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Review Article

HPV vaccines – A review of the first decade

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HIGHLIGHTS

- Do not use Gardasil9 as a booster vaccine for those already vaccinated.
- Gardasil9 and Cervarix are equivalent in efficacy against CIN 2+ regardless of HPV type.
- Only two doses of HPV vaccine for 9–15 year olds at 6 month or 1 year intervals.
- Cervarix has 91% efficacy in women older than 25 years lasting for at least 7 years.
- HPV vaccines reduce abnormal screening tests, colposcopies and excisions.

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ABSTRACT

Pre-adolescent girls (9–15 years) have the option of receiving a two dose HPV vaccine series at either a six month or one year interval to provide protection from HPV 16, the most prevalent type associated with cervical cancers, as well as several other less prevalent types. This series of vaccinations is highly likely to protect her from HPV infection until she enters the routine screening program, whether that be primary HPV testing or a combination of HPV testing and cytology. The two dose program has been recommended by the World Health Organization (WHO) since 2015. For women 15 years and older, the three dose vaccine schedule is still recommended.

The past ten years of Gardasil use has provided evidence of reduced HPV 16/18 infections in countries where there has been high coverage. Gardasil9 has replaced Gardasil. Gardasil9 has the same rapid anti-HPV 18 and HPV45 titer loss as Gardasil did. Cervarix remains equivalent to Gardasil9 in the prevention of HPV infections and precancers of any HPV type; Cervarix also has demonstrated sustained high antibody titers for at least 10 years.

One dose of Cervarix provides protection against HPV 16/18 infection with robust antibody titers well above natural infection titers. This may offer the easiest and most cost effective vaccination program over time, especially in low and lower middle income countries. Cervical cancer screening must continue to control cancer incidence over the upcoming decades.

Future studies of prophylactic HPV vaccines, as defined by the WHO, must demonstrate protection against six month type specific persistent infections, not actual cervical cancer precursor disease endpoints, such as cervical intraepithelial neoplasia grade 3 (CIN 3) or adenocarcinoma in situ (AIS). This simplifies and makes less expensive future comparative studies between existing and new generic vaccines.

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1. Introduction

Human papillomavirus (HPV) associated cancers include those of the cervix, vulva, vagina, penis, anus, rectum and oropharynx [1]. Because over 80% of all HPV associated cancers occur in the cervix, nearly all of the evidence for prophylactic vaccine prevention of incident type-specific HPV infection is in cervical disease [2]. The first vaccine to be approved, Gardasil, has been replaced by Gardasil9 whose overall prevention of CIN 3 disease is non-inferior to that of the competing cervical cancer HPV vaccine, Cervarix [3,4]. We discuss all three vaccines relative to their cancer prevention potential in this review.

2. Vaccine composition

All three vaccines contain synthetically manufactured virus like particles (VLPs) of the L1 epitope. Table 1 presents the differing vaccine components. Gardasil9 contains more than twice the antigenic load and more than twice the aluminum load of Gardasil; Gardasil9 has increased concentrations of L1 virus like particles (VLPs) for HPV 16 and 18 in order to induce antibody responses that are non-inferior to Gardasil [5]. Cervarix has the least antigenic concentration of the three vaccines, and contains an advanced adjuvant for enhanced immunogenicity, AS04 [6]. AS04 mimics a Toll-like receptor 4 agonist providing direct stimulation of antigen presenting cells, pronounced cellular and humoral immune responses, and long lasting antibody responses [7].

Table 1
Vaccine composition of a 0.5 ml dose of HPV vaccine [3,4].

	Gardasil	Gardasil9	Cervarix
Oncogenic protein subunit component L1 VLP, μg			
HPV 16	40	60	20
HPV 18	20	40	20
HPV 31		20	
HPV 33		20	
HPV 45		20	
HPV 52		20	
HPV 58		20	
Verrucous protein subunit component L1 VLP, μg			
HPV 6	20	30	
HPV 11	40	40	
Manufacturing components			
Sodium chloride, mg	9.56	9.56	4.4
L-Histidine, mg	0.78	0.78	
Polysorbate 80, μg	50	50	
Sodium borate, μg	35	35	
Sodium dihydrogen phosphate dihydrate, mg			0.624
Adjuvant			
Amorphous aluminum hydroxyphosphate sulfate, μg	225	500	
3-*O*-Desacyl-4′-monophosphoryl lipid (MPL) A, μg, adsorbed on			50
Aluminum hydroxide salt, μg			500
Expression system			
Recombinant *Saccharomyces cerevisiae*	Yeast	Yeast	
Trichoplusia ni insect cells			Baculovirus

3. Immunogenicity

3.1. Immunogenicity as an endpoint

The World Health Organization (WHO), the National Cancer Institute (NCI), and the International Agency for Research on Cancer (IARC) agreed in 2013 that immunologic non-inferiority was a sufficient endpoint for VLP based HPV vaccine trials for those 16–26 years of age after persistent type-specific infection protection for at least six months was established [8]. For those younger than 16 years, WHO standards indicate that immunobridging studies showing non-inferior antibody titers to those in the 16–26 year old group are the only acceptable endpoint; and, for those older than 26 years, prevention of persistent infection for at least 6 months with vaccine specific HPV types was acceptable for declaring prevention at the cervical, anal and oral anatomical sites. Vulvar/vaginal protection must be proven by actual disease prevention defined as grade 2/3 HPV 16/18 specific intraepithelial neoplasia (VaIN 2+/VIN 2+).

Antibody titers, while the primary recognized endpoint in VLP based HPV vaccine studies, to date do not define a surrogate level of protection against cancer or its precursors. Nevertheless, because there are very limited long term disease based endpoint studies, antibody titers over time are the surrogate used to estimate duration of population protection after vaccination. The titers are highly dependent on the number and timing of vaccine doses. Natural infection titers do not provide protection against same type infection [9] and hence serve as a comparator to long term induced geometric mean titers (GMTs) for inferences about duration of protection against type specific HPV infection. Natural infection titers are higher than the seropositive cut-off values for assay detection.

3.2. Comparison of the immunogenicity of three doses of HPV vaccine

Head to head trials of three doses of Cervarix vs Gardasil in women [10–13] and in 12–15 years old adolescents [14] are complete. Seropositivity for anti-HPV16 titers after 5 years is high for both Cervarix and Gardasil, but the actual induced GMTs measured by pseudovirion based neutralization assay (PBNA) are significantly lower for Gardasil than Cervarix; the decrease in titers might affect the long term duration of protection. Gardasil has significantly lower seropositivity retention and GMTs for anti-HPV18 titers than Cervarix. Cervarix also exhibited significantly greater serum binding antibody responses for both HPV 16/18 than Gardasil [14]. Gardasil9 induces similar anti-HPV16/18 responses as Gardasil. Likewise, Gardasil is inferior compared to Cervarix both in percentage and geometric mean number of $CD4^+$ T cell responders against both HPV16 and 18; as well as the significantly lower geometric mean number of memory B cells for HPV18 at 48 months [14].

Duration of antibody response is critical for clinical prevention of HPV infection. Cervarix has high anti-HPV16 and HPV18 antibody titers for at least 9.4 years [15] in longitudinal follow-up studies; Gardasil has

plateaued anti-HPV16 titers well above natural infection titers for at least 9 years, but anti-HPV18 titers that are not different from natural infection titers as early as 24 months after vaccination [16].

Gardasil9, in three doses, has the same loss of seropositivity and decline in GMTs for HPV18 as Gardasil had [17]. Nearly 20% of Gardasil9 recipients had a loss of detectable anti-HPV18 titers after 24 months. In Gardasil recipients, after 1.5 years over 10% of women had no detectable anti-HPV18 titers, after 3 years over 20% of women lost detectable titers, and after 5 years nearly 35% of women lost detectable titers [18]. Nearly 15% of Gardasil9 recipients had a loss of detectable anti-HPV45 (an alpha 7 phylogenetically related type to HPV 18) titers after 24 months. The loss of antibodies to these two HPV types is significantly greater than the minimal loss seen among Gardasil9 recipients for anti-HPV16 titers, and potentially has implications for duration of protection. The seropositivity and GMTs associated with Gardasil9 for anti-HPV31, 33, 52 and 58 followed the anti-HPV16 decay pattern over 24 months [17]. Dosing intervals change the GMT responses, which is discussed below.

