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Chapter 27: Research needs following initial licensure of virus-like particle HPV vaccines

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Abstract

Human papillomavirus virus-like particle (HPV VLP) HPV vaccines currently evaluated for licensing are likely to be available soon. Licensure will be based on evidence that the vaccine is well tolerated and provides near complete type-specific protection against HPV infections and their resulting lesions in the first few years after vaccination. Several important questions will remain to be answered after licensure to guide vaccine implementation and to permit the rational evaluation of vaccination in cancer prevention programs. These include the long-term safety and efficacy of vaccination, the optimal ages for vaccination, efficacy against HPV types not included in the vaccine and against existing infections, and efficacy in males. Modulators of vaccine efficacy (e.g., HIV infection) and immune mechanisms of long-term protection also remain to be defined. The real-world effectiveness of vaccination programs will need to be assessed. Issues related to the implementation of a vaccine that targets pre-adolescents and early adolescents and to the acceptability of a cancer vaccine targeted against a sexually transmitted infection will need to be understood before vaccination programs can be successful. It is hoped that continued improvements to the current HPV vaccines will lead to the introduction in future years of second generation vaccines that simplify delivery and/or expand its coverage. Finally, the natural history of HPV types not covered in the candidate vaccines will need to be carefully studied following vaccination. Public health authorities in various countries will play a pivotal role in determining if these questions are answered in a timely manner.
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1. Introduction

Published data on the first-generation virus-like particle (VLP) HPV vaccines suggest that HPV vaccines produced by Merck Pharmaceuticals (HPV-6/11/16/18 vaccine, Gardasil) and GlaxoSmithKline (GSK) Biologicals (HPV-16/18 vaccine, Cervarix) are highly effective at preventing persistent infection and cytological lesions associated with the target HPV types. Large-scale phase III efficacy trials are underway. These ongoing efforts are discussed in Chapter 13 of this monograph. Results from these trials will provide the data on vaccine safety and efficacy necessary for licensure of these two vaccines in various countries in the near future.

While initial vaccine licensure will be based on evidence of short term (<5 years) safety and efficacy, many questions remain to be answered to guide important decisions about whether and how country-specific vaccination programs should be implemented. Unlike other vaccines already on the market, the HPV vaccine will be licensed at a time when effective secondary prevention alternatives exist in some regions for the prevention of HPV-associated cervical disease (cytological and HPV-based screening) [1,2], and

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when other effective vaccines (e.g., rotavirus) [3,4] that target important public health problems are competing for limited resources in countries with a high disease burden. HPV vaccines also differ from most other available vaccines in targeting an adolescent age group not previously the focus of vaccination efforts in most countries. This makes implementation of vaccine programs more difficult, complex, and potentially costlier than for other vaccines. In addition, the main disease to be prevented is cancer, which occurs years after the target age for vaccination, and HPV is a sexually transmitted infection making vaccination in early adolescence potentially controversial.

This chapter focuses on summarizing some of the important questions that need to be answered to guide rational implementation of HPV prevention programs worldwide. While some of these questions can be answered from existing or already planned studies, others may require extended follow-up of participants in current studies and/or the establishment of new or longer term studies. Since, these studies will be conducted post-licensure, designs other than classical randomized clinical trials may be required.

2. Gaps in our understanding

The remainder of this chapter will focus on describing important questions that are expected to remain unanswered at the time of initial licensure of virus-like particle HPV vaccines. Specific studies designed to address some of the questions raised herein will be discussed in the chapter that follows (see Chapter 28).

