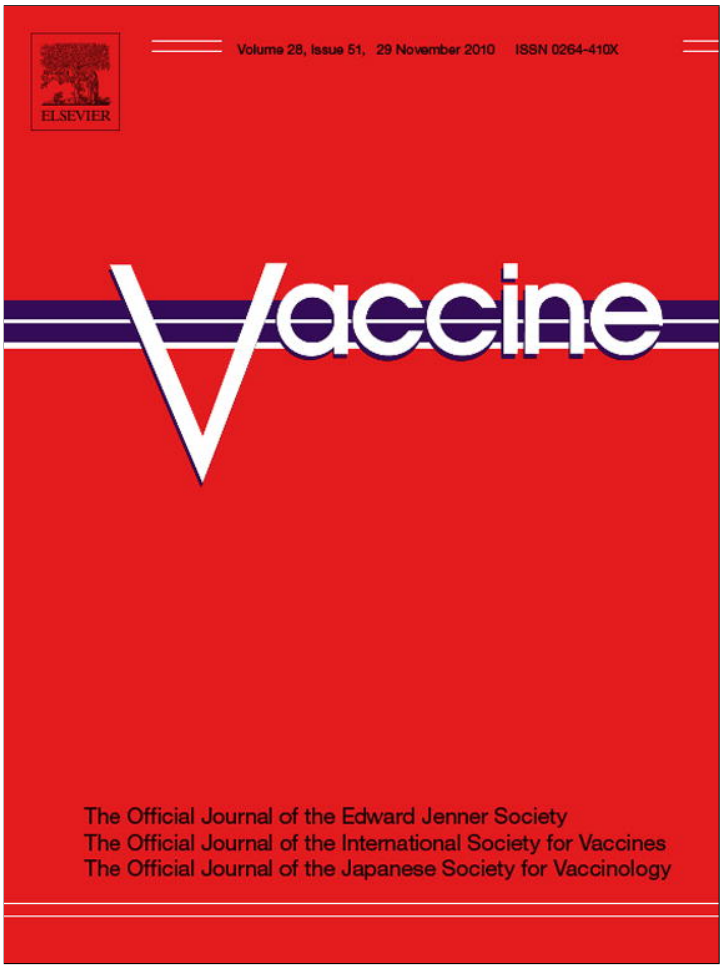

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Review

Benefits of vaccinating young adult women with a prophylactic quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine

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ABSTRACT

Cervical cancer is a leading cause of cancer-related deaths worldwide. The causal role of human papillomavirus (HPV) infection in the pathogenesis of cervical cancer has prompted the development of vaccines against HPV. The highest risk of HPV infection is in women aged 16–25 years. Almost all young adult women can benefit from HPV vaccination. There is strong epidemiological and clinical support for vaccination programmes that target sexually active women in this age group to prevent HPV infection, and thus avert the development of HPV-related disease. Furthermore, the implementation of HPV vaccination programmes may benefit the development or awareness of cervical cancer prevention strategies and ultimately reduce the burden of cervical cancer and improve cervical cancer control.

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1. Introduction

More than 130 genotypes of human papillomavirus (HPV), a double-stranded DNA virus, have been classified. About 30–40 of these infect the mucosa of the genital tract. Genital HPV infection is usually acquired through sexual contact [1]. Infection with the so-called 'low-risk' types rarely results in the development of anogenital cancer as these HPV types are primarily associated with benign anogenital warts, and just two types–HPV 6 and 11–are

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responsible for 86% of anogenital warts [2]. By contrast, infection with the 'high-risk' HPV types is associated with anogenital cancers such as cervical, vaginal, vulvar, anal or penile cancer. HPV 16 and 18 account for approximately 76% of cases of cervical cancer and 50% of high-grade cervical lesions, and 40%, 60% and 80% of vulvar, vaginal and anal cancers, respectively [3–7]. The causal association between HPV infection and cervical cancer, and the status of this disease as a leading cause of cancer-related deaths worldwide [8], have prompted the development of vaccines against HPV.

