HUMAN PAPILLOMAVIRUS VACCINATION FOR THE PREVENTION OF CERVICAL AND OTHER RELATED CANCERS

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ABSTRACT

Academic research described in the late 1980's the causal association between human papillomavirus (HPV) and cervical cancer, later expanded to significant fractions of all other genital tract cancers in both genders as well as a proportion of the cancers of the oral cavity and oropharynx. Prophylactic phase III HPV vaccine trials have shown complete type specific vaccine efficacy against two HPV types, namely HPV 16 and 18, that together account for over 70% of cervical cancer worldwide. HPV vaccines have proven in trials to have an excellent safety record. Most developed populations have introduced HPV vaccines as part of their routine vaccination schemes and introduction into developing countries is being actively planned. In 2012, over 100 million vaccine doses have been delivered and records of continuous efficacy and safety are encouraging. Comprehensive strategies of HPV vaccination and HPV based screening tests could theoretically eliminate cervical cancer in defined populations.

TABLE OF CONTENTS

1 Establishment of the causality link between HPV infections and cancer.

1.1 Etiology

The etiology of cervical cancer has been significantly linked to persistent infection with up to 15 strains of Human Papillomavirus (HPV). The association is consistent worldwide and causality has been generally accepted based on molecular epidemiological studies, including prevalence surveys, case control studies, cohort studies using cervical intraepithelial neoplasia (CIN) of grade 2/3 as surrogate endpoints, and screening studies. More recently, HPV vaccination trials have consistently concluded that vaccination against HPV types 16 and 18 could virtually eliminate the occurrence of HPV 16/18 related CIN 2/3 if given to individuals not carrying the infection at the time of vaccination, thus providing the ultimate proof of causality in human populations.

The International Agency for Research on Cancer (IARC) Monograph Working Group(International Agency for Research on Cancer (IARC). 2007) concluded that there was sufficient evidence in humans for the carcinogenicity of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 in the cervix. HPV types 26, 66, 68 73, and 82 were found to be associated with cervical cancer in some case-control studies, but the prevalence was very low in case series. For some rare types (HPV types 26, 53, 68, 73, and 82), the odds ratios (OR) observed are of similar magnitude to that of HPV 66 but, given the low prevalence observed in cases, these types were temporarily classified as "probably" carcinogenic or, for HPV 66, as "limited evidence"(Bouvard and Baan et al. 2009). The consensus to date is that HPV is the central and necessary cause of cervical cancer and that at least fifteen HPV types are capable of inducing an invasive cancer.

1.2 HPV DNA type distribution in cervical cancer and rationale for HPV 16 and 18 vaccines

The distribution of HPV types in cervical cancer has been published in a pooled analysis of about 3000 cases from the IARC program (Munoz and Bosch et al. 2004) and in a meta-analysis of about 14,000 cases(Smith and Lindsay et al. 2007) The eight most common HPV types detected in both series, in descending order of frequency, were HPV types 16, 18, 45, 31, 33, 52, 58, and 35, and these are responsible for about 90% of all cervical cancers worldwide. Two of the types - HPVs 16 and 18 - are consistently found associated with at least 70% of the cases on several worldwide estimates(Bosch and Manos et al. 1995; de Sanjose and Quint et al. 2010; Munoz and Bosch et al. 2004) and these were identified as the two types included in the first generation of Virus like particle (VLP) HPV vaccines. The results have been recently confirmed in two landmark studies, one in the US population(Wheeler and Hunt et al. 2009) and a large international survey, including specimens from close to 40 countries and slightly over 10,000 cervical cancers cases (de Sanjose and Quint et al. 2010)

These two studies are critical because they used unified criteria for the field work, centralized laboratory protocols both for pathology and for HPV testing and typing and unified statistical treatment of the data, particularly on the causality attribution to any given HPV type when multiple infections were detected in a specimen. These two

studies largely overcome the limitations inherent to metanalyses and other forms of literature summaries. The HPV type distributions in cancer are geographically consistent in identifying HPV 16 and 18 followed by 45, 31 and 33 as the leading HPV types with moderate variability in the third and subsequent types (for example in the cases from Asia - particularly from Japan - where HPV types 58, 33 and 52 were relatively common). These distributions are sensitive to the technologies employed for HPV testing and typing as well as to the methods used to attribute causality when there are multiple HPV types in a given specimen. Of interest is the finding that cervical adenocarcinoma is a subtype of cervical cancer related almost solely to three HPV types (16, 18 and 45), with a 10-fold gap in prevalence between the third most common type and any other type (de Sanjose and Quint et al. 2010).