2.1. Questions regarding vaccine efficacy

2.1.1. Long-term safety profile

Results from phase II trials suggest that VLP-based HPV vaccines are safe and well tolerated (see Chapter 13). Phase III pivotal trials should provide additional safety data for a period of up to 4 years on a group of close to 50,000 individuals. However, since licensure is likely to occur based on interim data obtained after an average of <2 years of follow-up post-vaccination, continued active follow-up of participants in phase III trials and active safety assessment in post-licensure phase IV trials will be important to our understanding of the long-term safety of HPV vaccines. Long-term safety data is essential for an HPV vaccine, since it will likely target hundreds of millions of young, healthy individuals worldwide who are otherwise not subject to epidemiological surveillance. For example, the HPV vaccine will target individuals in adolescence and young adult life, a period when several chronic diseases are often first diagnosed (e.g., diabetes and autoimmune conditions). Determination of whether disease rates after vaccination of young individuals occur at expected population rates or represent adverse experiences linked to vaccination will require careful and active follow-up of vaccinated populations.

2.1.2. Vaccination of young women and pregnancy

HPV vaccination will likely be offered to women at or close to their peak reproductive ages. The risk to a developing fetus from vaccination during pregnancy is primarily theoretical. No evidence exists of risk from vaccinating pregnant women with subunit viral vaccines [5,6]. Data from HPV vaccine trials to date have not suggested any adverse effects on pregnancy outcomes. Nonetheless, since women in their reproductive prime may be included in populations targeted for HPV vaccination, the evaluation of the effects of vaccination on pregnancy and pregnancy outcomes will be important. Only careful and active safety assessment post-licensure will enable a formal and comprehensive evaluation of this issue.

2.2. Questions regarding vaccine efficacy

2.2.1. Duration of protection

Establishing duration of protection following HPV vaccination is of paramount importance. Data available to date suggest that HPV vaccines are close to 100% effective in the first few years following vaccination. Prevention of cervical cancer will require many more years of protection, however, or at least protection that lasts through the peak years in which individuals are most at risk of HPV infections that could lead to cancer. While it is likely that boosters would be able to extend protection, should protection wane over time, the need for periodic vaccine boosters beyond the initial doses would render vaccination programs more complex and costly. These issues will be of great importance when evaluating the cost-effectiveness and overall desirability of such programs relative to alternative cervical cancer prevention based on screening or a combination of vaccination and screening.

2.2.2. Defining optimal ages at vaccination

Given that the current HPV vaccines are likely to provide excellent prophylactic protection but at most limited therapeutic benefit, and that prevalence of HPV infection is usually highest in the first few years after initiation of sexual activity, HPV vaccination programs should target young adolescents or pre-adolescents. However, should protection afforded by HPV vaccination be long-term or even lifelong, incorporation of HPV vaccination into existing childhood vaccination programs might ultimately prove to be a rational and cost-effective approach in many countries. This highlights the importance of understanding the durability of HPV vaccine protection.

Also poorly understood is whether vaccination of adults is likely to be an effective way of reducing cervical cancer morbidity and mortality. The potential benefit of vaccinating adults of various ages hinges on an understanding of the dynamics of HPV infection. While prevalence of HPV infection peaks in the few years after sexual debut, not all women are infected with the HPV types that current vaccines are designed to prevent, and a sizeable proportion of first HPV infections with types included in the vaccine might occur

in later years. Also, individuals who are infected with HPV types included in the vaccines and who clear these infections might be protected through vaccination against re-infection with the same HPV types in later years. An important question is whether protecting from re-infection women who successfully cleared previous HPV infections in the absence of vaccination would reduce cervical cancer rates. It is possible that efforts might be wasted on protecting those who do not require protection, while neglecting to protect those who are not innately able to clear infection and who are, therefore, at highest risk of developing cancer.

2.2.3. *Protection against HPV types other than HPV-16/18 (cross-protection)*

Animal studies have suggested that protection afforded by VLP-based HPV vaccination will be type-specific (see Chapter 12). Limited data from published human trials using the Merck vaccine confirm this expectation [7]. In contrast, preliminary results suggest the possibility that an HPV-16/18 vaccine might protect against infection by other HPV types that are phylogenetically related to either HPV-16 or HPV-18 [8]. Additional formal evaluation of this question is needed so that the degree of coverage provided by current generation vaccines can be well understood.