Head to head trials of Cervarix vs. Gardasil9, the new comparison, which also varies the number of doses given, have yet to be started in Tanzania (NCT02834637).

3.3. Third dose as booster dose after a two dose Gardasil series

Canada trialed a two dose, six month interval, Gardasil vaccination series followed by a booster three years after initial vaccination in girls 9–10 years old [19]. The booster was randomized to either Cervarix or Gardasil. Those receiving Cervarix had significantly higher anti-HPV16/18 titers one month post booster dose than those receiving Gardasil.

3.4. Booster doses after a three dose Gardasil series

The pre-adolescent girls vaccinated with three doses of Gardasil have no significant antibodies to other oncogenic HPV types than HPV16/18. With Gardasil9 replacing Gardasil, there is a temptation to re-vaccinate these young girls for the purpose of preventing five more oncogenic HPV types. A randomized trial tested this hypothesis [20] giving three doses of Gardasil9 one to three years after the initial three doses of Gardasil compared to giving three doses of Gardasil9 de novo. GMTs measured at peak (one month after the third dose) showed that among the girls already vaccinated with Gardasil, there was an anamnestic response for HPV 16/18 with titers two to three fold higher than among the girls vaccinated de novo with Gardasil9. Unfortunately, though, the revaccinated girls had significantly lower anti-HPV31/33/45/52/58 titers than among the girls receiving Gardasil9 de novo, with no indication that these low titers would provide HPV type specific infection protection. In addition, while Gardasil was able to induce a small anti-HPV31 response, there was no anamnestic response seen in anti-HPV31 titers when revaccinated with Gardasil9, as there was with HPV 16/18. These results, as well as the cost effectiveness analysis [21] conclusively indicate that Gardasil9 should not be used to revaccinate those already vaccinated with three doses of Gardasil.

3.5. Immunogenicity of fewer than three doses

Cost effectiveness analyses have consistently indicated that if three doses of prophylactic HPV vaccine do not provide protection from type-specific HPV infection for at least 15 years, cervical cancer will only be postponed, not prevented [22]. Compliance with three dose schedules is difficult, however, especially in underserved areas and developing countries. Balancing the opportunity for fewer than three doses with the antibody mediated long term protection is now necessary, as the WHO and the Centers for Disease Control and Prevention (CDC) currently recommend a two dose schedule at six or twelve month intervals for those 9–15 years old [23,24].

Both Cervarix and Gardasil induce the same antibody titers in two doses as in three doses, for their respective vaccine, if the two doses are six months apart. Figs. 1 (Cervarix) and 2 (Gardasil) show anti-HPV16 and HPV18 titers for vaccination schedules of fewer than three doses [25,26]. Fig. 1 is based on women 18–25 years old; Fig. 2 is based on girls 10–18 years old. Females are both seronegative and PCR DNA negative for the vaccine relevant HPV types. While an increased interval between the initial two doses is logistically easier, the immediate antibody titers induced do not necessarily increase above natural infection titers until after the second dose, where natural infection titers are known not to be protective against new infection. A meta-analysis points out that a six month interval, two dose Gardasil scheme results in inferior antibody responses compared to three doses for HPV18 within 18 months; and inferior antibody responses compared to three doses of Cervarix for HPV 16 within 2 years [27]. This may indicate less long term protection with two doses of Gardasil than three; longer term follow-up studies are needed.

Shortening the interval to one month, instead of six for Cervarix induces a lower peak titer, but a plateau level at 48 months that remains substantially above the natural infection titer level, and only slightly below plateaus of three doses and two doses at six month intervals. Similarly a shorter interval of two months for the Gardasil second dose induces a lower peak titer than any other dosing scheme but plateaus to the same GMT at 36 months as three doses of Gardasil [26]. While two doses within 3 months is not formally recommended, the similar plateau GMTS by 36 months indicate that titers are sufficiently above natural infection titers and mirror the plateaus of the longer two dose interval and three dose schedules; the only question becomes the duration for which the short interval two dose antibodies are maintained.

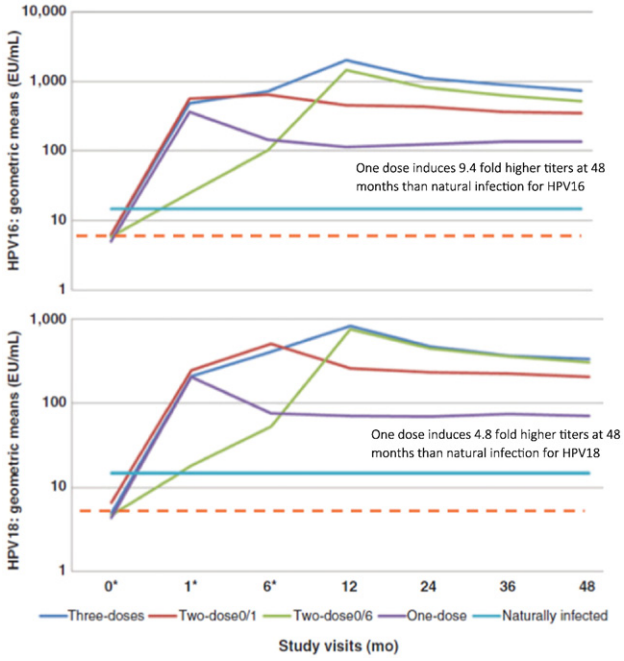

Fig. 1. Anti-HPV16 and anti-HPV18 response following fewer than three doses of Cervarix over 48 months [24]. *Vaccination could occur at month 0, 1, and 6 months. Total vaccinated cohort defined as 7466 women randomized to HPV or hepatitis A vaccine and followed for 4 years; 20% received fewer than 3 doses. Dashed orange line represents the laboratory determined seropositivity cutoff (HPV16 = 8 EU/ml; HPV18 = 7 EU/ml). Solid blue line represent natural infection titers determined from seropositive women at enrollment. HPV16: One dose induces 9.4 fold higher titers at 48 months than natural infection for HPV16. HPV18: One dose induces 4.8 fold higher titers at 48 months than natural infection for HPV18. EU/ml means ELISA unit/milliliter.

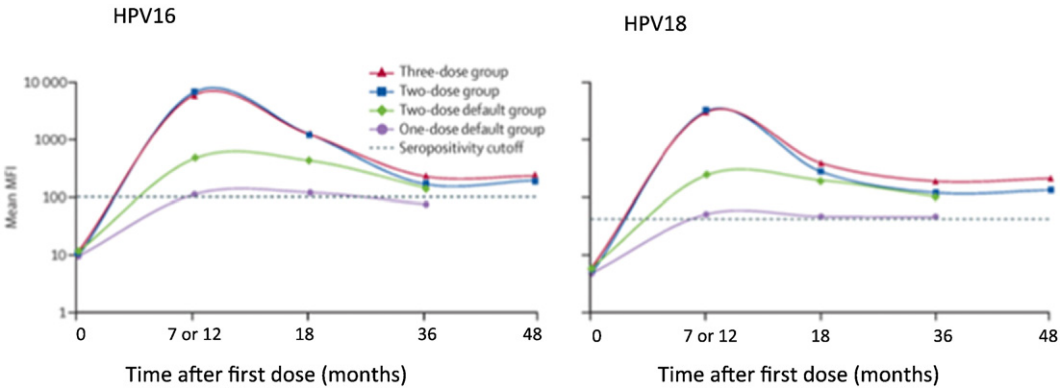

Fig. 2. HPV16 and HPV18 antibody concentration following fewer than three doses of Gardasil over 48 months [25]. MFI means median fluorescence intensity of the Luminex based multiplex serology. Three doses: 0, 2, 6 months. Two doses: 0, 6 months. Two dose default: 0, 2 months. **Natural infection titers have not been established for mean fluorescence intensity units but in general are 2–4 fold higher than the seropositive cutoff**. Seropositivity cutoffs for seroconversion were calculated for each HPV type, based on the MFI values of serum samples obtained from the participants at baseline after allowing for 5% seropositivity in the total baseline samples. The immunogenicity measure was the geometric mean of MFI.