1.3 The role of HPV in genital cancers other than cervical

The available clinical and epidemiological studies indicate that cancers of the vagina and of the anus resemble cancer of the cervix with respect to the role of HPV. In both cases, HPV DNA is detected in the majority of tumors and particularly of their precursor lesions. In recent reviews, between 64% and 91% of vaginal cancer cases and 82% and 100% of vaginal intraepithelial neoplasia of grade 3 (VAIN 3) lesions are HPV DNA-positive. In anal cancers in both genders, HPV DNA is detected in 88–94%. An estimated 40-50% of cancers of the vulva have also been associated with HPV as have some 40% of the penile carcinomas. The evidence available for some of these sites is not as comprehensive as for cervical cancer, although causality has been generally recognized (Forman D. 2012; International Agency for Research on Cancer (IARC). 2007)

In all HPV positive anogenital cancers, HPV 16 is the most common HPV type detected, followed by HPV types 18, 31, and 33. The combined contribution of HPV 16 and 18 has been estimated in a range of 88-93 %, significantly higher that the relative contribution to cervical cancer. (de Vuyst and Clifford et al. 2009; Miralles-Guri and Bruni et al. 2009)

1.4 The role of HPV in head and neck cancers

HPV DNA can be consistently identified in a significant fraction of cancers of the oropharynx (i.e. in the 40 to 50% range) and in smaller proportions of the specimens of the remaining cancer of the oral cavity and the larynx (5 to 15%)(Gillison. 2012; Gillison and Koch et al. 2000)

Cancers of the head and neck and particularly of the oropharynx are becoming of increasing interest since time trends suggests that incidence is on the rise; it strikes young individuals of both genders, is unrelated to alcohol or tobacco consumption and linked to patterns of sexual behaviour involving multiple partners and oral sex.(D'Souza and Fakhry et al. 2007; Heck and Berthiller et al. 2010; Rintala and Grenman et al. 2006). For these cancers no screening opportunities have been previously identified. In estimates and projections of the cancer incidence in the US, it has been estimated that numerically these cancers are likely to become more frequent than cervical cancer (Chaturvedi and Engels et al. 2011) Similar trends have been observed in the Nordic countries (Nasman and Attner et al. 2009). However, the natural history of oral HPV infections and the additional risk factors of neoplastic transformation as well as the

characterization of the pre-neoplastic lesions that could be amenable to screening are largely unknown.

Of interest is the observation that HPV related head and neck cancers are of increased sensitivity to treatments with chemotherapy and radiotherapy as compared to the HPV unrelated cases, usually linked to alcohol and tobacco consumption. HPV testing is increasingly adopted as part of the routine diagnostic work up of these cancers and is a useful guide to clinical management (Ragin and Taioli. 2007).

2 Phase III vaccination trials: synthesis of the critical results

There are currently two HPV vaccines identified as Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ, USA) and Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium). Gardasil targets two oncogenic HPV types (16 and 18) and two non oncogenic HPV types (6 and 11) responsible for genital warts and respiratory papillomatosis. Cervarix targets two oncogenic HPV types (HPV 16 and 18) and is formulated with a novel adjuvant ASO4 included to boost the immune response. The essential results of the Phase III clinical trials have been already provided and these two vaccines are currently licensed in over 120 countries. Most developed countries have introduced HPV vaccines into routine vaccination programs with specific recommendations and more than one hundred million doses have already been distributed in 2011.

Phase III results for both vaccines are available for women in the 15-26 age range (see table 2.1). Trials have examined vaccine efficacy (VE) in several cohorts of HPV unexposed and exposed women and in several age ranges. For simplicity, results in table 2.1 are presented in qualitative format and reflect VE in the most appropriate study cohort. In addition, several ancillary protocols have been completed or are under way including bridging studies in the 9-15 years of age for both girls and boys and in the 26-45 years of age women. More limited information is also available of the VE in adult men and in special populations (immunosuppressed transplant patients, HIV infected populations, infants and other).

