HPV vaccination against cervical cancer in women above 25 years of age: key considerations and current perspectives

Xavier Castellsagué [a,*], Achim Schneider [b], Andreas M. Kaufmann [b], F. Xavier Bosch [a]

[a] Cancer Epidemiology Research Program, Institut Català d'Oncologia, IDIBELL, CIBER-ESP, Barcelona, Spain
[b] Charité Universitätsmedizin Berlin, Berlin, Germany

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ABSTRACT

Objective. Vaccination of young women (15–25 years of age) against human papillomavirus (HPV) has been shown to be very efficacious in preventing the development of moderate or severe cervical precancerous lesions associated with HPV-16 or -18. As the highest rates of new infections with high-risk (i.e., oncogenic) HPV types occur in the first years following sexual debut, most existing guidelines and recommendations advise on vaccinating young girls. We consider oncogenic HPV infection and the risk of developing cervical cancer in women over 25 years of age and whether they would also benefit from vaccination against HPV.

Methods. We reviewed all available literature on oncogenic HPV infection and the risk of developing cervical cancer in women over 25 years of age.

Results. HPV vaccination is likely to be beneficial to sexually active women due to their continuous risk of acquiring new HPV infections and of developing cervical intraepithelial neoplasia (CIN) and cervical cancer. Clinical trial data show that the HPV-16/18 AS04-adjuvanted vaccine is safe and immunogenic in women up to the age of 55 years, whilst preliminary data with the quadrivalent vaccine demonstrated evidence of safety, immunogenicity and high-level efficacy in women 24 to 45 years of age. HPV vaccination in women over 25 years of age is already approved in several countries, and these women are individually seeking advice on vaccination from healthcare professionals. The predicted reduction in cost benefit of vaccination with increasing age, however, is likely to limit the implementation of routine vaccination beyond the late 20s.

Conclusion. The priority of routine vaccination programmes must be to target girls and young women, with catch-up programmes that extend to age 25/26 when resources allow. For sexually active women over the age of 25, HPV vaccination can be considered on an individual basis, as most will have the potential to benefit from vaccination.

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Introduction

Cervical cancer is the second most common cancer in women worldwide and the third leading cause of cancer death in women [1]. A persistent infection with an oncogenic type of the human papillomavirus (HPV) is the necessary cause for developing cervical cancer. Indeed, HPV DNA is found in 99.7% of all cervical cancer cases [2]. Studies show that 40 of the 100 HPV types identified to date infect the genital tract and at least 15 of these are specifically associated with cervical cancer [3]. In particular, HPV genotypes 16 and 18 are responsible for about 70% of all cervical cancer cases, whilst HPV types 45 and 31 are responsible for a further 10% of cervical cancer cases worldwide [3].

All sexually active women are at risk of oncogenic HPV infection, with up to 80% infected with HPV during their lifetime [4–6], of which 75% will involve an oncogenic HPV type [7]. The highest prevalence of infection is found in adolescence and early adulthood, soon after the onset of sexual activity [8–10], then prevalence rates usually decline during the 20s and 30s. Whilst in some cohorts studies, such as that conducted in Portland, USA, oncogenic HPV prevalence appears to plateau at this point, others conducted in Costa Rica and Colombia show a second smaller peak in oncogenic HPV prevalence later in life [9,11]. This observation is supported by studies of HPV prevalence in women with normal cytology in Europe, North America and Central and South America. In each of these populations, an increase in overall HPV prevalence was seen in the late 4th and 5th decade [12].

The incidence of oncogenic HPV infection, i.e., the rate of newly acquired infections has also been studied in several cohorts, including those from Costa Rica and Colombia, in addition to Canada and Brazil [11,13–15]. These studies show that the risk of acquiring new oncogenic HPV infections remains throughout a woman's sexually

* Corresponding author. Cancer Epidemiology Research Program, Institut Català d'Oncologia, IDIBELL, CIBER-ESP, Gran via s/n, km 2.7, 08907 L'Hospitalet de Llobregat, Barcelona, Spain. Fax: +34 93 2607787.
E-mail address: xcastellsague@iconcologia.net (X. Castellsagué).

active lifetime, with ≥5% of women over 25 at risk of new infections in most studies.

It is known that the majority of HPV infections are transient, with approximately 90% clearing after 2 years [16]. In some cases, however, the infection will persist, and it is these persistent infections that increase the risk of developing cervical cancer [13,17,18]. The development of cellular changes from the onset of genital HPV infection to the development of cervical cancer can take 10–20 years, although in a few cases it may only take 1–2 years [19]. Cervical adenocarcinoma, a type of cervical cancer that arises in the glandular epithelial cells of the endocervix [19,20], is thought to progress more rapidly than squamous cell carcinoma [21] and is of particular concern because it may not be detected as easily by cervical screening [22]. Most cervical adenocarcinoma cases worldwide (>90%) are caused by HPV types 16, 18, 45 and 31 [12].

The knowledge that infection of the cervix with an oncogenic HPV type is a necessary but not sufficient cause for the development of cervical cancer has led to the development of highly effective prophylactic vaccines, designed to protect against the two most prevalent cervical cancer-causing HPV types, HPV-16 and -18. These vaccines are likely to have a major impact on the incidence and mortality of cervical cancer in the future.