Lengthening the interval to one year after the initial Gardasil dose for girls 11–13 years results in 12 month plateau titers for anti-HPV16 and HPV18 that are equivalent to the plateaus maintained for a three dose Gardasil schedule [28,29]. Administration of two yearly interval doses may increase compliance; a third dose at month 24 may increase longevity of antibody duration. Protection during the vaccination process has not been evaluated.

Single dose schemes have also been investigated. One dose of Cervarix induces significant antibody titers for both HPV16 and 18 that are above natural infection titers by 9 and almost 5 fold, respectively [25]. On the other hand, one dose of Gardasil induces antibody titers that fall below the seropositivity cutoff after 18 months for both HPV 16 and 18 [26]. One dose of Cervarix at a pre-adolescent age combined with a once or twice in a lifetime cervical cancer screening program may be cost effective in resource limited countries.

A head to head trial of two doses at a six month interval of either Cervarix or Gardasil among girls 9–14 years old showed significantly greater GMTs for Cervarix than Gardasil at one year: 1.7 fold higher for anti-HPV16, and 5 fold higher for anti-HPV18 [30]. In addition to two doses of Cervarix inducing higher titers than two doses of Gardasil, two doses of Cervarix also induced significantly higher GMTs than three doses of Gardasil: 1.4 fold higher for anti-HPV16, and 2.8 fold higher for anti-HPV18 [30].

Two doses of Gardasil9 at a six month interval induces peak GMTs that are equivalent to the titers Gardasil induces against both HPV 16 and HPV18 in a two dose six month interval schedule [31]. Gardasil9 induces higher peak GMTs than Gardasil when the two dose interval is 12 months instead of six: 1.8 fold higher for anti-HPV16, and 1.5 fold higher for anti-HPV18. In fact, all seven oncogenic HPV types in Gardasil9 have higher peak GMTs when dosed at a year compared to at six months. Based on Gardasil studies, the peak titers have no relationship to the plateau titers at 36 months and beyond, potentially making the timing of the second Gardasil9 dose at six vs. 12 months irrelevant to final protection, thus, providing latitude in clinical implementation.

3.6. Immunogenicity in women older than 25 years

Both Gardasil [32] and Cervarix [33] were trialed in women 25–45 years old (mid-adult) using three doses. Peak antibody titers for anti-HPV16 among mid-adult Gardasil recipients are non-inferior to those induced in 16–26 year old young women; likewise, four month follow-up plateaus are similar for both age groups. Retention of seropositivity for anti-HPV16 remains above 97% for both mid-adult and younger women over time. By contrast, though, Gardasil induced anti-HPV18 titers in mid-adult women are significantly lower at peak than in younger women and drop to non-protective natural infection titer levels by 24 months. Loss of seropositivity over four years for anti-HPV18 remains problematic regardless of age of Gardasil administration with only 60% of 16–26 year olds retaining seropositivity, and only 48% of mid adult women. There are no trials of Gardasil9 in mid adult aged women.

Cervarix on the other hand, induces at least a 50 fold higher peak titer than natural infection for both anti-HPV16 and HPV18 among women older than 25 years, similar to the response in 16–25 year old women [34]. Plateau titer levels after six years [33] remain non-inferior to the younger women for anti-HPV16 titers in the mid adult women; and, while anti-HPV18 titers are below the plateau of 16–25 year olds by six years in mid adult women, they remain substantially above natural infection titers. All mid adult women retained seropositivity for anti-HPV16 at six years, with 97% retention for anti-HPV18. At 10 years after vaccination, 96% of women expressed anti-HPV16 seropositivity and 84% of women expressed anti-HPV18 seropositivity [35].

4. Efficacy

Efficacy, as defined by prevention of persistent type specific HPV infection, has been reported for those women who are seronegative and PCR DNA negative for each vaccine relevant HPV type [34,36–51]. Other variables within this population include the number of vaccine doses received, baseline cytology, whether women were negative for all 14 oncogenic HPV types at baseline, and whether new cases of infection or disease were counted from the first day of the study or after the third vaccination. The Supplementary Table defines the analytic cohorts to determine efficacy against infection and disease used by the vaccine manufacturers for regulatory approval. All women were 15/16–24/26 years old, with the majority being 18–24 years.

4.1. Efficacy against incident infection and disease

A compilation of all vaccine efficacy reports for WHO defined endpoints of infection and cervical disease for the three vaccines are presented in Table 2 [34,36–51]. The efficacies are reported for the most HPV naïve populations and are reported with 95% confidence intervals. Using prevention against HPV 16/18 infection as endpoints is pertinent to the 70% of cervical cancers which are caused by HPV 16/18; both Gardasil and Cervarix provide excellent prevention against persistent HPV 16/18 infections. Gardasil and Cervarix protection against HPV 16/18 infections lasts at least 5 years and 10 years, respectively. HPV 16/18 infections were not a study endpoint for Gardasil9, though, inferring efficacy only from non-inferior antibody titers.

The disease endpoint of cervical intraepithelial neoplasia grade 2 or worse (CIN 2, CIN 3, adenocarcinoma in situ (AIS), adenocarcinoma and carcinoma, "CIN 2+") caused by any HPV type is prevented equally well

Table 2
Summary table of vaccine efficacies against cervical HPV infection and disease endpoints [34–50].

	Gardasil	Gardasil9	Cervarix
Among women 15/16–26 years			
4–6 months HPV 16/18 infection	96% (83, 100)	na	94% (92, 96)
6 month HPV 31/33/45/52/58 infection	18% (5, 29)	96% (94, 98)	na
6 month HPV 31 infection	46% (15, 66)	96% (91, 98)	77% (69, 83)
6 month HPV 33 infection	NS	99% (95, 100)	45% (25, 60)
6 month HPV 45 infection	NS	97% (92, 99)	74% (58, 84)
6 month HPV 51 infection	na	na	17% (4, 28)
6 month HPV 52 infection	NS	97% (95, 99)	na
6 month HPV 58 infection	NS	95% (91, 97)	na
CIN 2+ related to HPV 16/18	98% (94, 100)	na	98% (88, 100)
CIN 2+ related to HPV 31	70% (32, 88)	100% (40, 100)	88% (68, 96)
CIN 2+ related to HPV 33	NS	100% (33, 100)	68% (40, 84)
CIN 2+ related to HPV 39	NS	na	75% (22, 94)
CIN 2+ related to HPV 45	NS	NS	82% (17, 98)
CIN 2+ related to HPV 51	NS	na	54% (22, 74)
CIN 2+ related to HPV 52	NS	100% (67, 100)	na
CIN 2+ related to HPV 58	NS	NS	na
CIN 2+ caused by any HPV type	**22% (3, 38)**	**63% (35, 79)**	**62% (47, 73)**
CIN 3+ caused by any HPV type	**43% (24, 57)**	**na**	**93% (79, 99)**
AIS caused by any HPV type	na	na	100% (31, 100)
Among women older than 25 years			
6 month infection or disease related to HPV 16/18	85% (68, 94)	na	91% (79, 97)
6 month HPV 31 infection	na	na	66% (25, 86)
6 month HPV 45 infection	na	na	71% (34, 88)

Vaccine efficacies are presented with 95% confidence intervals.
NS means not significant; na means not applicable/available.
Bold signifies the clinically important outcomes.

by both Gardasil9 and Cervarix. Gardasil, on the other hand, has significantly less protection than Cervarix against CIN 2+ from any HPV type. For the CIN 3+ endpoint caused by any HPV type, Cervarix provides 93% protection significantly higher than Gardasil; Gardasil9 has no reported data for this endpoint.