Two prophylactic HPV vaccines are currently available. Gardasil®/Silgard® (Merck & Co. Inc., Whitehouse Station, New Jersey, USA; Sanofi Pasteur MSD, Lyon, France) is a quadrivalent vaccine containing virus-like particles (VLPs) composed of L1 proteins from HPV types 6, 11, 16 and 18, and Cervarix® (GlaxoSmithKline, Rixensart, Belgium) is a bivalent vaccine containing VLPs for types 16 and 18. A number of countries have introduced HPV vaccination programmes for girls aged about 12–14 years as the primary target population, in addition to current screening for cervical cancer starting at the age of 20–25 years (Table 1). Some countries have also introduced catch-up programmes targeting women of various ages up to 26 years old.

Lack of knowledge about risks of sexual behaviour and the cause of cervical neoplasia have been shown to be barriers both for the successful implementation of routine gynaecological screening and HPV vaccination [10]. Women's understanding of cervical cancer, the causal role of HPV, and the prevention of cervical cancer with an HPV vaccine improves with the provision of information about the perceived risk of cervical cancer and has increased as a result of the awareness and vaccination campaigns following the introduction of HPV vaccines [11,12]. HPV vaccination represents an important element in cancer control strategies aimed at reducing the global burden of cervical cancer. Organized vaccination and screening programmes are essential for the successful control of cervical cancer [13] and stronger measures and incentives may be required than those currently recommended [9]. The integration of primary protection and secondary prevention (screening) programmes in a comprehensive approach will result in increased protection not only against cervical cancer but also against other HPV-related diseases. In addition, restriction of transmission by vaccinated individuals (herd immunity) might indirectly protect disadvantaged groups that are often hard to reach through screening programmes [14].

Girls, before their sexual debut and thus before potential exposure to HPV, are the primary target population for HPV vaccination. This is the population that will have optimal protection from vaccination. However, although young women are at high risk of anogenital HPV infection after sexual debut, the probability that they will have been infected with the four HPV types 6, 11, 16 and 18 targeted by the quadrivalent vaccine is very low so they could still benefit from vaccination. This review paper will focus on the potential benefits arising from the extension of the current target population of girls and adolescent females to women aged 16–25 years.

2. Epidemiological rationale for vaccinating young adult women

Epidemiological studies have shown that women aged 16–25 years are at higher risk of HPV infection and associated disease that develops later in life than any other age group. Data from the National Health and Nutrition Examination Survey (NHANES) for 2003–2004 show that the prevalence of HPV infection in women in the United States was greatest in those aged 20–24 years [15]. In 2003–2004, the overall prevalence of HPV infection in the United States was 26.8% (95% confidence interval [CI] 23.3–30.9%) in women between the ages of 14 and 59 years, with the prevalence increasing significantly ($P < 0.001$) from 24.5% (95% CI 19.6–30.5%) in those aged 14–19 years to 44.8% (95% CI 36.3–55.3%) in those aged 20–24 years [15]. More recent studies in Denmark, Spain and Portugal have reported an overall prevalence of 26.4%, 14.3% and 19.4%, respectively with a peak in women aged 20–24 years [16–18]. Similarly, in a study involving 7986 women from the Guanacaste province of Costa Rica, the incidence of HPV type 16 seroconversion was highest among women aged 18–24 years, and declined steadily thereafter [19]. In a review of published studies, the global adjusted HPV prevalence was estimated to be 10.4% (95% CI 10.2–10.7%) varying from 8.1% (95% CI 7.8–8.4%) in Europe to 22.1% (95% CI 20.9–23.4%) in Africa. The peak of infection was seen in women aged less than 35 years old, with a second peak occurring after age 45 years in Africa, the Americas, and Europe [20].

Further insights into the risk of HPV infection in young adult women can be obtained from studies of the incidence of anogenital warts, as the delay between infection and disease is short. Data from the United Kingdom show that the number of new diagnoses of anogenital warts in adults aged 16–24 years is about three times higher than in those aged 25–44 years (around 600 per 100,000 vs. 200 per 10,000) [21]. In another study in Spain, it was estimated that the overall prevalence of genital warts in women was 162 per 100,000 and the total annual cost was estimated to be about €50 million [22]. In France, the estimated annual incidence in 2005 was 229 per 100,000, which resulted in an annual cost of about €25 million [23]. In an analysis of the placebo arm of two randomized Phase III trials of the quadrivalent HPV vaccine (in which the inclusion criteria limited the number of sexual partners to four or fewer), 3.4%

Table 1
Cervical cancer screening programmes in Europe [9].