2.2.4. *Treatment of established infections*

HPV-DNA testing has been incorporated into cervical cancer screening programs in some countries [2]. This has resulted in the detection of asymptomatic HPV infections in large numbers of women who have no or only mild cytological evidence of disease. Women with evidence of oncogenic HPV infections might want to avail themselves of HPV vaccination. Whether or not vaccination should be encouraged for such women is still unclear. Animal studies have suggested that the effect of VLP-based HPV vaccines are limited to prophylaxis, and that vaccination is unlikely to protect those already infected with the virus (see Chapter 12). Very preliminary human data suggest that any therapeutic benefit of VLP-based HPV vaccination will be limited at best [9]. Rapid, formal evaluation of this question will be possible since large numbers of women with prevalent infection have already received HPV vaccination in phase III trials.

2.2.5. *Efficacy in males*

While the HPV vaccine is expected to be highly immunogenic for both genders, it is unclear whether vaccination of males is warranted or required for the prevention of HPV-associated diseases, particularly, neoplasia. Given that the male external genitalia is not bathed in antibody-containing mucus as is the case for the female reproductive tract, one might speculate that vaccination of males would be less effective at preventing HPV infection in males than vaccination of females. However, since the establishment of HPV infection is believed to require skin abrasion and exposure of cells in the basal layer of the epithelium, it is also plausible that antibody transudation resultant from abrasion would be sufficient to protect males against infection. Another important aspect of the HPV vaccine that is poorly understood is whether male vaccination would reduce transmission of HPV infection from males to females via reductions in infection in men or in viral load; if so, two-gender vaccination programs might provide additional impact. Given that disease burden associated with HPV infection disproportionately affects females, the ultimate decision of whether to vaccinate females only or both females and males will likely be based in part on whether an emphasis on achieving high coverage of vaccination among females is more or less effective than a strategy that targets both genders. Societal issues, including the need to avoid stigmatizing women by targeting vaccination against a sexually transmitted infection to a single gender, will likely also influence decisions of whether males should be vaccinated. Furthermore, by including HPV types 6 and 11, the Merck vaccine may prevent genital warts in males. This additional benefit may impact decisions about vaccinating males. To assist policymakers, data from efficacy studies in males are needed in conjunction with modeling efforts to evaluate the marginal costs and benefits of including men in vaccination programs.

2.2.6. *Modulators of vaccine immunogenicity/efficacy*

While carefully controlled trials have shown excellent efficacy among healthy individuals, it is not yet known whether this high degree of protection will be broadly observed. It is not known, for example, how the vaccine will perform among individuals infected with HIV. Similarly, it is not known how the vaccine will perform among individuals with chronic conditions, such as malaria, helminth infections or malnutrition. Answering these questions is of particular relevance for African populations with high rates of HIV and other chronic conditions affecting immune response.

Also, in some countries, vaccines other than the HPV vaccine are recommended for adolescents. Although, most non-live vaccines can be administered simultaneously without cross-interference on the immune response, simultaneous administration of HPV vaccines with other vaccines should be assessed.

2.2.7. *Defining immunological mechanisms of action*

A unique opportunity exists with the HPV vaccine to help our understanding of immunological mechanisms of protection against mucosal and sexually transmitted infections. Thoughtful use of biological specimens and information collected from participants in phase III trials would permit an in-depth evaluation of protection mechanisms, which in turn would help define minimal levels of immune response required for protection (below which boosting may be recommended), surrogate markers of a protective immune response that could be used to expedite the development of second-generation vaccines (see below and Chapter17), and could potentially inform efforts at developing new vaccines targeting other mucosal infections.

2.3. Design considerations for post-licensure studies of safety and efficacy

Many questions will need to be answered using data collected after licensure. Once a vaccine is licensed, the ethics of conducting new placebo controlled trials could be questioned, making post-licensure evaluation of the HPV vaccines more difficult. While it is beyond the scope of this chapter to review study designs that could be considered for post-licensure studies, the following points are offered.

