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An Update of Prophylactic Human Papillomavirus L1 Virus-Like Particle Vaccine Clinical Trial Results

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Abstract

This review focuses on recent publications of clinical trials of two prophylactic Human Papillomavirus (HPV) vaccines: Gardasil® (Merck & Co., Whitehouse Station, NJ USA), a quadrivalent vaccine containing L1 virus-like particles (VLPs) of types −6, 11, 16, and 18, and Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), a bivalent vaccine containing VLPs of types −16 and 18. In efficacy trials involving young women, both vaccines produced outstanding efficacy against primary and secondary endpoints associated with the vaccine type HPVs and were highly and consistently immunogenic. Both had excellent safety records and, as expected, the most frequent vaccine-related adverse was moderate injection site sequelae. No evidence of waning protection was observed after four years for endpoints examined ranging from incident infection to cervical intraepithelial neoplasia grade 3 associated with the vaccine type HPVs. Gardasil® was also highly efficacious at preventing vaginal/vulvar lesions and genital warts. However, neither vaccine demonstrated therapeutic efficacy against prevalent infections or lesions, regardless of the associated HPV type. Cervarix® has shown limited cross-protection against infection with specific closely related types while preliminary results of limited cross-protection have been presented for Gardasil®. As expected, more limited efficacy was noted for both vaccines when women with prevalent infection were included or end points associated with any HPV type were evaluated. Immunological bridging trials involving adolescent girls and boys were also recently published. For both vaccines, serum VLP antibody levels in girls were non-inferior to those generated in young women and antibody response to Gardasil® was also non-inferior in boys. The results of these studies have led to the approval of Gardasil® and Cervarix® by national regulatory agencies in a number of countries.

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LLV: Advisory Board (Merck Sharp & Dohme).
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Keywords

HPV vaccines; cervical cancer

1.0 INTRODUCTION

This article reviews the results of Human Papillomavirus (HPV) virus-like particle (VLP) vaccine clinical trials published in 2006 and 2007. An impressive number of important studies were published in this short time frame. Information on earlier clinical trials is provided by Laura Koutsky and Diane Harper in the previous monograph [1]. The trials to be discussed fall into two categories, efficacy studies involving virologic and disease endpoints and immunologic bridging studies where the endpoints were limited to safety and VLP serum antibody titers. While the clinical trials of Gardasil® (Merck & Co., Whitehouse Station, NJ USA) and Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) are presented together, caution must be taken when directly comparing the results with the two vaccines due to differences in trial design, statistical analyses and methodologies used to generate the published analyses.

2.0 VACCINE FORMULATIONS

Gardasil® and Cervarix® are both composed of HPV L1 proteins that spontaneously self assembled into VLPs. However, they have different valencie and adjuvants and are produced in different types of cells (Table 1) [2]. Cervarix® was designed to prevent infection by HPV-16 and 18, the two types that cause 70% of cervical cancer. Gardasil® targets the same two cancer causing types and, in addition, is intended to prevent infection by HPV-6 and 11, which cause 75–90% of external genital warts. Both vaccines must be refrigerated and are administered by intramuscular injection in the deltoid area, but differ slightly in the timing of the second dose.

Each VLP type is produced and purified separately and during final formulation the different types are mixed. In addition to valency, another difference between the two vaccines is the choice of adjuvants. Different aluminum salts are used in the two vaccines. The Gardasil® vaccine uses an aluminum adjuvant (aluminum hydroxyphosphate sulfate), whereas the Cervarix® adjuvant system, called AS04, containing monophosphosphoryl lipid A (MPL), a detoxified form of lipopolysachharide (LPS) and aluminum hydroxide. Aluminum salt-based adjuvants typically induce a Th2 type of response and this was observed when Merck's aluminum adjuvant was combined with HPV VLPs. However, MPL activates innate immune responses via toll-like receptor molecules and so can induce a mixed Th1/Th2 differentiation pattern in human T cells [3,4]. Th1 responses are generally sought in therapeutic vaccines designed to generate cell mediated immune responses, in contrast to prophylactic vaccines designed to generate antibody responses. Th1 and Th2 responses induce antibody responses that typically have different ratios of specific immunoglobulin types and IgG subtypes, but at present there is no evidence that the various antibody species differ in HPV neutralizing potential. GlaxoSmithKline (GSK) has published that VLP antibody titers in women are modestly higher (~2-fold) when their VLPs are formulated in AS04 rather than simple aluminum hydroxide. A more complete review of adjuvants and immune responses is discussed in this monograph by Stanley M *et al*. [5]. There has been no direct comparison between VLPs adjuvanted with AS04 and aluminum salts of Gardasil® to date.

3.0 EFFICACY TRIAL DESIGNS

Results from two small phase II and three relatively large phase III efficacy studies were reported in the last two years (Table 2) [6–10]. All of the trials were blinded, randomized, and

placebo controlled trials of young women (mean age 20 years). Participants were recruited at multiple sites in Europe, North America, South America, Asia and Australia. A community-based efficacy trial of Cervarix® is also underway in Costa Rica, but prophylactic efficacy data is not yet available [11].