	Age range targeted (years)	Recommended screening interval (years)	Type
Austria	18+	1	Non-population based
Belgium	25–64	3	Non-population based
Denmark	23–59	3 in those aged 25–50 years 5 in those aged >50 years	Population based
Finland	30–60	5	Population based
France	25–65	3	Non-population based (nationwide) Population based (regional pilot)
Germany	20+	1	Non-population based
Italy	25–64	3	Population based (nationwide, roll-out ongoing)
Netherlands	30–60	5	Population based
Norway	25–69	3	Population based
Portugal	25–64	3	Population based (regional, roll-out ongoing)
Spain	30–59[a]	3 or 5	Non-population based
	30–65[a]	3	Population based (regional)
Sweden	23–60	3 in those aged 25–50 years 5 in those aged >50 years	Population
United Kingdom	20–64	3 or 5	Population

[a] With regional variations.

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Table 2
Brief description of four randomized double-blind placebo-controlled trials assessing the clinical efficacy of Gardasil [37–40]. All trials were multicentre, international trials in which women were randomized to receive vaccine or placebo at month 0, month 2 and month 6. Women who had had more than four life-time male sexual partners (five for the Phase IIa trial), who had had an abnormal Pap test result, or known previous HPV diseases were excluded from the trials.

Study design feature	Phase IIa trial [40]	Phase IIb trial [39]	Future I [37]	Future II [38]
Trial registry number	NCT00365378	NCT00365716	NCT00092521	NCT00092534
Vaccine	HPV16 (monovalent)	Gardasil (quadrivalent)	Gardasil (quadrivalent)	Gardasil (quadrivalent)
Sample size	2409	552	5455	12,167
Study dates	1998–2004	2000–2004	2001–2007	2002–2007
Visit schedule	Months 0, 7, 12, 18, 24, 30, 36, 42 and 48	Months 0, 7, 12, 18, 24, 30 and 36	Months 0, 3, 7, 12, 18, 24, 30 and 36	Months 0, 7, 12, 24, 36 and 48
Age for inclusion	16–23 years	16–23 years	16–23 years	15–26 years
Timing of Pap test screening	About every 6 months	About every 6 months	About every 6 months	About every 12 months

(298/8800) developed genital warts during an average follow-up time of 3.6 years. HPV DNA was detected in 90.8% of the lesions, with HPV types 6 and 11 detected in 86% of these lesions. High-risk HPV types were found in 31% of the lesions [2]. The incidence of cervical cancer also increases sharply after the age of 25–30 years, and reaches a first peak in women aged 35–44 years in the UK [21,24], but the age of the peak varies in different countries [25].

Cohort studies have shown that the increasing risk of HPV infection in young adult women becomes apparent within months after first sexual intercourse. In one such study, which included 242 women who were recruited within 6 months of first sexual intercourse and had only one sexual partner, the cumulative risk of cervical HPV infection after 3 years was 46% (95% CI 28–64%), and the median time from first intercourse to first detection of HPV was 2.6 months (range 0.3–59.0 months) [26]. Similarly, in the Guanacaste study, HPV was detected in 53.4% of women within a median of 3.6 years after first sexual intercourse, and the prevalence of infection increased from 15.7% at 1 year to 49.8% after 5 years [27].

Although the risk of infection with any HPV type is high in young adult women, the risk of infection with all four quadrivalent-vaccine-related types (6, 11, 16 or 18) is low. The pooled data from pivotal clinical trials with Gardasil in women aged 16–26 years show that only 0.1% of the women were infected with all four of the types targeted by the vaccine [28], and approximately 72% of the women in these studies were naïve to all four types as judged by serology or polymerase chain reaction (PCR) [29]. In women aged 14–59 years in the NHANES survey, the seroprevalences of HPV types 6, 11, 16 and 18 were 17.0%, 7.1%, 15.6% and 6.5%, respectively, and the overall seroprevalence for any of these HPV types was 32.5%; only 0.4% of women had antibodies to all four types [30]. Similarly, in the Guanacaste study, approximately 15% of women (median age 38 years) had antibodies to HPV types 16 or 18, and 10% had antibodies to either of these plus at least one other type [31]. However, the development of antibodies after infection can be slow and the seroconversion rate is approximately 60% within 8–12 months of infection [32,33].