Among women already HPV DNA vaccine type specific positive at the time of vaccination, none of the vaccines induce clearance of the infection or disease [9,45]; these are strictly prophylactic vaccines.

Among women already seropositive for a vaccine relevant HPV type, but HPV DNA negative, at the time of vaccination, both vaccines induce antibody titers and inferred future protection. Gardasil induces an anamnestic response that is higher than peak anti-HPV16 titers induced in an HPV naïve female which remain higher for at least 36 months [52,53]; on the other hand, those seropositive, but DNA negative for HPV18 induced an equivalent antibody response as those who were seronegative [52]. Cervarix induces very high anti-HPV16/18 antibodies that are equivalent for both seropositive and seronegative women at peak and throughout the plateau phase [53]. These results indicate that prophylactic vaccination for future same type infections is possible among women already HPV exposed [9,45].

HPV Faster is a protocol in place in Central and Eastern Europe that proposes to vaccinate women older than 30 years at the same time as undergoing a primary HPV screen with triage and treatment if necessary [54] as a program to accelerate reductions in cervical cancer incidence among those who may already have been HPV exposed [54].

4.2. Prevention against abnormal screening and its sequelae

Table 3 presents the available data calculated from the HPV vaccine trials showing a reduction in the proportion of women with abnormal screening tests, by level of abnormal screen [41,42,46]. The subsequent need for diagnostic colposcopies decreases proportionately to the screening results (e.g. the absolute number of ASCUS HR HPV positive screens is greater than the absolute number of HSIL screens, so the reduction in absolute number of diagnostic colposcopies for ASCUS HR HPV positive screens is higher than the absolute number of diagnostic colposcopies for HSIL screens). The reduction in excisional therapies, though, is significantly greater both in proportion and in importance. The cost reductions in diagnostic and therapeutic procedures enabled by HPV vaccination contribute to their societal value.

4.3. Efficacy against non-cervical endpoints

Non-cervical disease endpoints were planned for regulatory evidence only for Gardasil and Gardasil9. The WHO vaginal/vulvar endpoints are VaIN 2/3 and VIN 2/3 disease for which Gardasil has

Table 3
Prevention of screening abnormalities, diagnostic procedures and treatments due to HPV vaccinations [40,41,45].

	Gardasil	Gardasil9	Cervarix
Abnormal cytology screens			
Atypical Squamous Cells of Undetermined Significance (ASCUS)	22% (9, 36)	na	20% (11, 28)
ASCUS with high risk HPV positive triage		na	29% (19, 38)
Atypical Squamous Cells - cannot rule out High Grade disease (ASC-H)		na	53% (13, 76)
Low Grade Intraepithelial Lesion (LSIL)	17% (9, 24)	na	25% (16, 32)
High Grade Intraepithelial Lesion (HSIL)	45% (4, 69)	na	59% (26, 78)
All abnormal cytology irrespective of HPV type (ASCUS high risk HPV positive+)	17% (10, 24)	44% (29, 56)	27% (21, 33)
Reduction in Colposcopies	20% (12, 27)	na	29% (22, 36)
HPV 31/33/45/52/58 related	na	92% (72, 99)	na
Reduction in cervical excisional therapies	42% (28, 54)	na	70% (58, 79)

na means not available/applicable.

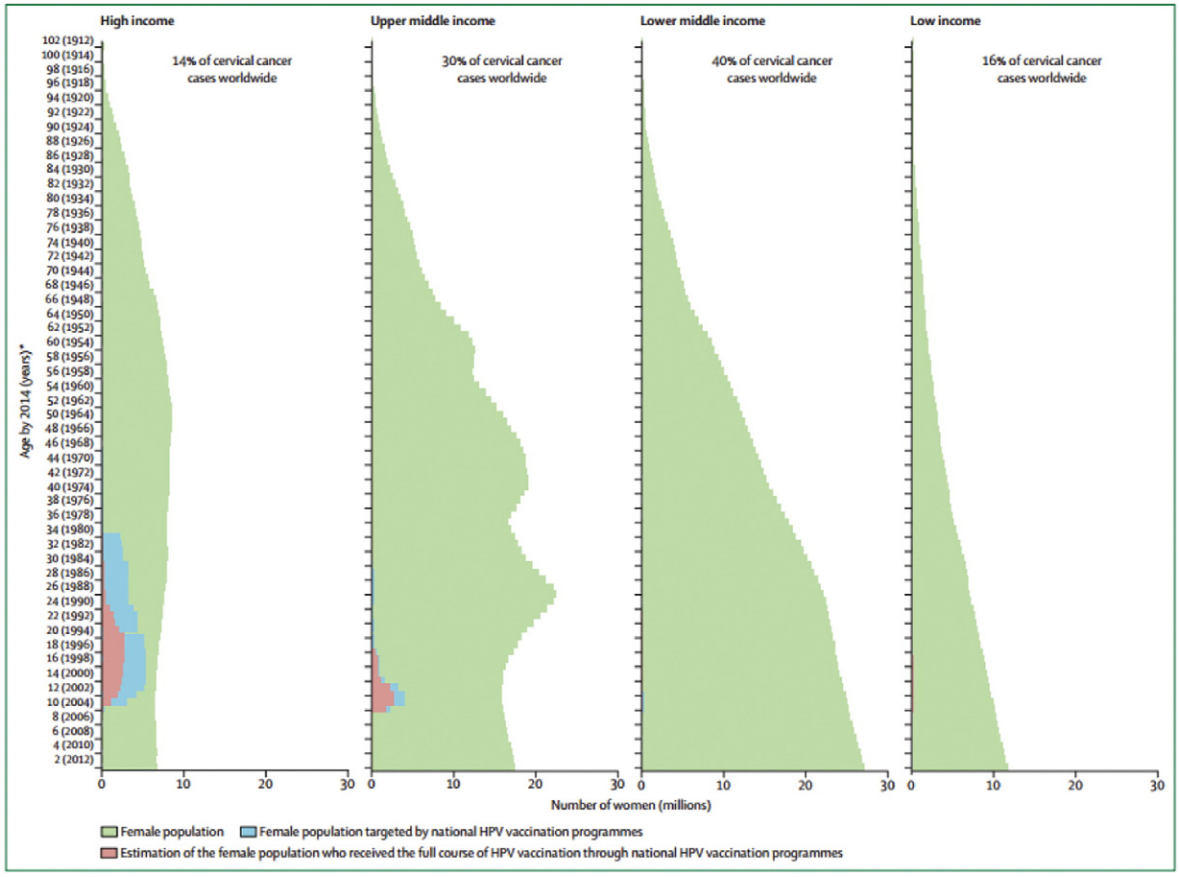

Fig. 3. Proportion of the global female population receiving HPV vaccine by age and income level [58]. Income classification follows World Bank classification of the world's economies based on estimates of gross national income (GNI) per head for the previous year.14 as of July 1, 2014, low-income economies are defined as those with a GNI per head, calculated with the World Bank Atlas method, of US$1045 or less in 2013; middle-income economies are those with a GNI per head of more than $1045 but less than $12,746; high-income economies are those with a GNI per head of $12,746 or more. Lower-middle-income and upper-middle-income economies are separated at a GNI per head of $4125. Low-income and middle-income economies are sometimes erred to as developing economies. Proportion of cervical cancer cases calculated from GLOBOCAN 2012, produced by the International Agency for Research on Cancer.12 HPV = human papillomavirus. *Birth cohorts of women are shown in parentheses.

efficacies in the per protocol population of 100% (95% CI: 50, 100) and 100% (56, 100), respectively, for those related to HPV 16/18 [39]. Gardasil9 does not have any reported efficacies for this endpoint or a VaIN/VIN 2/3 related to HPV 31, 33, 45, 52, 58 endpoint [40]. The intent to treat population analysis shows infinitely broad 95% confidence intervals around the 100% efficacy for HPV 16 VIN 1 (no worse grade outcome was reported) and 95% confidence intervals of 37 to 97 around the 86% efficacy for HPV 16 related VaIN 1; there was no efficacy for HPV 18 related VIN/VaIN 1 [38]. Gardasil and Gardasil9 did not have anal endpoints for women; and did not include oral HPV 16/18 infection endpoints.