In keeping with the primary goal of evaluating immunoprophylaxis, an exclusion criterion for number of lifetime sexual partners, less than five for the quadrivalent vaccine or less than seven for the bivalent vaccine, was included in the efficacy trials to reduce the percentage of women with prior exposure to genital HPV infection. However, women with prevalent infection, as measured by the presence of genital tract HPV DNA, or evidence of past exposure, as measured by serum antibodies to VLPs, were not excluded from randomization or vaccination, with the exception of GSKs study 001/007. The phase II studies focused more on infection endpoints because of their smaller trial size, whereas the pivotal phase III trials are focused more on disease endpoints, particularly cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+). This endpoint has been recommended as a surrogate clinical endpoint for cervical cancer by the US Food and Drug Administration (FDA) and other national regulatory authorities. Specific primary and secondary endpoints used in the individual trials are indicated in Table 2.

All clinical trials were designed to follow-up women for up to at least four years. The phase III studies with CIN endpoints had defined interim analyses when a pre-determined number of disease events accumulated, and these analyses have been published [7,9]. Importantly, these interim analyses are the basis for regulatory approval in many countries.

The screening interval was six or twelve months. This interval is an important variable because more cases of infection and disease are detected with the shorter interval. However, the increase may well largely represent cases of transient infection. The composition of the control vaccine is important to note because safety data on the investigational vaccine is often presented in reference to data for the control vaccine, either aluminum based adjuvants alone (for the Gardasil® trials) or an active vaccine (hepatitis A vaccine for the Cervarix® trials). These control vaccines are associated with some, albeit relatively minor and acceptable, side effects. In only one instance, an immunogenicity bridging study of Gardasil® discussed below [12], was a true placebo (saline) used as the comparator.

4.0 EFFICACY TRIAL STATISTICAL ANALYSES, METHODS AND GROUPS

Understanding the published results of clinical trials can be difficult for the public in general because several types of analyses can be reported including according-to-protocol (ATP), modified intention-to-treat (MITT) and intention-to-treat (ITT). While the specifics for inclusion of study participant into each type of analysis vary among studies, ATP analysis is the most restricted, including only the “ideal” participants who correctly adhere to all aspects of the study protocol. Thus, an ATP analysis can be viewed as a best-case scenario for the effectiveness of the intervention under study. At the other end of the spectrum is the ITT analysis, which includes all individuals who participate in the trial. In vaccine trials, “participation” is usually defined as receiving at least the first dose of vaccine. ITT analyses can be viewed as an approximation of the effectiveness of the intervention in the general public, although the volunteers in the clinical trial may not be entirely representative of the general public. MITT analyses fall somewhere in between ATP and ITT, excluding some participants that violate specific aspects of the trial protocol.

The primary analyses reported for all but the Papilloma Trial Against Cancer in Young Adults (PATRICIA) trial of Cervarix® were ATP. ATP analyses were limited to women who were sero-negative to the vaccine-targeted HPV types at enrolment, DNA-negative for the vaccine-targeted HPV being analyzed at enrolment and through the full course of vaccination (GSK

001/007) or until one month after the last dose (Merck 007, Females United To Unilaterally Reduce Endo/Ectocervical disease (FUTURE) I/II), who received all three doses of the vaccine within specified time limits, and had no protocol violations (Table 3) [8]. Women in the GSK 001/007 study had to be negative for other high risk HPV DNA at enrolment as well. Case counting for ATP analyses started one month after receiving the third dose, except for the Cervarix® GSK 001/007 trial that started at the completion of vaccination. ITT and MITT analyses included women that received at least one dose and case ascertainment began one month after receiving the first dose (Table 3). However, a very important difference between ITT (Merck FUTURE I and II) and MITT (GSK 001/007, Merck 007 and GSK PATRICIA) is that in the MITT analyses women who were DNA positive for a vaccine type at enrollment were excluded from the analysis for that type, whereas in ITT analyses, women were included even if they had prevalent infection or cervical lesions by a vaccine type. Most of the ATP and MITT analyses were specific for the vaccine-specific HPV types, although protection against a broader range of HPV types was reported in some instances.

5.0 PROPHYLACTIC EFFICACY AGAINST VACCINE TYPES

The prophylactic efficacies in the five trials against persistent infection and genital disease associated with the vaccine-targeted HPV types are presented in Table 4. Remarkably, efficacy was greater than 95% against all reported vaccine-type specific endpoints in the ATP analyses. In most instances, efficacy was lower in the MITT analyses, perhaps reflecting, at least in part, less protection after one dose of vaccine than after three. Some cases in the MITT analyses could also be due to prevalent infection reaching the minimum level for detection in the first month after enrolment.