Given the high risk of HPV infection in young adult women, and the fact that women of this age do develop cervical cancer, and some even die [34], there is a strong case for vaccination as a means to prevent HPV infection, and thus prevent HPV-related diseases. Furthermore, the finding that infection with all four HPV types targeted by the quadrivalent vaccine is extremely uncommon in this age group suggests that vaccination offers an opportunity to prevent primary infection in young women who have not yet been exposed to the vaccine HPV types. It would further block infection in women already exposed to at least one vaccine-related HPV type, but who remain naïve to other HPV types (DNA negative and seronegative) or who may have cleared the infection with that type (DNA negative and seropositive) [28,35]. In addition, although HPV prevalence is high in younger women, persistent infection which is essential for cervical carcinogenesis, is associated with older age [36].

3. Clinical rationale for vaccinating young adult women

3.1. Efficacy of the quadrivalent HPV vaccine

The efficacy of the quadrivalent HPV vaccine Gardasil has been investigated in two pivotal clinical trials, FUTURE I and II (NCT00092521 and NCT00092534, respectively), which involved a total of approximately 18,000 women aged 16–26 years [37,38]. In addition, the efficacy of Gardasil was evaluated in a Phase II trial involving 552 women aged 16–23 years [39], and an earlier trial investigated the use of a vaccine against HPV type 16 in women of the same age [40]. The design features of these trials are summarised in Table 2. In each of these studies, women were randomized in a 1:1 ratio to receive vaccine or placebo at baseline and after 2 and 6 months. The efficacy of Gardasil to reduce the occurrence of HPV 16/18-related cervical intraepithelial neoplasia (CIN) grades 2/3 or adenocarcinoma in situ (AIS) was assessed; CIN 2/3 and AIS are obligate precursors of cervical cancer. Other endpoints included vulvar and vaginal intra-epithelial neoplasia (VIN/VaIN), low-grade cervical neoplasia, and genital warts related to HPV 6, 11, 16 and 18.

The data from the four trials were pooled and in this combined population 21% of the sexually active women (limited to no more than 4 or 5 sexual partners, depending on the trial) had evidence of prior or current infection with at least one HPV type (HPV types 16 or 18) and 12% already had an abnormal Pap test result [41]. A per-protocol susceptible population was analysed, which included women who were PCR-negative and seronegative to the relevant vaccine HPV type at enrolment, remained PCR-negative to the same HPV type until 1 month post-dose 3 (month 7), received three doses of vaccine or placebo, and did not violate the protocol. Vaccination with Gardasil resulted in 98.2% efficacy (95% CI 93.2–99.8%) in preventing HPV 16/18-related CIN 2/3 or AIS with a mean follow-up of 3.0 years (SD 0.66) after the first dose. Another analysis was performed on an unrestricted susceptible population that included women without evidence of prior or current infection with HPV types 16 and/or 18 (i.e. were seronegative and PCR negative) and who received at least one dose of vaccine or placebo. In this study, vaccination with Gardasil resulted in 100% efficacy (95% CI 90.5–100%) in preventing HPV 16/18-related CIN 3 [42].

The 4-year follow-up data pooled from the FUTURE I and II trials [37,38,42] (mean follow-up of 3.6 years, maximum 4.9 years) confirmed that vaccination with Gardasil showed similar efficacy for preventing HPV-related CIN or genital lesions. This was found in women who had previously been exposed to HPV (DNA positive at baseline to any of 14 HPV types and seronegative to HPV 6/11/16/18) as well as those who had not (DNA negative at baseline to any of the 14 HPV types and seronegative to HPV 6/11/16/18) [42,43]. Using the risk difference (subtracting the rate in the vaccine group from the rate in the placebo group) it was estimated that vaccination of 100,000 women with Gardasil would prevent 1320–1380 cases of cervical cytological abnormalities, and 170–180 cases of histologically proven CIN 3 or AIS, irrespective of

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Table 3
Efficacy of Gardasil in preventing CIN or AIS in women enrolled in the FUTURE I and II trials and followed up for a mean of 3.6 years (maximum 4.9 years) [42].