First, when the objective is to evaluate the vaccine in groups where safety and efficacy is not yet established (e.g., HIV-positive individuals), conduct of placebo-controlled trials will remain ethical post-licensure. Second, consideration should be given to whether cytology and/or viral screening constitutes an adequate alternative to vaccination within clinical studies, and if so, whether implementation of such programs would permit designs that include a non-vaccination arm. It should be noted that high-quality screening could protect recipients more broadly than vaccination, since it is designed to detect cervical lesions regardless of the HPV type involved. In contrast, available HPV vaccines are designed to protect only against lesions caused by a subset of oncogenic HPV types. Finally, in instances where the conduct of trials with a non-vaccination arm are deemed unethical, consideration should be given to the need for studies within populations with systematically collected historical rates that can be used as comparators for outcomes of interest. For example, when evaluating the long-term safety of vaccination in a study without a placebo arm, historical rates from population-based hospital registries would be useful. Similarly, when evaluating the long-term impact of vaccination on rates of cytological abnormalities, data from population-based cytology registries would be ideal. To the extent that population-based registries are used as comparators in these studies, the group of individuals selected for study should be representative of the population from which the registry data derive. In these instances, active follow-up might also be required, to avoid underestimation of rates that result from more passive follow-up studies.

2.4. Questions regarding vaccine effectiveness

Pre-licensure studies focus on evaluating efficacy of a vaccine under carefully controlled conditions. Strict eligibility criteria are applied when selecting individuals for such studies, and analyses used for licensure are typically restricted to participants who comply with all protocol criteria. These include receipt of all three doses of the vaccine within predefined, restricted time windows, and the absence of evidence of HPV exposure and disease prior to or during the vaccination period. While these restrictions are justified for formal evaluation of the ideal/maximal level of efficacy expected from a new vaccine, vaccination programs implemented post-licensure may not achieve such maximal levels of success. Evaluation of vaccine effectiveness post-licensure is, therefore, critical to determine the real world impact of vaccination programs. This is particularly true for the HPV vaccine, where the success of vaccination programs and their associated costs will need to be evaluated against that of or in combination with alternative cytological and/or HPV-DNA screening programs [10,11].

In the chapter that follows (Chapter 28), some examples of demonstration projects post-licensure are discussed. In principle, these studies should be designed to answer the following question: "What is the impact of vaccination on disease burden in my population?" Outcomes considered to address this question will vary by population, depending in part on whether effective and comprehensive cervical cancer screening programs already exist, but could include cervical pre-cancers (cervical intraepithelial neoplasia grade three and *in situ* cancers), and cytological abnormalities and/or HPV infections detected within existent screening programs that require medical interventions (e.g., colposcopic referral or more intensive screening). As highlighted above, it would be ideal to conduct such demonstration projects in regions with established tumor/cytology registries to permit complete ascertainment of outcomes. In regions where registries are not in place or are incomplete, active follow-up may be required to ensure that the impact of the vaccination program can be measured with accuracy. In such instances, virological outcomes should be considered, as they represent necessary intermediate outcomes that precede the development of cervical pre-cancers and cancer.

Unlike efficacy trials, demonstration projects that assess vaccine effectiveness are likely to vary by population, where social, behavioral, economic, and geographic conditions vary. This makes results from such studies generalizable only to regions with similar conditions to those where the demonstration project was conducted. Questions that need to be addressed within the context of vaccine introduction include the possible impact on sexual behavior and health seeking behavior related to cervical cancer screening in countries with existing programs.

A unique aspect of post-licensure projects of the HPV vaccine, in countries where implementation of cervical cancer screening programs are also envisioned, will be the need to evaluate alternative prevention methods that rely on vaccination alone, cytology or HPV DNA screening alone, or a combination of the two. Due to its complexity, evaluation of these demonstration projects should be conducted in the context of formal economic evaluation analyses that permit careful comparisons between various prevention strategies (see Chapter 21) [10,11].

2.5. Logistics of HPV vaccine implementation

The greatest benefit of HPV vaccines will be achieved if vaccination is targeted to pre-adolescents and early adolescents before sexual debut. The most appropriate age range will vary by country according to age of sexual initiation and

other important characteristics, such as school attendance or health insurance availability.