The notably lower efficacy in ITT analyses of FUTURE I and II, largely reflects two aspects of the study design and analyses. The first is the inclusion of prevalent infections in the analysis. The second is the presumably relatively high frequency of women who progress to disease from vaccine type-associated prevalent infection compared to the number of women who develop disease from new infections during the relatively short duration of the follow up on which the analyses are based. It is worth noting that the single CIN2/3 case in which a vaccine type HPV DNA was detected in the ATP analysis of one of the Gardasil® trials (FUTURE II), and in two CIN2/3 cases in the MITT analysis of the Cervarix® phase III trial (PATRICIA), HPV-16 or 18 DNA was detected on a single occasion and another high-risk type was persistently detected and/or specifically detected in the lesion. Although these cases fall under the pre-specified definition of vaccine-type associated cases, they could well represent cervical dysplasia induced by non-vaccine types. These examples highlight the difficulties of assigning a case to a specific type when a women is infected with multiple types during follow up.

The combined analysis of Merck's three Gardasil® trials and HPV-16 monovalent vaccine trial was recently reported [13]. Protection against vaccine type associated CIN3, the most definitive cervical cancer precursor, was 98% (95% confidence interval (CI): 89 – 100) in the ATP analysis. In a separate analysis of adenocarcinoma in situ (AIS), the efficacy was 100% (95% CI: 31 – 100). Efficacy against HPV-16/18 associated CIN3 was 44% (95% CI: 31 – 55) in the ITT evaluation that included women with prevalent HPV-16/18 infection at the time of first vaccination. Combined analysis of Gardasil®'s effects on incident high-grade vulvar and vaginal dysplasias (VIN2/3 and VaIN2/3) have also been reported [14]. In the ATP cohort, the vaccine was 100% effective (95% CI: 72 – 100) against VIN2/3 or Va2/3 associated with HPV-16/18. In the MITT cohort, vaccine efficacy was 71% (95% CI: 37 – 88). In a combined ATP analysis of 4,722 women from FUTURE I and II with evidence of current or past infection with one or more of the vaccine targeted HPV types, Gardasil® was 100% effective at preventing CIN2+ or AIS associated with vaccine targeted types to which the vaccinee had no evidence of prior exposure [15]. Thus prior or prevalent infection by one type does not appear

to influence the efficacy of the vaccine against other types. However, ITT analyses, which might better predict the overall population effectiveness of vaccinating women with prevalent infection, were not reported.

6.0 CROSS-PROTECTION

Results on protection against infection by non-vaccine HPV types have been published for the two Cervarix® trials. In the extended follow-up period of the GSK 001/007 trial (follow-up through 25/4–53 months) the vaccine had an efficacy against incident infection in MITT analysis of 94% (95% CI: 63 – 100) for HPV-45 and 55% (95% CI: 12 – 78) for HPV-31 [8]. However there was no significant protection against types −33, 52 or 58. In the MITT cohort of the PATRICIA trial, Cervarix® had an efficacy against 6 month persistent infection of 60% (97.9% CI: 3 – 85) for HPV-45, 36% (97.9% CI: 1 – 60) for HPV-31, and 32% (97.9% CI: 4 – 52) for HPV-52 [9]. There was no significant protection against types −33 and 58. Unpublished data from the FUTURE I/II trials (reported at scientific conferences) indicates that Gardasil® also has partial prophylactic efficacy against persistent infection and against incident CIN2/3 caused by non-vaccine HPVs, although the results for individual types were not reported.

It is encouraging that both vaccines appear to have some protection against HPV types that are not specifically targeted by the vaccine. However, *in vitro* neutralization studies indicate that cross-neutralizing titers are at least ten-fold lower than are type-specific titers, even for very closely related types, such as HPV-45 and 18 [16]. Therefore, a key question is whether this partial cross-protection will wane more rapidly than the almost complete type-specific protection. In this regard, it is encouraging to note that cross-protection against HPV-45 and 31 infection was detected in years three and four in the GSK 001/007 study, after the time when serum antibody levels to the VLPs had plateaued [8].

The limited/partial activity of the VLP vaccines across types is reflected in the lower efficacy seen in ITT or MITT analyses in which lesions causes by any HPV type are included. The lower efficacy is especially prominent in ITT analysis where women with prevalent infections by any HPV type are included. In FUTURE I and II, the efficacy of Gardasil® in preventing biopsy-confirmed CIN 2/3 or AIS was 20% (95% CI: 8 – 31) and 17% (95% CI: 1 – 31), respectively. In FUTURE I, protection from external genital lesions was 34% (95% CI: 15 – 49).

Efficacy is expected to increase over time as prevalent infection is similarly cleared in the vaccinees and controls and new infection is preferentially prevented in the vaccine group. The HPV type-independent MITT analyses reported for the GSK 001/007 trial are quite different because women with any of 14 high-risk HPV infections at entry were excluded. Based on cervical cytology, the vaccine efficacy for CIN2/3 and CIN1-3 was 73% (95% CI: 1 – 95) and 52% (95% CI: 9 – 78), respectively. Although based on a relatively small number of events, the results are currently the best indication of how the vaccines will perform in preventing CIN in an HPV naïve population, such as adolescent girls before sexual debut. However, the likelihood of exposure to HPV may be different for sexually active women who are negative for the 14 oncogenic types compared to what is expected for virginal women. This difference in exposure prevalence is like to impact vaccine effect, particularly when evaluated on an absolute scale.