While Cervarix studies did not have regulatory trial data for extracervical sites, the NCI Costa Rica Vaccine Trial group investigated prevention of oral, vulvar and anal persistent HPV 16/18 infection four years after vaccination in an intent to treat population [55–57]. The HPV vaccine efficacy against vulvar HPV 16/18 infection was 54% (95% CI: 5, 79) [56], and efficacy against oral HPV 16/18 infection was 93% (95% CI: 63, 100) [55] four years after vaccination. In the full analysis approximating the intent to treat population, the efficacy against anal HPV 16/18 infection was 62% (95% CI: 47, 73) four years after vaccination; and efficacy against anal non-vaccine related HPV 31/33/45 infections was 49% (95% CI: 30, 64) [57]. HPV 16/18 infections often occurred at both the cervix and anal sites, with vaccine efficacy against HPV 16/18 infection regardless of cervix, anal or oral site at four years of 71% (95% CI: 63, 78) [58] in the full cohort. These analyses show that Cervarix is protective against HPV 16/18 infection regardless of the anatomic site of infection.

5. Global reaction to HPV vaccination over the past decade

From June 2006 when the regulatory approval of the first HPV vaccine occurred, through October 2014, 68 countries and 12 territories adopted a HPV vaccine implementation program [59]. Gardasil9 was not approved until December 2014, hence is not included as a vaccine possibility in this historical review. The WHO two dose schedule was not recommended until late 2014, and is also not reflected in this historic review.

Nine high income countries have continued follow-up of the female three dose HPV vaccine series: USA, Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada, and Germany. Seven years of follow-up, 2007–2014, shows a population–level impact after female vaccination when population vaccine coverage rates exceed 50% [60]. The incidence of HPV 16/18 infections decreased by 64% after HPV vaccination program initiation in girls younger than 20 years. The decrease in HPV 16/18 incidence was proportional to the population three dose vaccine coverage rate: the higher the coverage rate, the higher the decrease in HPV16/18 incidence. In addition, the incidence of HPV 31, 33 and 45 decreased by 28% in the same cohort of girls indicating population evidence of cross protection that was seen in the Cervarix trials. In women 20–24 years old, the incidence of HPV 16/18 decreased by 31% over the same time frame, and was also proportional to the vaccine coverage rate achieved by the catch up vaccination programs in each of the countries (e.g. the greater the proportion of 20–24 year olds who received three HPV doses, the greater the decrease in HPV 16/18). There was a small increase in the non-vaccine high-risk HPV types (RR =

1.09, 95% CI: 0.98–1.22) among the population with the lowest uptake of HPV vaccine among the 20–24 year olds, but no increase among populations with high coverage. Only one study documented a 21% decrease in CIN 2+ lesions seven years after girls 15–19 years old received three doses of HPV vaccine [61].

While these targeted successes in high income countries are locally hopeful for cervical cancer incidence reduction, a global perspective is not as positive. During this seven year timeframe, 118 million women ages 9–45 years were **targeted** for HPV vaccination through "primary targets" aged 9–15 years and as "catch up targets" (either opportunistically or organized programs) from 15 to 45 years. These 118 million women represent a very small percentage of the at risk population for cervical cancer: 3.5% of all females globally, 8.7% of those 15–26 years old and 12% of those 10–14 years old. Of the targeted population, 47 million received the full three dose vaccination series: this represents only 1.4% of the global female population and 6.1% of all 10–20 year old females. An additional 12 million received fewer than three doses of vaccine bringing the global vaccinated female population to 1.7%; of the 118 million targeted population, the proportion receiving at least dose reached 50%.

Dividing the world into four economic strata and overlaying each stratum's population by birth cohort provides the basis of understanding how little HPV vaccination efforts to date have made towards reducing cervical cancer incidence. Fig. 3 displays the proportion of cervical cancer burden worldwide in each of four economic strata; it shows the small targeted population for HPV vaccine campaigns against the current population; and shows where HPV vaccination has been accomplished. The highest global cervical cancer burden occurs in the lower middle income stratum at 40%, where there is no evidence of targeted HPV vaccination. The upper middle income stratum holds 30% of the global cervical cancer burden with 7.2% of its 10–20 year old female population fully three-dose vaccinated. While the high income strata have 34% of the targeted population fully vaccinated, only 14% of cervical cancers worldwide occur in these women who have a screening option.

Global reductions in cervical cancer incidence are imputed from this review over a 65 year time frame. The comparatively small 118 million targeted population for vaccination is the basis for the imputations; all calculations for cervical cancers averted assumed life time protection after three doses of vaccine and no access to screening programs. This work indicates that 444, 627 cervical cancers will have been averted by vaccination, 15% were assumed to have had only one vaccine dose. While this is positive, 675,571 cervical cancers will still occur globally.

Sensitivity analyses of the imputed data show that even as the high income countries drive their vaccination rates to 100% coverage, the impact on averted cancers is negligible because of the relatively small contribution to the global incident rate of cervical cancers therein. The emphasis on cervical cancer prevention must be in the upper and lower middle income strata with both vaccination and screening programs adapted to once in a lifetime.

6. HPV vaccination changes subsequent screening patterns

Pertinent to the reduction in cervical cancer incidence is quality of the screening programs available in the high income and upper middle income countries. Without continued participation in these screening programs, the incidence of cervical cancer will increase [62]. Early studies report on the effect of HPV vaccination campaigns on continued uptake in the cervical cancer screening programs.

In the US, a study of high risk, low income women showed that those who received, at any age, one dose of HPV vaccine were most likely to participate in screening at 21 years or older, significantly more than those receiving two, three or no doses [63]. Most often the women participated in an initial screening within 15 days of their vaccination. Long term, though, *continued* screening compliance occurred significantly more often among those receiving three doses of vaccine; these highly compliant women were significantly more likely to participate in every 3 year screening over 7 years than those receiving fewer than three or no doses [63]. Nevertheless, participation in screening was dependent on the age at which women received vaccination. Women who were fully three dose vaccinated at or older than 21 years had a significantly higher initial screening rate than women fully three dose vaccinated younger than 21 years: 84% vs 24% [64]. This low rate of initiating cervical cancer screening among the targeted age for vaccination should cause alarms for cancer control officers.

Insurance status is a significant predictor for participation in US cervical cancer screening programs. The result, opposite to that seen in the high risk population, was seen among privately insured women; those who were vaccinated at or older than 19 years and received three HPV vaccine doses were significantly more likely to present for an initial screening within the next 3 years [65]; unfortunately, the study did not follow for continuity screening. This study exhibits the behavior where the 'worried well' continue to consume more health resources despite being at the lowest risk of disease: those receiving three doses of vaccine were also those most likely to be screened.

In Australia, the reverse happened. Women were vaccinated in the nationally funded targeted age and catch up HPV vaccination programs and aged into the Australian screening program. Their participation in cervical cancer screening was significantly lower among vaccinated women in both the 20–24 and 25–29 year old age groups compared to same aged unvaccinated women [66]. In addition, among women 30–34 years old who electively received HPV vaccination, only 28% participated in screening, whereas 61% of unvaccinated 30–34 year olds participated in screening [66].