Current existing HPV guidelines and recommendations advise on vaccinating young girls before their sexual debut. This is based on the public health argument and the scientific rationale that these cohorts are likely to draw the greatest benefit from a prophylactic vaccine [23]. Universal mass vaccination (UMV) programmes are now being implemented globally in girls and young women between the ages of 9 and 19, with the precise age range for vaccination varying considerably from country to country. Catch-up vaccination is also being implemented in most countries with UMV, starting in the age group immediately above that covered by the UMV programme. The extent of catch-up vaccination programmes also varies greatly, for example in the UK, catch-up is being implemented up to the age of 18 and in Greece up to the age of 26 years.

Currently, the US Center for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of 11–12 year old girls, with vaccination from the age of 9 years permissive. Catch-up vaccination is also recommended for girls and young women aged 13–26 who have not completed the vaccine series, regardless of clinical evidence of previous HPV infection, including a history of genital warts, abnormal Pap test, or positive HPV DNA test [24,25]. There is a great need

however for clear guidance for healthcare professionals already confronted with requests from women of all ages seeking vaccination.

Immunogenicity data following vaccination with the HPV-16/18 AS04-adjuvanted vaccine show that women up to the age of 55 years develop strong HPV-16 and -18-specific antibody responses. Although an age-dependent decrease in antibody titers is observed, titers in the oldest age group (46–55) remained at least 8-fold higher than those associated with natural infection in 15- to 25-year-old women (Phase III PATRICIA trial) [26]. In these immunobridging studies, efficacy may be inferred in the immunobridge study population if the antibody titers measured in the immunobridge and original efficacy studies are of similar magnitude. Indeed, immunobridging data have been accepted as the basis for licensing the HPV-16/18 AS04-adjuvanted vaccine in approximately 50 countries worldwide. Clinical trials to assess vaccine efficacy in women aged 15–55 are ongoing [26]. In a Phase III trial with the quadrivalent vaccine in women aged 24–45, only a small percentage of study participants (0.4% and 0.3% of the vaccine and control groups, respectively) had serological and/or HPV DNA evidence of infection with all vaccine types at baseline [27].

The natural history of HPV infection and cervical cancer development in younger populations of women is well known, but not as well understood in older populations. We therefore reviewed the literature to look into the ongoing susceptibility to HPV infections later in life and the risk of these developing into precancerous lesions and cervical cancer. We also assessed the immunological basis of HPV infection and other factors that could explain why these women remain at risk. The results of HPV vaccine clinical trials were also reviewed.

Oncogenic HPV infection in women over 25

Oncogenic HPV prevalence in women over 25

HPV prevalence (as estimated from HPV DNA detection in cytological samples using PCR analysis) is highest among young women soon after the onset of sexual activity and falls gradually with age until the fourth or fifth decade when, in some populations, there is a second peak followed by another decline [3,9,13,16,19,28–30] (Fig. 1).

Several studies show that oncogenic cervical HPV DNA is present in at least 5% of women over 25 years of age [7–10,15,31–33]. Indeed, a study in the US showed that the prevalence of oncogenic HPV, though declining from a peak of almost 35% at 16 years, was still over 15% in the 26+ age group and over 10% in the over 30 [9]. A similar age-related prevalence of oncogenic HPV was shown in 3305 women
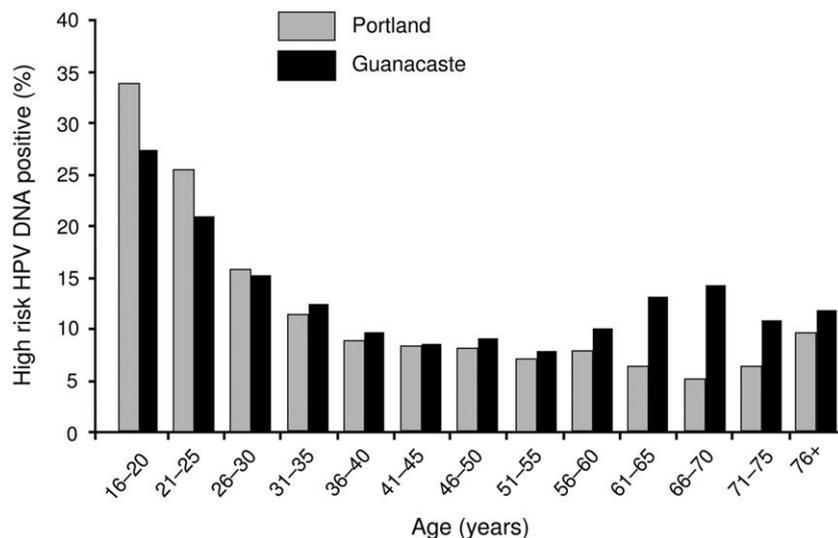

Fig. 1. Age-specific prevalence of oncogenic types of HPV among 20,810 women in Portland, USA (1 April 1989–30 June 1999) and in 9165 women in the Guanacaste Project, Costa Rica [9]. Adapted from Schiffman et al. [9].

aged 15–69 years with cytologically normal smears in the Netherlands. The overall prevalence appeared highest in women aged 25–29 years (15.2%) and decreased to 3.9% in women ≥30 years [10]. In the UK, the HART study (HPV in Addition to Routine Testing) showed an overall prevalence of oncogenic HPV in women 30–60 years old of 6.0% [31] and in a cohort study in Manchester, oncogenic HPV prevalence of 5.7% was found in women 25–55 years of age [7]. Similar findings were reported in Brazil and Sweden with oncogenic HPV prevalence of 5.4% and 6.8% in women ≥35 years old and 32–38 years old, respectively [15,32]. Recent data from women who were enrolled in Phase III trials of the HPV-16/18 AS04-adjuvanted vaccine support these findings. Baseline data from 5750 women with a mean age of 37 years (range 26–72 years) showed that approximately 4% were DNA positive for either HPV-16 or -18, while 0.2% were DNA positive for both HPV-16 and -18 [34].