7.0 THERAPEUTIC EFFICACY

Although the VLP vaccines were designed specifically to generate neutralizing antibodies and thereby prevent infection, they were also shown to induce cell mediated immune responses to L1 in animal models and some clinical trials [17,18]. It is therefore of interest to examine

whether the vaccines can act to induce regression of HPV infections or genital lesions. The therapeutic activity of Cervarix® was examined in an ancillary analysis of the Costa Rican trial [11]. No significant differences in clearance rate of prevalent HPV-16 or HPV-18 infection was detected in the VLP vaccine *versus* control arms either six or twelve months after first vaccination (33.4% *versus* 31.6% and 48.8% *versus* 49.8%, respectively). Similarly, the vaccine did not induce the clearance of genital infections by other HPV types. The therapeutic activity of Gardasil® was also examined in the FUTURE II trial. No significant difference in the rate of progression of prevalent HPV-16 or HPV-18 infection to CIN2+ was seen in the VLP vaccine *versus* placebo control arm (11.1% *versus* 11.9%) [6]. Thus HPV VLP vaccines appear to have no significant effect on either the rates of clearance or progression of cervical HPV infection. Therapeutic activity against external genital lesions has not been reported. However, L1 in these lesions, as in cervical dysplasias, is not expressed at detectable levels in the basal epithelium where virus infection is thought to be maintained. It therefore seems unlikely that VLP vaccine will induce regression of external genital lesions.

8.0 SAFETY

VLPs are noninfectious protein subunit vaccines and therefore might be expected to have safety profiles similar to other protein subunit vaccines such as tetanus or hepatitis B virus vaccine. Safety data from the three large phase III trials extended similar findings from earlier clinical trials supporting this conjecture. The vaccines were generally well tolerated and there were very few dropouts due to vaccine-related symptoms. The most common vaccine related adverse events were local transient mild to moderate pain and erythema at the site of injection. These reactions were significantly elevated compared to controls. For instance, local pain reported in VLP vaccinees and controls was 90.5% and 78.0% in the PATRICIA study, and 85.3% and 75.4% in FUTURE I, respectively [7,9]. Potentially vaccine-related general systemic symptoms were nominally higher in the vaccine groups than in the control groups. For instance in the GSK PATRICIA study, fever within 7 days of vaccination was reported in 12.4% of VLP vaccinees and 10.9% of controls. Similarly in the Merck FUTURE I study, fever within five days of vaccination was reported in 14.8% of VLP vaccinees and 11.5% of controls. It is noteworthy that neither local nor systemic symptoms increased with each subsequent dose and symptoms were not more severe in women with evidence of prior exposure to one of the vaccine types [7]. The proportion of women experiencing serious adverse events of any type was much the same in VLP vaccinees and controls. The vaccine is not recommended for pregnant women, due to limited safety data. To the extent that vaccination might be recommended to women in their prime reproductive years, additional evaluation of the impact on pregnancies and their outcome is warranted.

9.0 IMMUNOGENICITY

Since the VLP vaccines were designed primarily to protect by inducing virion neutralizing antibodies, type-specific antibody responses to the VLPs have been the primary focus of immunogenicity studies (see Stanley M *et al.*, this issue [5]). Both vaccines were shown to be highly immunogenic in clinical trials, resulting in essentially 100% seroconversion. Peak geometric mean antibody titers (GMTs) were approximately 10- to 100-fold higher that the GMTs generated after natural infection [19,20].

It is important to note that different assays were used to measure the antibody responses to the two vaccines. Gardasil® was evaluated using a Luminex-based assay that measures competitive binding against a single type-specific neutralizing monoclonal antibody. Cervarix® was evaluated using a VLP-based enzyme-linked immunosorbent assay (ELISA). Therefore, quantitative comparisons of the antibody responses for the two vaccines cannot be made based on the published results. Interestingly, the antibody response to HPV-16 VLPs

was as strong after vaccination with the quadrivalent vaccine as it was after vaccination with a similar monovalent HPV-16 VLP vaccine [21]. Thus there is no indication that the VLPs exert immune interference against other HPV VLP types when combined into a multivalent vaccine.

Co-administration of Gardasil® and a recombinant hepatitis B vaccine (Recombivax HB®, Merck & Co. Whitehouse Station, NJ USA) did not significantly reduce antibody responses to the HPV VLPs, but GMTs to Recombivax HB® were slightly reduced [22]. Age and seropositivity at entry were the only variables that influenced antibody responses to Gardasil® [23]. Peak GMTs varied inversely with age, whereas peak GMTs were, as expected, higher in women who had previously mounted an antibody response to the virion capsid protein [20].

Titers for both vaccines generally peaked one month after the third dose (given at month 6), declined over the next year and then remained relatively stable for the duration of follow-up (an additional 4.0 and 4.5 years for Cervarix® and Gardasil®, respectively) [8,10]. At the plateau stage, titers remained above the GMT observed after natural infection for Cervarix®. For Gardasil®, in a minority of vaccines, HPV-18 titers dropped below the level of detection. Whether this exception is a reflection of the intrinsic immunogenicity of the HPV-18 VLPs using the vaccine or a quirk of the HPV-18 monoclonal antibody competition assay remains to be determined.