	Incidence in Gardasil group (per 100 person-years)	Incidence in placebo group (per 100 person-years)	Risk difference (placebo–Gardasil) (95% CI)	Number of cases prevented annually per 100,000 vaccinated women (95% CI)
HPV-naïve population (n = 9296)				
Any CIN (CIN 1–3 or AIS)	1.68	2.39	0.71 (0.40–1.02)	710 (400–1020)
CIN 3 or AIS	0.22	0.39	0.17 (0.05–0.28)	170 (50–280)
Any Pap smear abnormalities	6.65	8.03	1.38 (0.76–1.99)	1380 (760–1990)
Definitive cervical therapy	0.79	1.37	0.58 (0.36–0.80)	580 (360–800)
HPV-exposed population (n = 17,160)				
Any CIN (CIN1-3 or AIS)	3.39	4.19	0.80 (0.48–1.12)	800 (480–1120)
CIN 3 or AIS	0.81	0.98	0.18 (0.03–0.33)	180 (30–330)
Any Pap smear abnormalities	10.36	11.68	1.32 (0.74–1.90)	1320 (740–1900)
Definitive cervical therapy	1.97	2.56	0.59 (0.35–0.083)	590 (350–830)

AIS: adenocarcinoma in situ; CI: confidence interval; CIN: cervical intraepithelial neoplasia; Pap: Papanicolaou.
HPV-naïve population: DNA negative at baseline to any of 14 HPV types[a] and seronegative to HPV6/11/16/18.
HPV-exposed population: DNA positive at baseline to any of 14 HPV types[a] and seronegative to HPV6/11/16/18.
[a]6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.

the HPV type involved and prior exposure or not (Table 3). In addition, it was estimated that vaccination of 100,000 women would avoid 830–1020 cases of genital warts, VIN 1–3 or VaIN 1–3 [42].

In another analysis combining end-of-study data from the three studies assessing the quadrivalent vaccine, the efficacy for preventing HPV type 6/11/16/18-related CIN was 98.2% (95% CI 93.3–99.8%), for preventing VIN 2/3 or VaIN 2/3 was 100.0% (95% CI 82.6–100.0), and for preventing CIN2/3 or AIS was 51.5% (95% CI 40.6–60.6%) in the intention to treat (ITT) population. In the ITT population the efficacy for preventing VIN 2/3 or VaIN 2/3 due to any HPV type was 49% (95% CI 18.0–69.0%) [44]. The time-to-event analyses for this endpoint showed a reduction in HPV 6/11/16/18-related CIN 2 or worse as the follow-up time increased. This suggests that efficacy would have continued to increase with longer-term follow-up [45]. However, the two Phase III trials were terminated for ethical reasons, to allow women in the placebo groups to receive Gardasil [46]. The efficacy against HPV 6/11/16/18-related external genital lesions was 99.1% (95% CI 96.8–99.9) in the per-protocol population [46].

The efficacy of Gardasil has been investigated in women in the FUTURE I and II trials with virological evidence of previous HPV infection [28,37,38]. At baseline, 19.8% of women were seropositive for at least one of the vaccine HPV types, and 14.9% were positive by PCR; overall, 26.8% were positive by either technique. In these women, vaccination was 100% effective (95% CI 79–100%) in protecting against CIN 2/3 or AIS caused by any of the vaccine-related HPV types for which the women were negative at enrolment (Table 4). The vaccine showed 94% efficacy (95% CI 81–99%) in preventing vulvar or vaginal premalignant lesions caused by vaccine-related HPV types for which the women were negative at enrolment.