In the United Kingdom, the Scottish Cervical Call and Recall system showed a general downward trend for screening participation by women born between 1988 and 1993 [67]. Participating in HPV vaccination abated the downward trend to some degree, as women who received three doses were more likely to screen than those with fewer than three or no doses of vaccine; but the downward trend still existed among those vaccinated as well. Fully vaccinated with three doses compared to unvaccinated was a stronger predictor than economic status for screening participation. Among the highest economic class of women, the unvaccinated had the lowest screening rate of 40% compared to 54% among those receiving three doses (with a little over 47% participating in screening after one or two doses). The screening rates among the most deprived Scottish women were 44% if they were not vaccinated or had one dose, 48% if two doses were received and 53% if three doses were received. Overall, the uptake of screening after the HPV vaccine introduction regardless of vaccine uptake has been lower than necessary to reduce population incidence of cervical cancer. This should be concerning to public health.

In Wales, participation in screening after the catch up program of HPV vaccination was followed from national databases. Women who were not vaccinated compared to fully vaccinated were significantly less likely to attend screening (39% vs. 55%), as were women who were most economically deprived vs least deprived (41% vs. 50%) [68]. While vaccination appears to be associated with higher screening rates than unvaccinated women, the rate of screening is still very low reaching only around half of the women.

Women in the Swedish population based health register were followed for participation in both screening and opportunistic HPV vaccination offered to those 19 years and older. The cervical cancer screening rates were similar to those seen in the US, at 86%, in fully vaccinated women, which is significantly higher than in unvaccinated women (75%) [69]. Likewise similar to the US population [63], the fully vaccinated women returned for the second round of screening significantly more often than the unvaccinated women.

7. Conclusions

Prophylactic HPV vaccines are commercially available and part of many high income nations' immunization budgets. While Cervarix remains the

most cost effective vaccine with proven efficacy in one dose, the WHO recommends two doses for either Gardasil9 or Cervarix for those up to 15 years of age, and three doses for women 15 years or older. The WHO recommendations are based on induced antibody titers at month 7 for Gardasil and Gardasil9 as there are currently no efficacy data for these vaccines in fewer than three doses. The WHO recommendations for Cervarix are based on efficacy data in addition to immunogenicity data.

Three dose efficacy preventing CIN 2 or worse by any HPV type is about 62% for both Cervarix and Gardsail9; the three dose efficacy preventing CIN 3 or worse by any HPV type is 93% for Cervarix and 43% for Gardasil, with no data for Gardasil9. All three vaccines lead to reduced numbers of colposcopies and excisional cervical therapies. Head to head trials indicate that Cervarix has superior immunogenicity compared to Gardasil for T-cell and B-cell functions for both HPV 16 and 18; there are no data for Gardasil9's comparable immunogenicity. The immunogenicity data for HPV 18/45 induced by Gardasil and Gardasil9 indicates that long term surveillance for HPV 18/45 disease breakthrough must be in place.

Revaccinating females already HPV vaccinated is expensive and causes harm with no evidence of any improved prevention of HPV infections. Gardasil and Cervarix approach 90% effectiveness in preventing HPV 16/18 infection or disease in women older than 25 years; Cervarix has nearly 70% efficacy against HPV 31 and 45 infections as well in this older population. Vaccinating these women in conjunction with a screening program offers opportunity to reduce cervical cancer incidence in countries with limited resources and high burden of disease.

The uptake of HPV vaccinations across the world has been less than 2% of females 9–45 years of age, and non-existent in those countries where the incidence rate of cervical cancer is the highest. Vaccination does not replace screening. Prevention of cervical cancer must still rely on participation in ongoing screening programs. As we move into the next decade, the surveillance of the results of vaccine and screening programs will remain necessary.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

[1] How many cancers are linked with HPV each year? [Internet] Available from www.cdc.gov/cancer/hpv/statistics/cases.htm.

[2] F. Bray, J. Ferlay, M. Laversanne, D.H. Vrewster, C. Gombe Mbalawa, Kohler, et al., Cancer incidence in five continents: inclusion criteria highlights from volume X and the global status of cancer registration, Int. J. Cancer 137 (2015) 2060–2071.

[3] L.M. Fernandez, M.E. Pendleton, R.B. Wright, D.M. Harper, Chapter 29 bivalent HPV vaccine approved for cervical cancer prevention in females, in: A. Ayhan, N. Reed, M. Gultekin, P. Dursun (Eds.), Textbook of Gynaecological Oncology, third ed.Gunes Publishing, Ankara 2016, pp. 247–278.

[4] A.S. LaJoie, L.M. Fernandez, M.E. Pendleton, D.M. Harper, Chapter 30 quadrivalent and nonavalent HPV vaccine approved for males and females for HPV associated diseases, in: A. Ayhan, N. Reed, M. Gultekin, P. Dursun (Eds.), Textbook of Gynaecological Oncology, third ed.Gunes Publishing, Ankara 2016, pp. 279–308.

[5] Gardasil9 package insert [Internet] Available from http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm426457.pdf.

[6] Cervarix Package Insert, GlaxoSmithKline Biologicals, Rixensart, Belgium, 2009http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm186981.pdf.

[7] S.L. Giannini, E. Hanon, P. Moris, M. Van Mechelen, S. Morel, F. Dessy, et al., Enhanced humoral and memory B cellular immunity using HPV 1/618 L1 VLP vaccine formulated with the MPL/aluminum salt combination (AS04) compared to aluminium salt only, Vaccine 24 (2006) 5937–5949.

[8] IARC HPV Working Group Report, Primary End-points for Prophylactic HPV Vaccine Trials, vol. 7, 2013 (Lyon, France. ISBN 978-92-832-2451-8).

[9] S.E. Olsson, S.K. Kjaer, K. Sigurdsson, O.E. Iversen, M. Hernandez-Avila, C.M. Wheeler, et al., Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection, Hum. Vaccin. 5 (10) (2009) 696–704.

[10] M.H. Einstein, P. Takacs, A. Chatterjee, R.S. Sperling, N. Chakhtoura, M.M. Blatter, et al., Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18–45 years: end-of-study analysis of a phase III randomized trial, Hum. Vaccin. Immunother. 10 (12) (2014) 3435–3445.

[11] M.H. Einstein, M.J. Levin, A. Chatterjee, N. Chakhtoura, P. Takacs, G. Catteau, et al., Comparative humoral and cellular immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18–45 years: follow-up through month 48 in a phase III randomized study, Hum. Vaccin. Immunother. 10 (12) (2014) 3455–3465, http://dx.doi.org/10.4161/hv.36117.

[12] M.H. Einstein, M. Baron, M.J. Levin, A. Chatterjee, B. Fox, S. Scholar, et al., Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18–45 years, Hum. Vaccin. 7 (12) (2011) 1359–1373.

[13] M.H. Einstein, M. Baron, M.J. Levin, A. Chatterjee, B. Fox, S. Scholar, et al., Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12–24 in a Phase III randomized study of healthy women aged 18–45 years, Hum. Vaccin. 7 (12) (2011) 1343–1358, http://dx.doi.org/10.4161/hv.7.12.18281 (Epub 2011 Dec 1).

[14] A. Godi, S.L. Bissett, E. Miller, S. Beddows, Relationship between humoral immune responses against HPV16, HPV18, HPV31 and HPV45 in 12–15 year old girls receiving Cervarix® or Gardasil® vaccine, PLoS One 10 (10) (2015 Oct 23), e0140926. http://dx.doi.org/10.1371/journal.pone.0140926.

[15] P.S. Naud, C.M. Roteli-Martins, N.S. De Carvalho, J.C. Teixeira, P.C. de Borba, N. Sanchez, et al., Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination, Hum. Vaccin. Immunother. 10 (8) (2014) 2147–2162, http://dx.doi.org/10.4161/hv.29532.

[16] M. Nygard, A. Saah, C. Munk, L. Tryggvadottir, E. Enerly, M. Hortlund, et al., Evaluation of the long-term anti-human papillomavirus 6 (HPV6), 11, 16, and 18 immune responses generated by the quadrivalent HPV vaccine, Clin. Vaccine Immunol. 22 (8) (2015) 943–948.