An additional dose of Gardasil® at year five was shown to induce a strong recall response, with titers for each type at least as high as the peak titer following the initial series of vaccinations [24]. Thus the vaccine induces the expected B cell memory response, a property of other vaccines with durable immune responses. Modeling exercises that assume long term memory estimate that detectable antibody levels will remain at least 12 years, and perhaps life-long in 99% of vaccinees [25]. Although the long term persistence of stable antibody levels is an encouraging finding, the antibody levels needed to prevent infection or disease are currently unknown. Thus, it remains uncertain whether the vaccines will confer life-long protection or whether an additional booster(s) will be needed.

10.0 SAFETY AND IMMUNOGENICITY BRIDGING STUDIES

The safety and immunogenicity of Cervarix® and Gardasil® in young women, whom efficacy has been demonstrated, has recently been compared to other study groups. The intent of these bridging studies is to generate data that can support applications for regulatory approval for vaccination of individuals that fall outside the range for which efficacy data was obtained. In two studies, Gardasil® was shown to be safe and immunogenic in adolescent boys and girls (Table 5) [12,26,27]. Using a competitive Luminex immunoassay (cLIA), the antibody response to the vaccine was non-inferior in boys compared to girls and the GMTs of VLP specific antibodies in both boys and girls were approximately two-fold higher than the responses in young women.

The safety data in the Reisinger KS *et al*. study is particularly noteworthy because it is the only trial to date in which a commercial vaccine was compared to a saline placebo. Vaccine recipients more frequently reported injection site adverse events than placebo recipients (75.3% *versus* 50.0%), but the rates of fever were similar [12].

In the Block SL *et al*. study, which did not contain a placebo arm, significantly more young women than girls or boys reported injection site erythema (9.7%, 6.8%, and 6.2%, respectively). In contrast, significantly more girls and boys than young women experienced a fever (12.8%, 13.8%, and 7.3%). However, 96% of the fevers were less than 39°C [26].

A bridging study of Cervarix® compared safety and immunogenicity in adolescent girls and young women (Table 5) [27]. The seroconversion rate was non-inferior in adolescent girls and the VLP GMTs were approximately two-fold higher in the girls compared to young women. There were no placebo control groups in this study, but the incidences of injection site symptoms were similar for the vaccinated girls and young women. There was no significant difference in the incidence of fever, but the incidence of any general symptom was somewhat lower in the adolescent girls than in the young women (16.5% *versus* 23.0%).

Both vaccines have been evaluated for safety and immunogenicity in trials of "older" women (ages 24–45 for Gardasil® and ages 26–55 for Cervarix®). Unpublished data presented at scientific conferences suggests that the vaccines are safe in older women and seroconversion rates were high regardless of age. Cervarix® was recently approved in Australia for girls from 10 years to women through age 45, on the basis of immunogenicity bridging results of the GSK trial. Conference presentations of the Gardasil® trial in older women also reported excellent protection from incident cervical and external genital lesions associated with the vaccine-targeted types.

11.0 LOOKING TO THE FUTURE

Although extremely valuable information has already been obtained from the phase III studies of Gardasil® and Cervarix®, it is important to emphasize that the publications to date report interim analyses. Further insights into the safety, immunogenicity and efficacy of these vaccines are expected in to next few years as these trials are completed and the complete data sets are analyzed. The larger data bases will allow for more precise estimates of vaccine efficacy against the full range of infection and disease endpoints. This is especially true for the PATRICIA study of Cervarix® in which the interim analysis was conducted after accruing relatively few events. The larger data sets should also facilitate a number of important subgroup analyses. For instance, it will be important to obtain estimates of the ITT effectiveness of the vaccines at preventing genital lesions, regardless of HPV type, according to age at vaccination. It will also be important to further refine the cross-protection and duration of protection against specific HPV types afforded by the vaccines. The impact of vaccination in the context of multiple infections is another topic that deserves further attention. In addition, valuable information should also be obtained from two longer-term community-based phase III-IV efficacy studies in the Nordic countries and the extended follow up planned for the Costa Rican trial [28]. These studies will evaluate long term vaccine safety and impact and the protection against cervical cancer and CIN3 using active and cancer-registry-based follow-up. These evaluations will further our understanding of the potential overall benefits of the vaccines in general use and so help public health decision makers to make informed decisions of how best to implement the vaccines.

Several additional VLP vaccines clinical trials have been initiated. A safety and immunogencity trial in young women evaluating a two versus three dose vaccination regimen has been initiated by the University of British Colombia, Canada [29]. Public and industry funded safety and immunogenicity trials are also underway in human immunodeficiency virus (HIV) positive individuals. Merck is testing safety, immunogenicity and efficacy of Gardasil® in young men, using the endpoints of HPV infection, genital warts and anal dysplasias (the latter only in men who have sex with men) [30]. As noted above, both companies are sponsoring trials to evaluate safety, immunogenicity and efficacy in mature aged women [30]. Gardasil® has been approved for general use in boys/young men and Cervarix® has been approved for general use in older women in some countries, based on immunogenicity bridging. However, it is expected that the ongoing trials, which should be completed in the next few years, will substantially contribute to our understanding of the performance of the vaccines in these secondary target populations for the vaccines. Interestingly, GSK has announced that it will

conduct a head-to head comparison of the safety and immunogenicity of Cervarix® and Gardasil®, involving approximately 1,000 women, ages 18–45. Finally, Merck has announced it's intentions to develop a vaccine that contains the VLPs of additional HPV types, to achieve effective protection against a greater percentage of genital HPV infections [30].