Another analysis from the FUTURE I and II trials examined the impact of vaccination with Gardasil in women who had serological evidence of clearance of a previous vaccine-type HPV infection (i.e. seropositive but PCR-negative) [35]. In the placebo group, seven women developed CIN (any grade) and eight women developed external genital lesions associated with a vaccine-type HPV to which they had previously been exposed; by contrast, there were no such cases of CIN or external genital lesions among women who received Gardasil. Thus, Gardasil showed 100% efficacy (95% CI 29–100% for CIN, 40–100% for external genital lesions) in preventing disease caused by reinfection or by reactivation of vaccine-type HPV in women with prior HPV infection.

3.2. Safety of the quadrivalent HPV vaccine

Large-scale clinical trials [37,38,47,48], in which most of the safety data have been gathered from sexually active women aged between 16 and 26 years, have shown that Gardasil has a favourable safety profile, be it in respect of minor or indeed severe complications. This has been confirmed in post-marketing surveillance [49]. The extensive safety documentation is supported by the favourable experience with Gardasil in routine clinical practice, which currently encompasses more than 50 million doses worldwide [50].

The most common adverse events reported for Gardasil in the Vaccine Adverse Event Reporting System are syncope and local site reactions, which have an incidence of 8.2 and 7.5 per 100,000 doses, respectively [49]. In general, the incidence of adverse events

Table 4
Efficacy of Gardasil in preventing CIN or AIS caused by vaccine-related HPV types in women enrolled in the FUTURE I and II trials who were seropositive or PCR positive for at least one HPV type at baseline [28].

	Gardasil			Placebo			Efficacy (%) (95% CI)
	n[a]	Cases	Rate/100 person-years at risk	n[a]	Cases	Rate/100 person-years at risk	
Any CIN	2188	4	0.1	2182	45	0.8	91.9 (75.7–97.7)
HPV type							
HPV 6-related CIN	1245	1	0.0	1230	10	0.3	90.2 (31.3–99.8)
HPV 11-related CIN	1245	1	0.0	1230	2	0.1	51.0 (<0.0–99.2)
HPV 16-related CIN	941	1	0.0	905	17	0.7	94.3 (63.7–99.9)
HPV 18-related CIN	1722	1	0.0	1728	22	0.5	95.4 (71.8–99.9)
Lesion type							
CIN 1	2188	4	0.1	2182	34	0.6	88.3 (67.1–97.0)
CIN 2 or worse	2188	0	0/0	2182	19	0.3	100.0 (78.6–100.0)
CIN 2	2188	0	0.0	2182	12	0.2	100.0 (64.0–100.0)
CIN 3/AIS	2188	0	0.0	2182	10	0.2	100.0 (55.3–100.0)

AIS: adenocarcinoma in situ; CI: confidence interval; CIN: cervical intraepithelial neoplasia; PCR: polymerase chain reaction.
[a] Women who received at least one injection and had at least one follow-up visit 30 days after day 1.

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is comparable with the background rates reported for other vaccines, and is broadly consistent with safety data from prelicensure trials [49].

4. Potential benefits for young adult women from HPV vaccination

Data from clinical trials with Gardasil can shed important light on what can be expected from vaccinating generally HPV-naïve women compared with HPV-exposed women for the prevention of HPV-related diseases (Table 3) [42]. The net benefit of HPV vaccination in women who have been exposed to HPV will depend on two opposing factors–the level of infection or disease within a population of women and how much of that is due to vaccine-related HPV types. As a pre-existing level of HPV infection or disease due to vaccine-related HPV types will be evident in a population previously exposed to HPV, the potential for this population to benefit from the vaccine is reduced compared with that in a population who have had no prior HPV exposure. However, as the absolute risk of vaccine-related HPV type infection or disease is greater in the ITT population of women exposed to HPV than in a population of HPV-naïve women, those women with a greater risk of HPV infection or disease will have a higher potential to benefit from the vaccine.