Research is needed to identify optimal strategies for reaching pre-adolescents and early adolescents, a population not traditionally targeted for routine or mass immunization programs and one which has historically exhibited low rates of health service encounters. Operational research could focus on identifying whether school-based or vaccination in traditional medical settings achieve higher coverage. In countries where primary or early secondary school enrollment is high or expanding, evaluation of the proportion of young people who could be reached in schools could be informative. The three-dose schedule will be challenging. For hepatitis B vaccine, compliance with the three-dose vaccine schedule in adolescents proved difficult to achieve in some countries, and despite success in reducing access barriers, differences in uptake persist across countries, and within countries by ethnicity, gender, and socio-economic class.

Any vaccination program should educate the population regarding the need for vaccination to increase community understanding. Most families are aware of the need for infant immunizations, but are uninformed of the need for immunization adolescence. Motivating individuals and parents to comply with vaccination recommendations could play a significant role in efforts to achieve high coverage.

2.6. Vaccine acceptability

The ultimate success of an HPV vaccination program will depend on variables related to healthcare systems, providers, and parents/adolescents. Research has shown a high acceptability of HPV vaccines among parents, predominantly motivated by a desire to protect their children [12]. Studies regarding parental approval of HPV vaccination identified perceived vulnerability of the child to infection and perceived emotional severity of STIs as influencing factors, although, concerns that vaccination leads to unsafe sex remained an important predictor of acceptance. Research directed towards health providers suggests acceptance is also high and that approval by professional organizations increases acceptance. Most research on HPV vaccine acceptability has been conducted in developed countries, which have particular cultural and economic considerations that preclude application of results in developing countries (see Chapter 24). Future research should focus at the level of healthcare systems, providers, and patients and their families to identify potential barriers and enablers for successful vaccination strategies, particularly in developing countries. This should include research on high risk, hard to reach populations to ensure uptake among those most at risk of cervical cancer death.

2.7. Questions regarding alternative delivery approaches and second-generation vaccines

Efforts to develop HPV vaccines should not end after proof that first generation vaccines are safe and effective. First generation vaccines are costly to produce and distribute, require that three doses be delivered intramuscularly to a difficult to capture adolescent population over a 6-month period (assuming lifelong protection), and provide coverage against two of the over one dozen oncogenic HPV types (assuming lack of cross-protection). Effective delivery of this first generation vaccine in poorer regions where HPV-associated disease burden is highest will be a difficult endeavor that could benefit from improvements in vaccine manufacturing, delivery, administration, and coverage.

Questions that should be the target of future investigations include whether simplified vaccination schedules are as effective as the standard three-dose schedule (e.g., two rather than three doses given one year apart). More research would be needed to determine whether alternative delivery modes could be developed which simplify distribution and administration of the vaccine (e.g., needle-free delivery; single dose delivery using live vectors), or whether vaccines with increased valency or that incorporate a therapeutic component (e.g., vaccines that include or protect against additional oncogenic HPV types) can be manufactured cost-effectively. The reader is referred to Chapter 17 for a discussion of second-generation vaccine development efforts.

Evaluation of alternative schedules, delivery methods, and second-generation vaccines will require studies that demonstrate equivalency/superiority of new approaches compared to existent vaccines [13,14]. Such evaluation could require large, costly, and time-consuming trials that would significantly slow progress. To minimize delays in getting better, cheaper vaccines to countries with modest or limited resources, validation of early surrogate measures of vaccine efficacy, particularly immunologic, and virologic surrogates are needed. As alluded to earlier, efforts to understand the immunological mechanisms of protection by HPV vaccines could lead to the identification of such surrogate markers of protection that could be used to shorten the time and cost associated with the evaluation of novel HPV vaccination approaches.