There are several factors that may contribute to the second peak in HPV prevalence observed in women over 25 years in some populations. One is the acquisition of new HPV infections, for which there is a large body of supporting evidence, as discussed below. Other possible contributory factors are the reactivation of latent HPV infections, although this concept has not yet been directly proven, and a possible cohort effect as a result of high lifetime exposure [12].

Oncogenic HPV incidence in women over 25

When considering preventive vaccination in women over 25, the risk of women acquiring new oncogenic HPV infections is the most important consideration. Several studies conducted in different regions of the world have shown that each year between approximately 5% and 15% of sexually active mid-adult women acquire a new infection with an oncogenic HPV type, as measured by detection of HPV DNA in previously DNA-negative women [11,14,15] (Fig. 2). In each of these studies, the pattern observed is similar to that of prevalence studies, i.e., the highest incidence of infection is found in adolescence and early adulthood, followed by a fairly sharp decline during the 20s to early 30s, with a smaller second peak seen later in life.

A total of 253 HPV-negative women enrolled in an earlier HPV prevalence survey in Canada were invited to participate in follow-up HPV testing one year later. The overall one-year acquisition rate of oncogenic HPV in women aged 25–49 years was 9.7% and ranged from 7.5% in 40–44-year-olds to a second peak of 14.7% in 30–34 year-olds [14]. In Colombia, a cohort of 1610 HPV-negative women, 15–85 years of age, and with normal cytology at baseline, showed an oncogenic HPV incidence of 5.0/100 woman-years [11]. The cumulative risk of HPV infection over a 5-year-period remained at 30% for 25–29-year-olds and approximately 22% for 30–44-year-olds in this study. A small increase in the incidence of oncogenic HPV infection was also seen in this cohort after the age of approximately 40, peaking at around age 50. Similarly, in Brazil, the acquisition of oncogenic HPV infections was studied among 1425 low-income women attending a maternal and child health program. In women ≥35 years of age, the incidence of oncogenic HPV infection was 4.8/100 woman-years [15].

In summary, although the risk of newly acquired HPV infections usually peaks during the third decade of a women's life and is followed by a general decline with age, a significant risk remains in sexually active women of all ages. It remains to be established whether the natural history of HPV infections acquired in older age is the same as that of infections acquired by adolescents and young women. For example it is not yet known whether women who have cleared a previous infection are more likely to clear a subsequent infection.

HPV-16/18 incidence in women over 25

As the HPV vaccines that are currently available are active against HPV-16 and -18, understanding the acquisition rates of these two specific types in sexually active women is critical. In a retrospective study in Nottingham, women 21, 31, 41 and 51 years of age had a comparable 3-year acquisition rate ranging from 3.7% in 21-year-olds to 3.0% in 51-year-olds for HPV-16, whilst peaking at 5.3% in 31 year-olds and declining to 3.8% by the age of 51 for HPV-18 [29] (Table 1).

Similar incidence rates were observed in Brazil (HPV-16/18 incidence of 1.2/100 woman-years) [15] and Colombia (HPV-16/18 incidence of 0.83/100 woman-years) [11].

In summary, approximately 5–15% of sexually active midadult women acquire a new infection with an oncogenic HPV type each year [11,14,15] and in approximately 1–2% of these women, the responsible oncogenic HPV types will be HPV-16 or -18 [11,15,29].
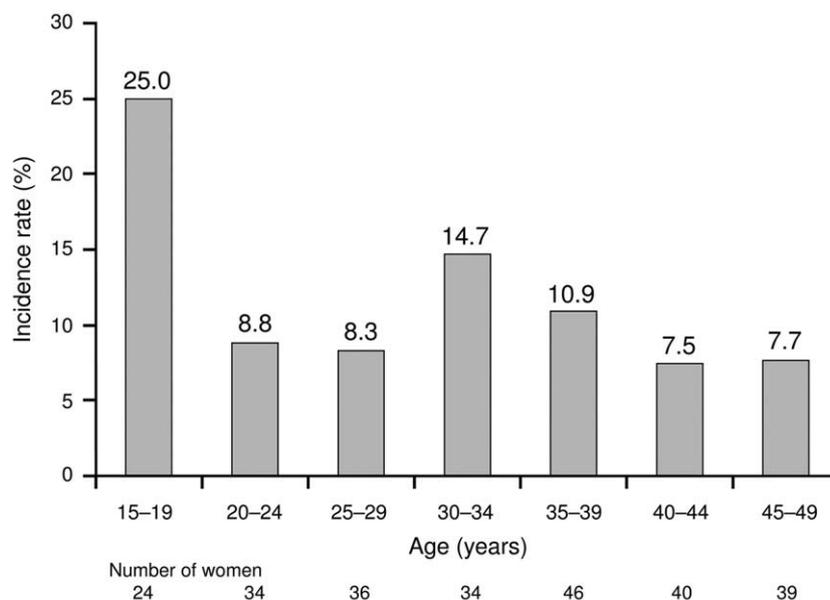

Fig. 2. Age-specific incidence of oncogenic HPV infections in Ontario, Canada [14]. Adapted from Sellors et al. [14].