[17] Statistical Review of Gardasil9-[Internet] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM428669.pdf.

[18] S.E. Olsson, L.L. Villa, R.L. Costa, C.A. Petta, R.P. Andrade, C. Malm, et al., Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine, Vaccine 25 (26) (Jun 21, 2007) 4931–4939.

[19] V. Gilca, C. Sauvageau, N. Boulianne, G. De Serres, M. Crajden, M. Ouakki, et al., The effect of a booster dose of quadrivalent or bivalent HPV vaccine when administered to girls previously vaccinated with two doses of quadrivalent HPV vaccine, Hum. Vaccin. Immunother. 11 (3) (2015) 732–738.

[20] S.M. Garland, T.H. Cheung, S. McNeill, L.K. Petersen, J. Romaguera, J. Vazquez-Narvaez, et al., Safety and immunogenicity of a 9-valent HPV vaccine in females 12–26 years of age who previously received the quadrivalent HPV vaccine, Vaccine 33 (48) (2015) 6855–6864.

[21] H.W. Chesson, J.F. Laprise, M. Brisson, L.E. Markowitz, Impact and cost-effectiveness of 3 doses of 9-valent human papillomavirus (HPV) vaccine among US females previously vaccinated with 4-valent HPV vaccine, J. Infect. Dis. 213 (11) (2016) 1694–1700.

[22] R.V. Barnabas, P. Laukkanen, P. Koskela, O. Kontula, M. Lehtinen, G.P. Garnett, Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modeling analyses, PLoS Med. 3 (2006), e138. .

[23] World Health Organization website Immunization Vaccines and Biologicals-Human Papillomavirus [Internet]. http://www.who.int/immunization/diseases/hpv/en/.

[24] E. Meites, A. Kempe, L.E. Markowitz, Use of a 2-dose schedule for human papillomavirus vaccination — updated recommendations of the Advisory Committee on Immunization Practices, MMWR Morb. Mortal. Wkly Rep. 65 (2016) 1405–1408, http://dx.doi.org/10.15585/mmwr.mm6549a5.

[25] M. Safaeian, C. Porras, Y. Pan, A. Kreimer, J.T. Schiller, P. Gonzalez, et al., Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial, Cancer Prev. Res. (Phila.) 6 (11) (2013) 1242–1250, http://dx.doi.org/10.1158/1940-6207.CAPR-13-0203.

[26] R. Sankaranarayanan, P.R. Prabhu, M. Pawlita, T. Gheit, N. Bhatla, R. Muwonge, et al., Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study, Lancet Oncol. 17 (1) (2016 Jan) 67–77, http://dx.doi.org/10.1016/S1470-2045(15)00414-3 (Epub 2015 Dec 2).

[27] R. Donken, M.J. Knol, J.A. Bogaards, F.R.M. van der Klis, Meijer CJLM, H.E. de Melker, Inconclusive evidence for non-inferior immunogenicity of two compared with three dose HPV immunization schedules in preadolescent girls: a meta-analysis, J. Infect. 71 (2015) 61–73.

[28] K.M. Neuzil, D.G. Canh, V.D. Thiem, A. Janmohamed, V.M. Huong, Y. Tang, et al., Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized non-inferiority trial, JAMA 305 (14) (2011) 1424–1431.

[29] D.S. LaMontagne, V.D. Thiem, V.M. Huong, Y. Tang, K.M. Neuzil, Immunogenicity of quadrivalent HPV vaccine among girls 11 to 13 years of age vaccinated using alternative dosing schedules: results 29 to 32 months after third dose, J. Infect. Dis. 208 (8) (Oct 15, 2013) 1325–1334.

[30] T.F. Leung, A.P. Liu, F.S. Lim, F. Thollot, H.M. Oh, B.W. Lee, et al., Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9–14 years: results to month 12 from a randomized trial, Hum. Vaccin. Immunother. 11 (7) (2015) 1689–1702, http://dx.doi.org/10.1080/21645515.2015.1050570.

[31] O.E. Iversen, M.J. Miranda, A. Ulied, T. Soerdal, E. Lazarus, K. Chokephaibulkit, S.L. Block, et al., Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women, JAMA 316 (22) (2016) 2411–2421.

[32] X. Castellsagué, N. Muñoz, P. Pitisuttithum, D. Ferris, J. Monsonego, K. Ault, et al., End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6,