5. Ethical aspects of HPV vaccination

The finding that almost all sexually active women aged 16–26 years could benefit from HPV vaccination creates a strong ethical rationale for vaccination. Women in this age group have the highest risk of HPV infection, and thus are likely to derive the greatest potential benefits from vaccination. HPV vaccination currently represents a great opportunity to protect young women. It could be argued that it would not be equitable to offer HPV vaccination solely to girls and adolescents below the age at which they are likely to be sexually active and first exposed to HPV, when it may also offer benefits to young women after sexual debut. This is not only an ethical issue; it is also a practical public health issue. In Australia, a free HPV vaccination programme with the quadrivalent vaccine, Gardasil, for adolescent and teenage girls and women under 27 years of age was introduced in mid-2007 [51]. Since 2008 there has been a substantial and significant decline in the incidence of genital warts in women aged 28 years and younger, but not in women over 28 years of age. In the same period, there has also been a significant fall in the incidence of genital warts in young heterosexual men, which may be consistent with reduced HPV transmission as a result of female vaccination. These significant changes in the incidence of genital warts in Australia are likely to be a result of the high level of coverage of women over a broad age range (12–26 years). Preliminary data released from the Australian National HPV Vaccine Register indicate a national uptake of up to 60% in women aged 18–26 years [52].

6. Potential early epidemiological impact of vaccinating young adult women

The epidemiological impact of vaccinating young adult women has been evaluated in studies using a dynamic transmission model. This model, originally developed for use in the United States, takes into account the natural history of HPV, sexual behaviour, and the proportion of women already infected with HPV [53]. These modelling studies have shown that vaccination programmes that include vaccination of girls at approximately 12 years of age and catch-up vaccination of adolescent and young adult women result in faster decreases in HPV-related disorders than when vaccination is confined to girls alone, as demonstrated in the Australian study [51]. Another modelling study from the UK assessed the impact of vaccination with Gardasil at age 12 years, alone and with catch-up vaccination at ages 12–14, 12–17 and 12–24 years. It was assumed that HPV vaccination would be combined with current cervical cancer screening and HPV-related disease treatment practices [54]. Vaccination of girls and women aged up to 24 years resulted in faster and larger reductions in HPV-related disease, compared with vaccination only of girls at age 12 years. This was attributable primarily to prevention of anogenital warts and other diseases related to HPV types 6 and 11; 97% of events prevented during the first 5 years after vaccination, and 94% of those during the first 10 years, were attributable to these virus types [54].

7. Impact of vaccinating young adult women on cervical therapy and obstetric outcomes

The introduction of systematic cervical cancer screening programmes facilitated the detection of precancerous lesions, and this has been reflected in an increase in the number of uterus-saving cervical therapeutic procedures, such as loop electrosurgical excisional procedure (LEEP), and laser conization. These procedures, however, are associated with an increased risk of adverse obstetric outcomes in women who subsequently become pregnant [55]. In a meta-analysis of 20 studies, of which one was a prospective cohort study and the others were retrospective cohort studies, cold-knife conization was associated with significant increases in the risk of perinatal death, low birth-weight and preterm delivery [56].

The impact of the quadrivalent HPV vaccine on rates of cervical therapy regardless of causal HPV types was evaluated in 18,150 individuals enrolled in Phase IIb and Phase III (FUTURE I and II) studies. In the HPV-naïve population (naïve to 14 common HPV types and with a negative Pap test at day 1), the proportion of women who experienced a cervical therapy (LEEP or cold-knife conization) was reduced by 42% (95% CI 28–54%) at end of study [57]. By reducing the incidence of HPV-related CIN and the need for further cervical therapy, HPV vaccination would be expected to avoid adverse pregnancy outcomes related to these procedures. These findings are consistent with those of a recent literature review, which concluded that vaccination against HPV types 16 and 18 could reduce the number of preterm deliveries by between 70 and 257 per 100,000 births by reducing the need for cervical therapy [58]. As the rate of cytological abnormalities in young adult women is higher than that observed in older women or younger women, the benefit from vaccination would also be seen much earlier.