Table 1
Acquisition and clearance rates by age for human papillomavirus types 16 and 18 over a 3-year follow-up period (1988–1991) in women from Nottingham, UK [29].

Age (years, baseline)	Number of women initially HPV− (1988)[a]		Number of women initially HPV+ (1988)[b]		HPV acquisition in 3 years, % (95% CI)	HPV clearance in 3 years, % (95% CI)[c]
	HPV− at follow-up (1991)	HPV+ at follow-up (1991)[a]	HPV− at follow-up (1991)[b]	HPV+ at follow-up (1991)		
HPV-16						
21	79	3	3	1	3.7 (1.3–10.2)	–
31	94	3	1	0	3.1 (1.1–8.7)	–
41	94	3	3	0	3.1 (1.1–8.7)	–
51	360	11	1	0	3.0 (1.7–5.2)	–
Total	627	20	8	1	3.1 (2.0–4.7)	88.9 (56.5–98.0)
HPV-18						
21	77	2	6	1	2.5 (0.7–8.8)	–
31	89	5	3	1	5.3 (2.3–11.9)	–
41	95	3	2	0	3.1 (1.0–8.6)	–
51	352	14	5	0	3.8 (2.3–6.3)	–
Total	613	24	16	2	3.8 (2.5–5.5)	88.9 (67.1–96.9)

Abbreviations: CI, confidence interval; HPV−, HPV DNA negative; HPV+, HPV DNA positive.
[a] The number of women who were initially HPV− and then HPV+ at follow-up indicates those who acquired an infection.
[b] The number of women who were initially HPV+ and then HPV− at follow-up indicates those who cleared an infection.
[c] Clearance rates not calculated for individual ages because of insufficient numbers.

The risk of developing CIN III and cervical cancer in women over 25

Persistent HPV infections in women over 25

It is clear from accumulated data that sexually active women >25 are still at considerable risk of acquiring HPV – and in particular oncogenic HPV – infections. In addition, a population-based cohort study of 7237 women in Costa Rica has shown that type-specific persistence increases with age [13]. In that study, persistence was defined as a positive result for the same HPV type at both enrolment and follow-up; the mean interval was 5.6 years (SD, 1.2 years) and median interval 5.1 years (range, 0.5–8.2 years). The trend was particularly strong for HPV-16: 15.2% for women< 25; 25.4% for those 25–34; 26.9% for the 35–44 age group; 41.7% for those 45–64; and 70% for women ≥65. Viral persistence is a necessary step in the development of cervical cancer. Although acquisition rates are higher in younger women, it is the persistence of the infection and the consequent risk of malignant change that gradually becomes more important with age [13]. Whilst it is clear that a proportion of women over 25 with persistent infections may have acquired these infections years earlier, the data suggest that the significant proportion of women still acquiring new infections beyond this age (up to 15%) combined with the increased likelihood of developing a persistent infection, puts these women at significant risk of developing cervical cancer.

Risk of developing CIN III and cervical cancer after HPV infection in women over 25

As shown in a number of studies, the potential for malignant change with oncogenic HPV types, specifically HPV-16 and -18, is at least as important in midadult women as it is in younger women [16,35,36]. In a subgroup of women >= 30 years with negative cytology included in a prospective cohort study of 20,514 women, the 10-year cumulative incidence rate (CIR) of ≥CIN III revealed considerably higher risk in women positive at enrolment for HPV-16 (10-year CIR, 20.7%; 95% CI 8.6–32.8) or HPV-18 (10-year CIR, 17.7%; 95% CI 0.0–36.0) compared with women positive for non-HPV-16/18 oncogenic types (10-year CIR, 1.5%; 95% CI 0.3–2.7) and high-risk HPV negative women (10-year CIR, 0.5%; 95% CI 0.3–0.7) (Fig. 3) [16]. The stratification by age (<30 years versus ≥30 years) demonstrated similar high risks associated with HPV-16 and -18 in both younger and older women.

In another 10-year study in women who were positive for oncogenic HPV as measured by the Hybrid Capture 2 test but with normal cytology at baseline, Kjaer et al. [35] showed that the incidence of ≥CIN III was 13.6% and 21.2% for those aged 20–32 and 40–50 years, respectively. Similarly, progression to severe dysplasia or worse was also higher in the older group (64%) than in the younger group (49%). These data are important in that they demonstrate not only that progression from HPV infection to severe dysplasia occurs in older women but also that it is even more likely to occur in older than in younger women.

It is interesting to note that in some studies, in the same way that the peak of oncogenic HPV infection in young women precedes the major peak in cervical cancer cases by approximately 10 years, the number of cervical cancer cases begins to rise again in older age (≥60 years of age), approximately 10 years after the second peak in oncogenic HPV prevalence observed in midadult women [37].

Why are women over 25 still at risk for developing cervical cancer from a newly acquired HPV infection?