11, 16, 18) recombinant vaccine in adult women 24–45 years of age, Br. J. Cancer 105 (1) (2011 Jun 28) 28–37, http://dx.doi.org/10.1038/bjc.2011.185 (Epub 2011 May 31).
[33] T. Schwarz, M. Spaczynski, A. Kaufmann, J. Wysocki, A. Gałaj, K. Schulze, et al., Persistence of immune responses to the HPV-16/18 AS04-adjuvanted vaccine in women aged 15–55 years and first-time modelling of antibody responses in mature women: results from an open-label 6-year follow-up study, BJOG 122 (1) (2015) 107–118.
[34] S.R. Skinner, A. Szarewski, B. Romanowski, S.M. Garland, E. Lazcano-Ponce, J. Salmerón, et al., Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study, Lancet 384 (9961) (Dec 20, 2014) 2213–2227, http://dx.doi.org/10.1016/S0140-6736(14)60920-X (Epub 2014 Sep 1).
[35] T.F. Schwarz, A. Galaj, M. Spaczynski, J. Wysocki, A.M. Kaufmann, P.V. Suryakiran, et al., Persistence of Immune Response 10 years After Administration of the Human Papillomavirus (HPV) 16/18 AS04-adjuvanted Vaccine to Women Aged 15–55 Years, European Research Organization on Genital Infection and Neoplasia (EUROGIN), 2016 Internet http://eurogin.com/2016/images/doc/eurogin-2016-1bstracts-part-2.pdf.
[36] L.L. Villa, R.L.R. Costa, C.A. Petta, R.P. Andrade, J. Paavonen, O.E. Iversen, et al., High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up, Br. J. Cancer 95 (11) (2006).
[37] Statistical Review of Gardasil9 [Internet] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM429166.pdf.
[38] FUTURE I/II Study Group, J. Dillner, S.K. Kjaer, C.M. Wheeler, K. Sigurdsson, O.E. Iversen, et al., Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial, BMJ 341 (2010) c3493 Clinical research ed.
[39] Medical Officer Review of Gardasil by FDA in 2008 [Internet] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111274.pdf.
[40] E.A. Joura, A.R. Giuliano, O.E. Iversen, C. Bouchard, C. Mao, J. Mehlsen, et al., A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women, N. Engl. J. Med. 372 (8) (2015) 711–723.
[41] N. Munoz, S.K. Kjaer, K. Sigurdsson, O.E. Iversen, M. Hernandez-Avila, et al., Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV associated genital diseases in young women, J. Natl. Cancer Inst. 102 (5) (2010) 325–339.
[42] A. Giuliano, E.A. Joura, O.E. Iversen, Efficacy of a novel 9-valent HPV L1 vaccine against disease irrespective of HPV type, 29th International Papillomavirus Conference and Public Health & Clinical Workshops, 2014 August 24, 2014. (Seattle, Washington).
[43] X. Castellsague, N. Munoz, P. Pitisuttithum, D. Ferris, J. Monsonego, K. Ault, et al., End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age, Br. J. Cancer 105 (1) (2011) 28–37.
[44] National, State and local Area Vaccination Coverage Among Adolescents Aged 13–17 years – United States, 2009 [Internet] available from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5932a3.htm?s_cid mm5932a3_w.
[45] J. Paavonen, P. Naud, J. Salmerón, C.M. Wheeler, S.N. Chow, D. Apter, et al., Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women, Lancet 374 (9686) (2009) 301–314.
[46] M. Lehtinen, J. Paavonen, C.M. Wheeler, U. Jaisamrarn, S.M. Garland, X. Castellsagué, et al., Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial, Lancet Oncol. 13 (1) (2012) 89–99.
[47] D. Apter, C.M. Wheeler, J. Paavonen, X. Castellsagué, S.M. Garland, S.R. Skinner, et al., Efficacy of human papillomavirus 16 and 18 (HPV-16/18) AS04-adjuvanted vaccine against cervical infection and precancer in young women: final event-driven analysis of the randomized, double-blind PATRICIA trial, Clin. Vaccine Immunol. 22 (4) (2015) 361–373.
[48] A. Harari, Z. Chen, A.C. Rodríguez, A. Hildesheim, C. Porras, R. Herrero, et al., Cross-protection of the bivalent human papillomavirus (HPV) vaccine against variants of genetically related high-risk HPV infections, J. Infect. Dis. 213 (6) (2016) 939–947, http://dx.doi.org/10.1093/infdis/jiv519 (Epub 2015 Oct 30).
[49] C.M. Wheeler, X. Castellsagué, S.M. Garland, A. Szarewski, J. Paavonen, P. Naud, et al., Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial, Lancet Oncol. 13 (1) (2012) 100–110, http://dx.doi.org/10.1016/S1470-2045(11)70287-X (Epub 2011 Nov 8).
[50] C.M. Wheeler, S.R. Skinner, E. Lazcano Ponce, M.R. del Rosario-Raymundo, S. McNeil, et al., Human papillomavirus (HPV)-16/18 AS04 adjuvanted vaccine efficacy in > 26 year old women: end of study (year 7) results from VIVIANE, a randomized multinational trial. 30th International Papillomavirus Conference, Abstract HPV15-0279, Lisbon, Portugal, 2011.
[51] S. Majewski, F.X. Bosch, J. Dillner, O.E. Iversen, S.K. Kjaer, N. Muñoz, et al., The impact of a quadrivalent human papillomavirus (types 6, 11, 16, 18) virus-like particle vaccine in European women aged 16 to 24, J. Eur. Acad. Dermatol. Venereol. 23 (10) (Oct 2009) 1147–1155, http://dx.doi.org/10.1111/j.1468-3083.2009.03266.x (Epub 2009 Apr 23).
[52] L.L. Villa, K.A. Ault, A.R. Giuliano, R.L. Costa, C.A. Petta, R.P. Andrade, et al., Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16, and 18, Vaccine 24 (27–28) (Jul 7, 2006) 5571–5583 (Epub 2006 May 15).
[53] N. Bhatla, V. Suri, P. Basu, S. Shastri, S.K. Datta, D. Bi, et al., Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women, J. Obstet. Gynaecol. Res. 36 (1) (2010 Feb) 123–132, http://dx.doi.org/10.1111/j.1447-0756.2009.01167.x.
[54] F.X. Bosch, C. Robles, M. Díaz, M. Arbyn, I. Baussano, C. Clavel, et al., HPV-FASTER: broadening the scope for prevention of HPV-related cancer, Nat. Rev. Clin. Oncol. 13 (2) (Feb 2016) 119–132, http://dx.doi.org/10.1038/nrclinonc.2015.146 (Epub 2015 Sep 1).
[55] R. Herrero, W. Quint, A. Hildesheim, P. Gonzalez, L. Struijk, H.A. Katki, et al., Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica, PLoS One 8 (7) (Jul 17, 2013), e68329. http://dx.doi.org/10.1371/journal.pone.0068329.
[56] K.A. Lang Kuhs, P. Gonzalez, A.C. Rodriguez, L.J. van Doorn, M. Schiffman, L. Struijk, et al., Reduced prevalence of vulvar HPV16/18 infection among women who received the HPV16/18 bivalent vaccine: a nested analysis within the Costa Rica Vaccine Trial, J. Infect. Dis. 210 (12) (Dec 15, 2014) 1890–1899, http://dx.doi.org/10.1093/infdis/jiu357 (Epub 2014 Jun 23).
[57] A.R. Kreimer, P. González, H.A. Katki, C. Porras, M. Schiffman, A.C. Rodriguez, et al., Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial, Lancet Oncol. 12 (9) (Sep 2011) 862–870, http://dx.doi.org/10.1016/S1470-2045(11)70213-3 (Epub 2011 Aug 22).
[58] D.C. Beachler, A.R. Kreimer, M. Schiffman, R. Herrero, S. Wacholder, A.C. Rodriguez, et al., Multisite HPV16/18 vaccine efficacy against cervical, anal, and oral HPV infection, J. Natl. Cancer Inst. 108 (1) (Oct 14, 2015) pii: djv302 10.1093/jnci/djv302 (Print 2016 Jan).
[59] L. Bruni, M. Diaz, L. Barrionuevo-Rosas, R. Herrero, F. Bray, F.X. Bosch, et al., Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis, Lancet Glob. Health 4 (2016) e453–e463, http://dx.doi.org/10.1016/S2214-109X(16)30099-7.
[60] M. Drolet, E. Benard, M.C. Boily, H. Ali, L. Baandrup, H. Bauer, et al., Population level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis, Lancet Infect. Dis. 15 (5) (2015) 565–580.
[61] J.M. Brotherton, M. Fridman, C.L. May, G. Chapell, A.M. Saville, D.M. Gertig, Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study, Lancet 377 (9783) (2011) 2085–2092.
[62] D.M. Harper, P. Nieminen, J. Paavonen, M. Lehtinen, Cervical cancer incidence can increase despite HPV vaccination, Lancet Infect. Dis. 10 (9) (2010) 594–595.
[63] S.D. Boone, C.M. Pinkston, K.B. Baumgartner, R.N. Baumgartner, S.M. Harper, A.J. Bonham, et al., Associations between prior HPV4 vaccine doses and cervical cancer screening participation, Cancer Epidemiol. 42 (Jun 2016) 108–114, http://dx.doi.org/10.1016/j.canep.2016.04.003 (Epub 2016 Apr 18).
[64] C.A. Paynter, B.J. Van Treeck, I. Verdenius, A.W. Lau, T. Dhawan, K.A. Lash, et al., Adherence to cervical cancer screening varies by human papillomavirus vaccination status in a high-risk population, Prev. Med. Rep. 2 (Jul 31, 2015) 711–716, http://dx.doi.org/10.1016/j.pmedr.2015.07.011 (eCollection 2015).
[65] J.M. Hirth, Y.L. Lin, Y.F. Kuo, A.B. Berenson, Effect of number of human papillomavirus vaccine doses on guideline adherent cervical cytology screening among 19–26 year old females, Prev. Med. 88 (Jul 2016) 134–139, http://dx.doi.org/10.1016/j.ypmed.2016.04.004 (Epub 2016 Apr 13).
[66] A.C. Budd, J.M. Brotherton, D.M. Gertig, T. Chau, K.T. Drennan, M. Saville, Cervical screening rates for women vaccinated against human papillomavirus, Med. J. Aust. 201 (5) (Sep 1, 2014) 279–282.
[67] T.J. Palmer, M. McFadden, K.G. Pollock, K. Kavanagh, K. Cuschieri, M. Cruickshank, et al., HPV immunisation and increased uptake of cervical screening in Scottish women; observational study of routinely collected national data, Br. J. Cancer 114 (5) (Mar 1, 2016) 576–581, http://dx.doi.org/10.1038/bjc.2015.473.
[68] H. Beer, S. Hibbitts, S. Brophy, M.A. Rahman, J. Waller, S. Paranjothy, Does the HPV vaccination programme have implications for cervical screening programmes in the UK? Vaccine 32 (16) (2014 Apr 1) 1828–1833, http://dx.doi.org/10.1016/j.vaccine.2014.01.087.
[69] E. Herweijer, A.L. Feldman, A. Ploner, L. Arnheim-Dahlström, I. Uhnoo, E. Netterlid, et al., The participation of HPV-vaccinated women in a National Cervical Screening Program: population-based cohort study, PLoS One 10 (7) (Jul 28, 2015), e0134185. http://dx.doi.org/10.1371/journal.pone.0134185 (eCollection 2015).