2.8. Questions regarding natural history of HPV and cervical neoplasia post vaccine introduction

Widespread implementation and use of effective preventative vaccines will lead to the rise of a new focus in HPV research post-vaccination, where the natural history of HPV types not protected against by vaccination and their associated diseases will be explored. Among the many issues to be addressed by this new generation of etiologic research is the question of whether reductions in HPV-16/18 infections result in changes in the rates and distribution of infections with other HPV types, particularly, other oncogenic HPV types. While previous data that different HPV types are acquired independently [15] and that infection with multiple HPV types is common [16] suggest that replacement of HPV-16/18 with other HPV types is unlikely, a formal evaluation of this issue is needed before final conclusions are made.

Table 1
Summary of gaps in our current understanding of HPV vaccines

Topic	Specific issues that need to be addressed
(1) Vaccine safety	Long-term safety profile Safety during pregnancy
(2) Vaccine efficacy	Duration of protection Protection against types other than HPV-16/18 Treatment of established infections Efficacy in males Modulators of vaccine immunogenicity/efficacy Defining immune markers of protection
(3) Vaccine effectiveness	Monitoring via registries and/or active follow-up Region-specific impact of vaccination on disease burden Cost-effectiveness relative to alternative vaccination/screening combinations
(4) Logistics of vaccine implementation	Defining strategies for reaching pre-adolescents and early adolescents
(5) Vaccine acceptability	Defining population-specific barriers/enablers of vaccination strategies
(6) Alternative delivery approaches and vaccines	Simplified vaccination schedules Alternative delivery modes Increased valency Addition of therapeutic component to vaccine
(7) Natural history post-vaccine introduction	Replacement of HPV-16/18 with other HPV types

3. Summary

Safe and highly effective HPV vaccines under review by licensing authorities are likely to become available for use shortly. Enthusiasm for these new vaccines, while warranted, should not obscure the need for continued efforts to address gaps in our knowledge and to answer questions required to assist in the development and implementation of rational programs aimed at preventing HPV-related diseases. Some of the gaps in our understanding have been highlighted in this chapter. These are summarized in Table 1. Other questions are likely to arise in the future. Continued inquiry and attempts to answer these residual questions will hopefully ensure that initial enthusiasm for the HPV vaccine can be effectively translated into prevention programs that save lives and improve the public's health in a substantive manner throughout the world.

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References

[1] Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002;52(6):342–62.
[2] Wright Jr TC, Schiffman M, Solomon D, Cox JT, Garcia F, Goldie S, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2004;103(2):304–9.
[3] Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354(1):11–22.
[4] Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354(1):23–33.
[5] Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338(16):1128–37.
[6] Grabenstein JD. Pregnancy and lactation in relation to vaccines and antibodies. Pharm Pract Manage Q 2001;20(3):1–10.
[7] Mao C, Koutsky LA, Ault KA, Wheeler CM, Brown DR, Wiley DJ, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2006;107(1):18–27.
[8] Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367(9518):1247–55.
[9] Barr E. http://www.cdc.gov/nip/acip/slides/feb06/1-hpv/5-barr.ppt, 2006.
[10] Schiffman M, Castle PE. The promise of global cervical-cancer prevention. N Engl J Med 2005;353(20):2101–4.
[11] Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, Gordillo-Tobar A, Levin C, Mahe C, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med 2005;353(20): 2158–68.
[12] Zimet GD. Improving adolescent health: focus on HPV vaccine acceptance. J Adolesc Health 2005;37(Suppl 6):S17–23.
[13] Ware JH, Antman EM. Equivalence trials. N Engl J Med 1997;337(16):1159–61.
[14] Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials 1982;3(4):345–53.
[15] Liaw KL, Hildesheim A, Burk RD, Gravitt P, Wacholder S, Manos MM, et al. A prospective study of human papillomavirus (HPV) type 16 DNA detection by polymerase chain reaction and its association with acquisition and persistence of other HPV types. J Infect Dis 2001;183(1):8–15.
[16] Clifford GM, Gallus S, Herrero R, Munoz N, Snijders PJ, Vaccarella S, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet 2005;366(9490):991–8.