When examining the risk of sexually active women acquiring oncogenic HPV infections and further development towards cervical cancer, the following diverse contributory, but relatively unquantifiable factors make it very difficult to identify a subgroup of women that would be at higher risk of acquiring an HPV infection.

Sexual behaviour of women and their partners

The sexual behaviour of both women and their partners is a major determinant of women's risk of developing cervical cancer. Several studies have demonstrated a strong association between lifetime number of sexual partners and genital HPV acquisition [38,39]. The acquisition of new sexual partners continues throughout all age groups [11,40,41]. In addition, studies have shown consistently that the risk of cervical cancer can be predicted as much by a woman's own sexual behaviour as by the sexual behaviour of her husband/partner [38,42–44]. The presence of HPV DNA in the penis and urethra of her sexual partner(s) is directly related to her HPV carrier status and therefore her risk of developing cervical cancer [38,42,44].

Fig. 4 shows a reanalysis of age-specific penile and cervical HPV prevalence in couples enrolled in the control arm of the International Agency for Research on Cancer (IARC) case–control studies conducted in Spain, Colombia, Brazil, Thailand, and the Philippines [45,46]. Control women were frequency-matched to the women with cervical
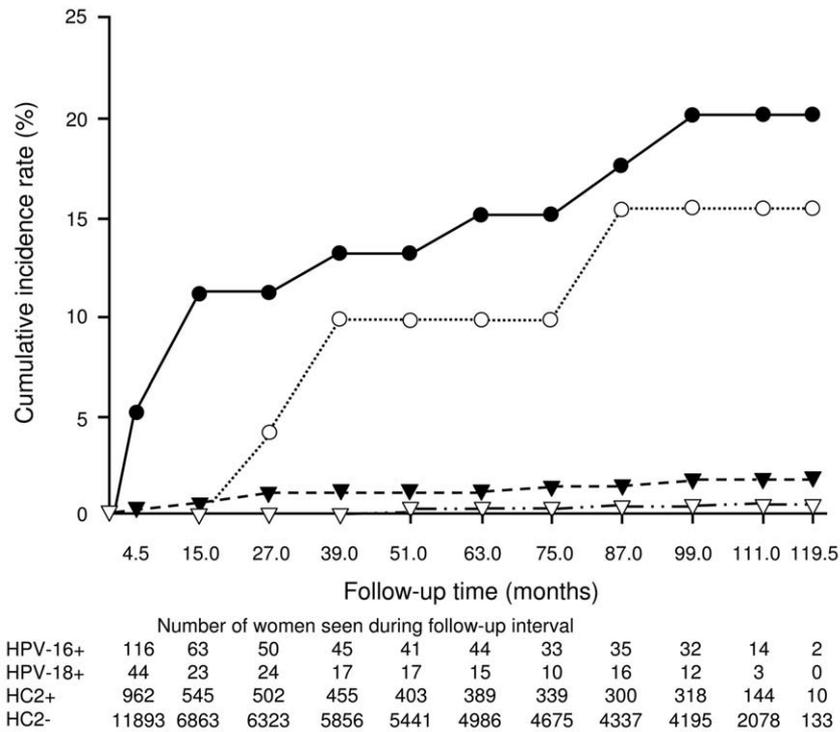
Fig. 3. Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (≥CINIII) over a 10-year period in 13,229 women 30 years and older from Portland, USA, according to oncogenic human papillomavirus (HPV) status at enrolment. (Study recruitment was conducted between April 1, 1989 and November 2, 1990 and follow-up carried out for up to 10 years thereafter). Adapted from Khan et al. [16]. HPV status is defined hierarchically as positive for HPV-16 (closed circles), positive for HPV-18 (open circles), positive for the non-HPV-16/18 oncogenic types in Hybrid Capture 2 (HC2) (closed triangles), or oncogenic HPV negative (open triangles).

cancer according to age. Men who were eligible for the analysis were the husbands or stable partners of the control women. Of the 1471 partners of control women, 533 yielded a valid result. Cervical HPV prevalence increases from 7.2% in young women to a plateau around 9–10% between 30 and 59 years of age, peaking up to almost 18% above the age of 60. For penile HPV prevalence, there is a clear peak in the young men below 30, followed by a steep decrease in the 30s, but increasing steadily thereafter until 60. This increasing prevalence of

penile HPV could explain why women at an older age are still exposed to HPV.