12.0 WHO TO VACCINATE

The results of ongoing and future vaccine trials are expected to provide important information for making national policy decisions on vaccine utilization. However, the recent licensing of the HPV vaccines by national regulatory agencies for vaccination of adolescent girls and young women (ages 9–26), and in some cases even for middle age (through age 45) women and/or adolescent boys (ages 9–15), make it difficult for national vaccination policy boards and medical associations to delay recommendations on who to include in publicly funded vaccination programs. The costs of both vaccines and the programs to administer them will be high. Decisions to limit public funding to specific subsets of the individuals eligible for vaccination will likely be made even in wealthier countries. However, significant private market uptake of the vaccine by individuals excluded from publicly financed vaccination programs is expected. Based on our understanding of genital HPV infection, its association with cancer, and the evidence from vaccine trials to date, the arguments for and against vaccination of the principal target groups for the vaccines, adolescent girls, "older women" and young men are discussed below.

It is widely acknowledged that vaccination of adolescent girls should be the first priority of vaccination programs [31]. The vast majority of HPV infections that cause cervical cancer (and also genital warts) are sexually transmitted. HPV infections are very common in young adults and they are frequently acquired soon after initiation of sexual activity. Since the vaccines do not induce regression of established infection, they will be most effective if given prior to the onset of sexual activity. Age is simply a surrogate for likelihood of being sexually active. Vaccination programs should target girls before the mean age of sexual debut in a population. It seems prudent to vaccinate relatively close to the age of sexual debut, since the duration of protection for these vaccines has yet to been determined. However, young adult women who have not become sexually active could potentially derive equal benefit from the vaccines. It is important to note that the efficacy of the vaccine has not been demonstrated in adolescent girls, because it would take too long to generate sufficient numbers of infection and/or disease outcomes in clinical trials. The immunogenicity bridging studies discussed above provide the only, and national regulatory agencies believe sufficient, evidence for approval of vaccination of adolescent girls.

Many sexually active young women could also potentially derive benefit from the vaccines, since only a subset of these women would have had prior exposure to all of the HPV types in the vaccines. The results of the efficacy trials in 15–26 year old women, most of whom were sexually active, illustrate this point. However, extrapolation of the clinical trials results to middle age adult women and to the general public is somewhat compromised by the selection criteria of the study participants, particularly the limitation in the age range and the number of lifetime sexual partners. Modeling exercises suggest that there would be a more rapid reduction in the rates of cervical cancer if young sexually active women, in addition to adolescent girls, were vaccinated in catch-up programs [32]. Cervarix® is approved for women through age 45 in Australia, and approval of both vaccines for middle age women is expected once the results of ongoing clinical trials become available. An argument against routine vaccination of middle age women is that the probability of prior exposure to the vaccine HPV types increases with age. In contrast, risk of acquisition of genital HPV infection tends to decrease because the number of new sex partners tends to decrease with age [33]. However, this is not always the case and male behaviors must also be considered. Also, it is currently unclear whether

protection from incident infection/low grade lesions is required for many older women, since many have had transient infections and so have presumably demonstrated an ability to resolve genital HPV infections without the need of vaccination. Finally, progression of incident infection to invasive cancer takes decades on average. Therefore preventing incident infections in middle age or older women may not substantially decrease cervical cancer death rates, even if they were to become exposed to vaccine preventable infections after vaccination.

In addition to the potential benefit to individual women, including sexually active women in vaccination programs might also lead to a more rapid development of effective herd immunity. In addition to preventing incident infections and thereby breaking the chain of transmission, it is possible the vaccination of women with prevalent infection could reduce their transmission rates to new partners. This might occur if the vaccine-induced antibodies in their cervicovaginal mucus neutralized the virus shed from their productive lesions. However this possibility has not been documented in a clinical trial. These arguments for and against vaccination of sexually active women make decisions on public funding for catch up vaccination of adult women difficult. Since all the arguments against vaccination become stronger with increasing age, it seems reasonable to concentrate limited resources on the youngest women, if it were socially and politically acceptable. Public sector funding for vaccination of middle age women is questionable at best, given the high cost of the vaccines and the limited public health benefits that are likely to result. This age group might be better served by investment in cervical cancer screen programs rather than vaccination programs [34].