A further pooled analysis of the FUTURE I and II data examined the impact of vaccination with Gardasil in women aged 16–26 years who subsequently underwent cervical therapy for HPV-related disease [59,60]. Therapy was performed at an average of 3.6 years after vaccination, and mean follow-up after therapy was approximately 1.5 years. Among women who had undergone cervical therapy, 31 of 587 (5.3%) vaccinated women subsequently developed CIN of any grade caused by any HPV type, compared with 66 of 763 (8.7%) placebo-treated women. Thus, the efficacy of Gardasil in preventing recurrent CIN in this population was 47% (95% CI 17–66%). Similarly, among women who underwent therapy for external genital lesions, HPV 6/11/16/18-related vaginal or VIN/VaIN or genital warts were less frequent in vaccinated women than in women receiving placebo, suggesting vaccine efficacy in preventing recurrent external genital lesions [59]. These data suggest that women who have undergone cervical conization or treatment for VIN, VaIN, or genital warts could benefit from vaccination with the quadrivalent vaccine through prevention of further diseases.

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8. 'Real world' benefits of HPV vaccination in young adult women

In a 'real world' setting, recent data from Australia [51] have confirmed the high and early impact of a quadrivalent HPV vaccination programme implemented with good uptake and broad coverage in girls, adolescent and young women aged up to 26 years. The study compared the proportions of new patients who presented with diagnosis of genital warts among all new patients attending a Sexual Health Centre, within the periods before (2004–2007) and after (2008) vaccine introduction. Overall, around 10% of new patients attending the Sexual Health Centre between 2004 and 2008 were diagnosed with genital warts.

Results showed that a significantly lower proportion of new patients presented with genital warts over the 1-year period after the implementation of vaccination compared with the period before. The highest impact on genital warts was observed in young women aged less than 28 years with an average change per quarter after the end of 2007 of–25.1% (95% CI–30.5% to–19.3%), compared with +1.8% (95% CI +0.2% to +3.4%) before the end of 2007 ($P < 0.0011$). These findings may be considered as a first marker of the potential for disease prevention expected in the longer term from a well implemented vaccination programme with the quadrivalent vaccine.

9. Current HPV vaccination recommendations

Current guidelines published by the European Centre for Disease Control and Prevention (ECDC) recommend that the primary target population for HPV vaccination should be girls at the age just before sexual activity becomes common, and that catch-up vaccination in older girls and young women is likely to accelerate the public health impact of vaccination, and increase the short-term benefits [61]. Catch-up vaccination in women up to 26 years of age is now recommended in Australia [62], Canada, the United States [63], and some European countries [61]. In Belgium and Switzerland, HPV vaccination is possible in sexually active young women up to 26 years of age on an individual basis [64,65]. French guidelines recommend vaccination in women up to 23 years of age before first sexual intercourse, or up to 1 year afterwards with a preferential recommendation for the use of the quadrivalent vaccine that protects against a wider range of HPV-related diseases [66].

10. Conclusions

Extensive epidemiological and clinical data support the inclusion of all sexually active women aged 18–26 years in HPV vaccination programmes. The probability that young women are infected with the four HPV types 6, 11, 16 and 18 targeted by the quadrivalent vaccine (or even the two 'high-risk' types 16 and 18) is very low. Thus almost all young adult women can benefit from HPV vaccination. In women with evidence of current infection with at least one vaccine HPV type, the quadrivalent vaccine may prevent diseases due to the remaining HPV types to which the women have not yet been exposed. In women with evidence of cleared infection with a specific HPV vaccine type, the quadrivalent vaccine has been shown to prevent recurrent diseases caused by the same type. Young adult women are at the highest risk of HPV infection and subsequent disease and hence can expect to benefit from vaccination. Of course, these data are from clinical trial settings that do not always reflect real life; surveillance programmes have been implemented to confirm that the expected benefits are observed.

In countries where cervical cancer screening programmes are non-existent or inadequate, the implementation of HPV vaccination programmes may provide an opportunity to organize cervical cancer prevention programmes that include both screening and prevention [61]. In countries where screening programmes are well established, vaccination may provide synergistic benefits by increasing women's awareness of HPV and cervical cancer, which might be expected to result in greater participation in screening. Hence, HPV vaccination of young adult women may offer opportunities to reduce the burden of cervical cancer by better uptake of screening, and thus improve cervical cancer control. Finally, from an ethical perspective, women with poor access to screening or low compliance could potentially get even more benefit from vaccination. This has the potential to minimize socioeconomic differences.

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