Lack of detectable oncogenic HPV-specific antibodies following natural infection

Cell-mediated immune mechanisms have been linked with clearance of existing HPV infections whilst antibody responses are
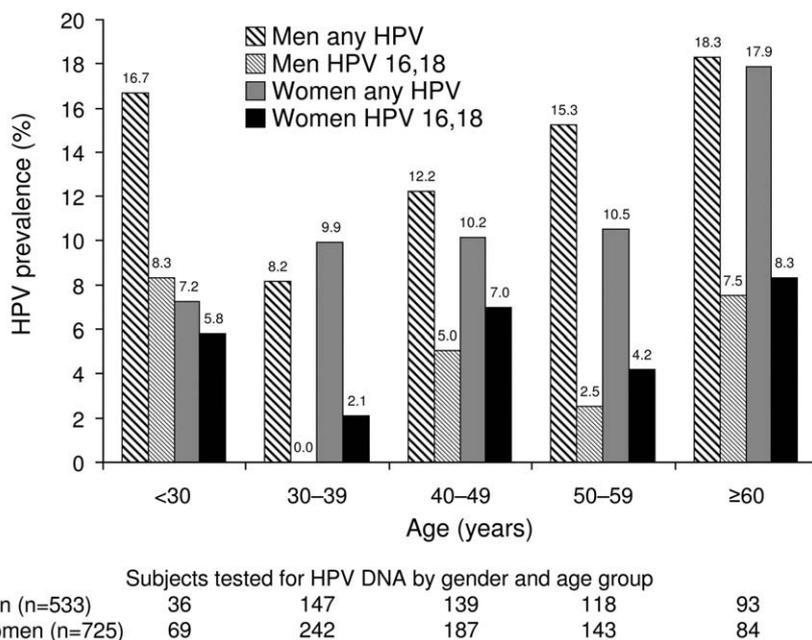
Fig. 4. Age-specific cervical and penile HPV DNA prevalence in couples participating as control subjects in a series of case-control studies of cervical cancer in Spain, Colombia, Brazil, Thailand, and the Philippines. (Data presented is from a reanalysis of data from studies reported by Castellsagué et al. [79], Franceschi et al. [45] and Munoz et al. [46].)

thought to play an important role in protection from HPV infection. However, anti-HPV antibodies are only detected in approximately 50% of women who are naturally infected with HPV [47]. When women develop antibodies following natural infection, the levels, even at peak, are generally very low [48]. Baseline data from women included in the HPV vaccine trials indicate that in a general population of sexually active women the proportion with detectable antibody levels is low [34]. In a Phase III trial with the quadrivalent vaccine in women aged 24–45, only a small percentage of study participants (0.4% and 0.3% of the vaccine and control groups, respectively) had serologic or HPV DNA evidence of infection with all the types covered by the vaccine at baseline [27].

Antibodies induced by natural infections are not always protective

Women who have had a previous infection and developed detectable antibody levels may still be at risk of subsequent infections. A population-based cohort study with 7046 women in Costa Rica concluded that serum antibodies to HPV-16, -18 or -31 elicited by natural infection were not associated with significant immune protection against re-infection with homologous HPV types or the two other heterologous types. Seropositive women had the same risk of subsequent HPV infection as seronegative women after 5–7 years [48]. Data from the placebo group of a phase III efficacy study involving the quadrivalent vaccine show that women who are seropositive but HPV DNA negative at study entry, may still develop cervical lesions [27]. Another study found that the risk of acquiring a new HPV type was not decreased among those with prior infection by a phylogenetically related or unrelated type [49].

Whilst neutralizing antibodies are thought to play a key role in protection from HPV infection following vaccination, other components of the immune system are also likely to be involved, such as cell-mediated immune responses, which are thought to be required for the clearance of established HPV infections and associated lesions [50].

Immunosenescence and increased HPV persistence with age

Aging is associated with a decline in the generation of new naive T and B lymphocytes and in the functional competence of memory lymphocyte populations [51]. This decline in immune function leads to a decreased capacity of the innate and adaptive immune system to respond to both new and previously encountered infections with a consequent increase in the frequency and severity of infectious diseases and an increased incidence of cancer. These phenomena are collectively known as immunosenescence [51,52]. Whilst the consequences of immunosenescence are most severe in the elderly, there is a gradual decline in immune function starting at puberty and lasting throughout life [53]. This pattern of declining immune response with age has been observed following vaccination with both the HPV-16/18. AS04-adjuvanted cervical cancer vaccine and the quadrivalent vaccine although antibody titers still remain several-fold above those following natural infection [54,55]. It may also explain the association of age with an increase in the proportion of persistent oncogenic HPV infections, which ranged from 25% to 70% for HPV-16 persistent infections in women aged 25 to ≥65, respectively [13,56,57].

HPV vaccination: clinical trial results

In women aged 15–25 years, the AS04-adjuvanted HPV-16/18 vaccine was highly immunogenic and conferred 100% protection against HPV-16 and -18 persistent infections and associated cervical lesions for up to 7.3 years [58]. The levels of both total IgG and neutralizing antibodies induced by the HPV-16/18 AS04-adjuvanted vaccine are several-fold higher than those induced by natural infection [54,58]. In an immunobridging study the immune responses to this vaccine in 26- to 55-year-old women (grouped as 26–45 and 46–55 years) were

compared to those of women 15–25 years of age, up to 24 months after vaccination [26]. All women seroconverted for both HPV-16 and -18 antibodies. Geometric mean antibody titers decreased with age, but in the oldest group these remained at least eight times higher after 24 months, than those observed in a control group of women who had cleared a natural infection [26]. The vaccine was generally safe in all age groups. The incidence of symptoms at the injection site tended to be lower in the 46–55 age group compared to the 26–45 age group. Based on these immunobridging data, efficacy can be inferred in this population. In fact, immunobridging data have been accepted by authorities worldwide as the basis for licensing the HPV-16/18 AS04-adjuvanted vaccine for use in older age groups in approximately 50 countries.