Gardasil® is approved for 9–15 year old boys in the European Union and elsewhere. Regulatory approval in other countries, for both adolescent boys and young men, can be expected if the ongoing efficacy trials in young men yield positive results. However, public financing of males would remain debatable, even if the vaccine is proven to be highly efficacious at preventing genital infections and anal lesions in men. The potential impact on cancer prevention would be limited, since only about seven percent of HPV-16/18-attributable cancers occur in men [35]. Vaccination of males might indirectly benefit women by producing a more rapid and a greater degree of herd immunity. However transmission models suggest that vaccinating males will have only modest effects on herd immunity if vaccination rates are high in females [36]. Therefore more cost effective herd immunity might be achieved by concentrating resources on vaccinating females, who would potentially derive more primary benefit from the vaccines. Prevention of genital warts could represent a substantial benefit of male vaccination with Gardasil®, and so address equity issues, since males and females have similar incidences of genital warts [37]. Vaccination of males would also address the issue of males assuming an equitable proportion of the health risks associated with vaccination, although risks appear to very low to date. The limited clinical trial data make decisions on public funding of male vaccination particularly difficult. At present it would seem preferable to concentrate resources, if limited, on vaccinating adolescent girls and young women, providing such a policy were socially and politically acceptable.

13.0 CONCLUSIONS

The broad outlines of the safety, immunogenicity and efficacy of HPV VLP vaccines in young women were established by the recently published clinical trial results. In all three areas, the vaccines have met or exceeded all reasonable expectations. The vaccines have limited cross-type prophylactic efficacy and are not effective therapeutically, but these limitation were predicted by preclinical studies. Substantially more information on the performance of the vaccine in males, mature women, immunosuppressed populations and young women with prior exposure should become available in the next few years as clinical trials in these groups are completed. The central unanswered efficacy question in young women is whether the initial vaccination series will provide lifelong protection from cervical cancer or whether booster

doses will be required. The central safety questions involve rare serious adverse event, serious sequelae that might arise long after vaccination and adverse effects of vaccination during pregnancy. None of these outcomes are expected for a protein subunit vaccine of this type, but continued diligence is certainly needed to evaluate these possibilities. The central question for immunogenicity is whether an immune correlate of protection, most likely neutralizing antibody titers, can be established in order to facilitate diversified manufacturing of these vaccines and development of second generation vaccines. Many of the most critical questions for these vaccines now revolve around implementation issues and their effectiveness in general use.

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Table 1

Characteristics of HPV VLP vaccines.

	Gardasil®	**Cervarix®**
Manufacturer	Merck	GlaxoSmithKline
VLP types	−6/11/16/18	−16/18
Dose of L1 protein	20/40/40/20 μg	20/20 μg
Producer cells	*Saccharomyces cerevisiae* (bread yeast) expressing L1	*Trichoplusia ni* (Hi 5) insect cell line infected with L1 recombinant baculovirus
Adjuvant	225 μg aluminum hydroxyphosphate sulfate	500 μg aluminum hydroxide, 50 μg 3-O-deacylated-4'-monophosphoryl lipid A
Injection schedule	0, 2, 6 months	0, 1, 6 months

VLP: Virus-like particle.

Source of data: [2]

Table 2

Outline of vaccine efficacy trials in young women.

Characteristic	GSK 001/007	Merck 007	PATRICIA	FUTURE I	FUTURE II
Vaccine	Cervarix®	Gardasil®	Cervarix®	Gardasil®	Gardasil®
Study phase	II	II	III	III	III
Control	500 μg aluminum hydroxide	225 μg aluminum hydroxyl-phosphate sulfate	Hepatitis A vaccine	225 μg aluminum hydroxyl-phosphate sulfate	225 μg aluminum hydroxyl-phosphate sulfate
# Participants	1,113	552	18,644	5,455	12,167
Mean age (years) (range)	20 (15–25)	20 (16–23)	20 (15–25)	20 (16–24)	20 (15–26)
Lifetime no. of sex partners	≤6	≤4	≤6	≤4	≤4
Screening frequency	6 months	6 months	12 months	6 months	12 months
Mean duration of follow up	48 months	60 months	15 months[a]	36 months[a]	36 months[a]
Primary efficacy endpoint	Incident -16/18 infection	−6/11/16/18 persistent infection and cervical or external genital disease	−16/18 CIN2+	-6/11/16/18 CIN1+ and external genital lesions	−16/18 CIN2+
Secondary endpoints	Persistent infection, CIN1+, adverse events	Adverse events	Persistent infection or CIN1 + by any type; Adverse events	Adverse events	Adverse events

[a] Interim analysis of projected four year follow-up trial

CIN: Cervical intraepithelial neoplasia; CIN1+: CIN grade 1 or worse; CIN2+: CIN grade 2 or worse; FUTURE: Females united to unilaterally reduce endo/ectocervical disease; GSK: GlaxoSmithKline; PATRICIA: Papilloma trial against cancer in young adults.

Sources of data: [6–10]

Table 3

Inclusion criteria for according to protocol (ATP) and modified intention to treat (MITT) or intention to treat (ITT) analyses.