The results of a Phase III safety, immunogenicity and efficacy study involving the quadrivalent vaccine in women aged 24–45 years were recently reported [55]. The quadrivalent vaccine demonstrated an efficacy of 83% against infection or disease related to HPV-16 or -18 in the per protocol population. In women who were naive to the relevant vaccine type, vaccine efficacy against HPV-16 or -18 related infection or disease was 72%. Efficacy studies involving vaccination of 16–26-year-olds with the quadrivalent vaccine showed 98% protection against development of HPV-16 and -18 related CIN II/III or adenocarcinoma in situ in the per protocol population [59]. Recent reporting on the final analysis of a large Phase III trial (PATRICIA) of the AS04-adjuvanted vaccine also demonstrated 98% efficacy for this endpoint in a comparable cohort of women aged 15–25 years [60].

As well as evaluating efficacy in women assumed to be naive to the vaccine types, clinical trials have assessed endpoints in intent-to-treat populations, which include women with existing infection and abnormal pap tests at baseline. As expected, efficacy is lower in these populations as the current HPV vaccines have no known therapeutic effects, only prophylactic effects. As many women clear infections, vaccination of these populations could appear more beneficial over the long term as vaccinated women who have cleared an infection could potentially be protected against subsequent infections. Analysis of quadrivalent vaccine efficacy in women with a current or past infection with the vaccine HPV types demonstrated that women positive for one type still benefited from protection against the other types. Women who were HPV seropositive and DNA negative, indicating that they had cleared an HPV infection, gained complete protection [61]. The findings are similar for the HPV-16/18 AS04-adjuvanted vaccine; complete protection was achieved in HPV DNA-negative women regardless of serostatus [62]. There was however little benefit in protection for women infected with a vaccine HPV type at baseline (i.e., HPV DNA positive) whether or not they were vaccine type seropositive [27].

Discussion

Through our review of the literature, particularly those data on HPV incidence and prevalence, sexual behaviour and HPV transmission, the absence of guaranteed immunity after natural infection and a general decline of immune function with age, we conclude that sexually active women, including those over 25, are still at risk of acquiring a new HPV infection that may evolve towards cervical cancer; studies have also shown that progression from HPV infection to severe dysplasia or worse takes place in older women, and it is likely to occur more quickly. Several studies in different regions of the world show consistently that the mean acquisition rate for all oncogenic HPV types is around 5% per year in these women and may be as high as 15% in some populations. Although the sexual behaviour of a woman and her partner is an important risk factor, risk assessment for HPV infections based on this is, in practice, unreliable.

It remains unclear whether new acquisition or reactivation of a latent infection is responsible for the higher detection rates observed in older women. It has been proposed that what we call incident infections at higher ages may be due to new infections as well as

reactivation of latent persistent infections [12,63]; however, there is little direct evidence to substantiate this theory [12]. The theory stems from the observation that the spontaneous regression of warts may not necessarily result in complete viral clearance, as viral genomes can be detected in apparently normal epithelium many months and years after wart regression [64]. The concept of latency of HPV is controversial and it is unclear whether a prophylactic vaccine can be efficacious in preventing reactivation of latent infection. Sterilizing immunity cannot be expected from a prophylactic HPV vaccine that is solely based on the L1 capsid protein. By contrast, neutralizing antibodies induced by the vaccine could limit intraepithelial reinfection, thereby preventing viral spread. Ongoing studies looking at the efficacy of the HPV vaccines in women up to the age of 55 should give definitive answers to these questions.

Vaccine clinical trials until now have shown that vaccination with the AS04-adjuvanted HPV-16 and -18 vaccine up to the age of 55 is safe and immunogenic, whilst immunobridging data have provided the basis for licensing of the HPV-16/18 AS04-adjuvanted vaccine in this age group in several countries worldwide. A trial comparing the immunogenicity of the AS04-adjuvanted vaccine and the quadrivalent vaccine in women aged 18–45 years found that the AS04-adjuvanted vaccine induced superior HPV-16 and -18 specific neutralizing antibody and B-memory cell responses at Month 7. Although the clinical significance of this difference is unknown today, they may represent determinants of differences in duration and cross protection for both vaccines [65]. Indeed, the PATRICIA trial, which included more than 18,000 women between 15 and 25 years of age, showed that the AS04-adjuvanted vaccine provided significant protection against the most common nonvaccine oncogenic types, HPV-31, -33 and -45 [60]. Protection beyond the HPV types included in the vaccine may contribute considerably to the overall protection offered. In fact, in the total vaccinated cohort, efficacy against any CIN II/III irrespective of HPV type was 30.4%. The cross protection could prevent an additional 11–16% of cervical cancer cases compared with a vaccine that is effective against only HPV-16/18 [60].

Interim efficacy results with the quadrivalent vaccine show good levels of protection in midadult women (24–45 years of age) against vaccine HPV types. Women 15–26 years of age were protected irrespective of their previous history of natural infection, provided they did not carry a current HPV-16 or -18 infection, identified through HPV DNA testing. However, the data available to date in this subpopulation of HPV-16/18 DNA-positive women are insufficient. So far no risk has been shown when vaccinating HPV-infected women including those over 25 years of age. Ongoing studies with the HPV vaccines in women of all ages will continue to provide more data to confirm this. It is, however, theoretically possible that vaccination of infected women may have an impact on the risk of HPV infection in their partners by reducing the transmission and infectivity potential.

Even though HPV-16 and -18 DNA type-specific testing is now commercially available, screening of all women for the presence of HPV-16 or -18 DNA prior to vaccination would lead to the identification of only a very small number of HPV-16 and -18 positive patients who would not benefit from vaccination and may therefore be a very costly and time-consuming exercise. Even if a woman is positive for one HPV vaccine type, she still has the potential to benefit from vaccination with another vaccine type with which she is not currently infected. Therefore the only women who may not benefit at all are those with current infections with all vaccine types. The prevalence of double infections with HPV-16 and HPV-18 in middle-aged women is consistently lower than 1% worldwide [8,33] indicating that the majority of women have the potential to benefit from vaccination. Additionally, most HPV infections are cleared by the immune system; therefore, currently infected women may also benefit from protection against future infection or reinfection. Also, a positive DNA test for oncogenic HPV should not constitute a contraindication for vaccination according to current knowledge on

safety. On the other hand, in women of any age who are vaccinated, a negative test for the 14 oncogenic HPV types has an extremely high negative predictive value for the subsequent development of precancerous lesions [66]. Thus, current screening intervals could be increased to 5 years or more in these women. Conversely, women who are being vaccinated but found to be infected with oncogenic HPV types may have to be screened at more regular intervals [66].

The critical consideration, however, is that, in all women, regardless of previous exposure or current infection with oncogenic HPV, cervical screening is still required. Current vaccines will not protect against all oncogenic HPV types, and women could still develop precancerous lesions due to other high-risk types not included in a vaccine. It is therefore important that women receive appropriate education and advice in order to understand the combined benefits of vaccination and screening. Further screening should also guarantee that, if a woman was already infected with HPV-16 or -18 prior to vaccination, detection of possible precancerous lesions that may develop from this infection will be achieved in time and appropriate treatment can be initiated. Modelling studies predict that combining vaccination with screening will be the most effective way to reduce the lifetime risk of cervical cancer [67]. Furthermore, there is a growing body of evidence that indicates screening of vaccinated women should include less frequent screening rounds (i.e., every 5+ years) and use HPV tests as the sole primary screening technique with cytology reserved for triage of HPV-positive women [68,69].

In this review, we have considered the need for HPV vaccination in women aged over 25 years, i.e., beyond the maximum age range for current mass vaccination and catch-up programmes. However to date, few countries have implemented catch-up programmes beyond the age of 18 worldwide despite the fact that vaccine efficacy approaches 100% in large Phase III trials spanning the 15–25-year-old age group. The benefits of vaccinating 18–25-year-olds was the subject of a recent review [70]. The authors concluded that the number of women who will have no benefit from vaccination in this age group is likely to be very small, and in light of the Australian cost-effectiveness analysis study which supported a publicly funded programme of vaccination of women aged 18–26 years [71], further consideration should be given for funded programmes specifically for this age group.

Public health recommendations for mass vaccination must also take into consideration the cost-effectiveness of vaccination programmes; limitations on resources force governments to prioritise which age groups to vaccinate. Modelling studies have shown that vaccination becomes less cost-effective with the increasing age of the target group for vaccination [72-74]. Therefore the priority of all public health recommendations to date has been to target girls and young women for routine vaccination, with catch-up programmes that extend to age 25/26 when resources allow. Since the cost–benefits become progressively less favourable with age, health authorities and governments cannot advocate the mass vaccination of older women. Nevertheless, sexually active women over the age of 25 also have the potential to benefit from vaccination and should be allowed the opportunity to choose to be vaccinated on an individual basis.

Currently, there is a need for healthcare providers to manage expectations appropriately, to ensure women who ask to be vaccinated clearly understand what to expect and do not harbour false expectations in relation to HPV vaccination. Women need to be made aware of the degree of individual benefit they are likely to receive, in particular that the vaccines provide no therapeutic benefit with respect to current infection or disease. Crucially, women and health care professionals need to understand that cervical screening must be continued even if women are vaccinated.

Future HPV vaccines may address the current vaccine limitations. Several polyvalent HPV vaccines are currently in development, including ones based on fragments of the L2 capsid protein [75] and on chimeric L1–L2 fusion proteins [76,77]. Preclinical animal studies have shown promising results, with one formulation shown to induce

antibody responses to up to 22 different HPV types. Development of a vaccine that protects against all oncogenic HPV types would have profound effects worldwide and would undoubtedly change present screening strategies. One proposed screening algorithm is for sexually active women to undergo a single initial screening step; those found to have normal cytology and who are HPV negative could receive a polyvalent HPV vaccine and not require any further screening [78]. Such broad spectrum vaccines would therefore be more cost-effective, enabling women over 25 years of age to be included in national immunization programmes.

Conclusions

While current guidelines and recommendations consistently advise on vaccinating young girls before their sexual debut, natural history studies indicate that all sexually active women are at risk of new oncogenic HPV infections and of development of cervical lesions and cancer throughout their lives. The reviewed data suggest that most sexually active women have the potential to benefit from HPV vaccination, with the exception of those with current infections with both oncogenic HPV vaccine types. Women of all ages should be able to make a well-informed decision when considering HPV vaccination. Current vaccines are generally safe and well tolerated and immunogenicity and interim efficacy data have indicated that they are potentially beneficial in the vast majority of women. With the increasing availability of the HPV vaccines to women over 25 years of age globally, it is particularly important that clear guidelines for HPV vaccination of women of this age should be developed for healthcare professionals, and educational materials should be made available for women emphasizing the benefits of vaccination combined with continued screening.

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