Study	ATP	MITT/ITT
GSK 001/007[a]	Seronegative for HPV-16 and 18; negative for high-risk HPV DNA at enrollment. HPV-16/18 DNA negative at month 6. Received all 3 doses. No protocol violations. Start case counting at dose 3 (month 6).	MITT: Seronegative for HPV-16 and 18; negative for high-risk HPV DNA at enrollment.. Received at least 1 dose. Start case counting at 1st dose.
Merck 007	-6/11/16/18 DNA- and seronegative at enrollment. Remained DNA-negative to same vaccine HPV type(s) (to which they were negative at enrollment) through 1 month post dose 3. Received all 3 doses within 1 year. No protocol violations. Start case counting 1 month post dose 3.	MITT: -6/11/16/18 DNA- and seronegative at enrollment. Received at least 1 dose. Start case counting at month 1.
PATRICIA	Not reported in interim analysis.	MITT: -16/18 DNA- and sero-negative at enrollment. Received at least 1 dose. Start case counting at 1st dose.
FUTURE I/II	-6/11/16/18 DNA- and seronegative at enrollment. Remained DNA-negative to the same vaccine HPV type(s) (to which they were negative at enrollment) through 1 month post dose 3. Received all 3 doses within one year. No protocol violations. Start case counting 1 month post dose 3.	MITT: -6/11/16/18 DNA- and seronegative at enrollment. Received at least 1 dose. Start case counting at month 1. ITT: All randomized participants regardless of HPV DNA or cervical disease status at entry. Start case counting at 1st dose.

[a] For the analyses reported in [8].

ATP: According to protocol; FUTURE: Females united to unilaterally reduce endo/ectocervical disease; GSK: GlaxoSmithKline; ITT: Intention to treat; MITT: Modified intention to treat; PATRICIA: Papilloma trial against cancer in young adults.

Table 4

Prophylactic efficacy of VLP vaccines against infection and lesions related to vaccine targeted HPV types.

Vaccine	Study	Number of subjects		Endpoints	Efficacy[a]		
		Vaccine group	Placebo group		ATP	MITT	ITT
Gardasil®	Merck 007	235	233	HPV persistence (4 months)	96 (83 – 100)	94 (83 - 98)	NR
	Merck 007	235	233	External genital lesions	100 (<0–100)	100 (<0–100)	NR
	Merck 007	235	233	CIN 1+, AIS	100 (<0–100)	100 (31 – 100)	NR
	FUTURE I	2,241	2,258	CIN 1+, AIS	100 (94 – 100)	98 (92 – 100)	55 (40 – 66)
	FUTURE I	2,261	2,279	External genital lesions	100 (94 – 100)	95 (87 – 99)	73 (58 – 83)
	FUTURE II	6,087	6,080	CIN 2+, AIS	98 (86 – 100)	95 (85 – 99)	44 (26 – 58)
	GSK 001/007	414	385	HPV persistence (6 months)	96 (75 – 100)	94 (78 – 99)	NR
Cervarix®	GSK 001/007	414	385	HPV persistence (12 months)	100 (52 – 100)	94 (61 – 100)	NR
	GSK 001/007	481	470	CIN 1+	NR	100 (42 – 100)	NR
	GSK 001/007	481	470	CIN 2+	NR	100 (−8 – 100)	NR
	PATRICIA	6,344	6,402	HPV persistence (6 months)	NR	80 (70 – 87)	NR
	PATRICIA	3,386	3,437	HPV persistence (12 months)	NR	76 (48 – 90)	NR
	PATRICIA	7,788	7,838	CIN 1+	NR	89 (59 – 99)	NR
	PATRICIA	7,788	7,838	CIN 2+	NR	90 (53 – 99)	NR

[a] 95% confidence intervals, except 97.9% confidence intervals used in PATRICIA.

AIS: Adenocarcinoma in situ; ATP: According to protocol; CIN: Cervical intraepithelial neoplasia; CIN1+: CIN grade 1 or worse; CIN2+: CIN grade 2 or worse; FUTURE: Females united to unilaterally reduce endo/ectocervical disease; GSK: GlaxoSmithKline; ITT: Intention to treat; MITT: Modified intention to treat; NR: Not reported; PATRICIA: Papilloma trial against cancer in young adults.

Table 5

Immunogenicity bridging studies.

Study	Vaccine	Study Groups/Age years (N)	Serologic Assay	% Sero-conversion[a]	Major Conclusions*
Reisinger KS *et al.* 2007 [12]	Gardasil®	Boys: 9-16 (567) Girls: 9-15 (617)	cLIA	≥99.5 for all types ≥99.6 for all types	GMTs for boys non-inferior to those in girls Boys GMT 1.1-1.5 fold higher than girls
Block SL *et al.* 2006 [26]	Gardasil®	Boys: 10-15 (510) Girls: 10-15 (506) Women: 16-23 (513)	cLIA	≥99.7 for all types 100 for all types ≥99.1 for all types	GMTs for boys and girls non-inferior to those in women Boys GMT 1.8-2.7 fold higher than women's Girls GMT 1.7-2.0 fold higher than women's
Pedersen C *et al.* 2007 [27]	Cervarix®	Girls: 10-14 (158) Women: 15-25 (458)	ELISA	100 for both types 100 for both types	GMTs for girls non-inferior to those in women Girl's GMT 2.1-2 fold higher than women's

[a] According to protocol (ATP) analyses one month after 3rd vaccine dose.

cLIA: Chelated ligand internalization assay; ELISA: Enzyme linked immunosorbent assay; GMT: Geometric Mean Titer.

Sources of data: [12,26,27].