[Table 2.1](Bosch and de Sanjosé et al. 2008; Schiller and Castellsague et al. 2008)

These two vaccines have shown to date a very high efficacy against the predefined endpoint lesions (HPV 16 or 18 related CIN 2 or superior [CIN2+]), adequate safety and tolerability profiles, high immunogenicity, duration of protection so far of 7-8 years, and strong indications of ability to induce immune memory. Interestingly, some degree of cross protection against CIN 2+ related to other HPV types (HPV 31 for both vaccines and HPV 33 and 45 for Cervarix) has been documented. Therefore, the global estimates of the protection against cervical cancer of the currently available vaccines in properly vaccinated populations range from strictly 70% of the cervical cancer cases attributed to HPV 16 and 18 to a range of 75-80% adding non-vaccine HPV type cross-protection. The latter however still requires some additional evaluation in terms of quantification of the vaccine efficacy estimates and on the potential duration of the protective effect of the types not included in the vaccine. None of the vaccines has shown therapeutic activity. Finally, it is important to note that these estimates show

little geographically variation, thus these vaccines should be considered of global validity.

The limitations of current vaccines are known and include the lack of therapeutic effect, the limited impact of the cross protection effect and, as a consequence of the two, the requirement to continue some form of screening programs among vaccinated women. Finally, the cost of the production technology is high translating into the high cost of the vaccine at least in the early years after introduction in developed countries(Global Advisory Committee on Vaccine Safety 2009; Centers for disease control and prevention. 2009; European center for disease prevention and control (ECDC). 2008; Markowitz and Dunne et al. 2007; Schiller and Castellsague et al. 2008).

In addition to the pivotal Phase III trials, additional research has generated critical information to guide the use of the HPV vaccines. Amongst the most relevant results, trials that have examined vaccine efficacy among women up to the age of 45 have shown that even though the antibody titers generated by vaccination are lower, protection against persistent infection and CIN 2+ lesions is high(Castellsague and Munoz et al. 2011). This observation prompts the suggestion of expanding the use of HPV vaccines beyond the currently recommended age groups.

Although protection against other cancer sites was not the primary objective of the phase III trials, vaccinated women showed a remarkable reduction of the incidence of pre neoplastic lesions of the vulva (VIN 2/3) the vagina (VAIN 2/3) and in some trials of the preneoplatic lesions of the anal canal (AIN 2/3). Trials of the Gardasil vaccine have shown very high efficacy in the protection against genital warts in both males and females.(Schiller. 2012; Schiller and Castellsague et al. 2008)

The vaccine efficacy observed in preventing genital warts in vaccinated men and the herd immunity observed among male populations coexisting with a highly vaccinated female population in Australia, allows the speculation that vaccination will also protect vaccinated males against the HPV-related fraction of penile carcinomas. It is unlikely that a specific trial would ever evaluate specifically the preventive potential of HPV vaccines against such a rare disease. However the observation deserves long term monitoring of trends in penile cancer incidence in populations that introduce male vaccination or that achieve very high vaccination rates among women.

There is little information on the preventive potential against the HPV related cancers of the oropharynx or on the reduction of respiratory papillomatosis of the newborn and infants following generalized introduction of the vaccine Gardasil that includes VLP’s of HPV 6 and 11 as antigens.

3 HPV vaccine introduction and early population-based results

HPV vaccines were first used in 2006 and gained rapid support among international and national licensing offices and advisory boards. General recommendations gave priority (and in many instances allocated state supported vaccination costs) to young girls / adolescents prior to the average ages at onset of sexual activity. Catch-up vaccination of sexually active women is more variable across countries. Licensing has

been generally granted to ages 45 based on a limited number of trials showing safety, immunogenicity and efficacy against persistent HPV infection and CIN 2+ lesions.

In countries with centralized programs and state supported vaccine costs, coverage of the target populations (adolescents and young girls) is very high and in a few settings, early evaluations of the clinical impact has already been shown. For example, in Australia an enlarged vaccination program offered for two years free vaccination to women up to the age of 26. The program was well coordinated amongst all stakeholders and coverage reached a significant 65-70% of the target population, girls 12-14, and some 50% coverage of the catch-up older population, women 15 to 26. In the program Gardasil was the only vaccine used. Early results were provided in an ecological type of study reporting on the relative contribution of genital warts to the series of clinical cases attended in a STD clinic in Melbourne (the average number of annual patients at the clinic was reported as close to 53,000 per year of which some 5000 attended because of genital warts). In this non controlled clinical observation, three years after vaccine introduction a significant reduction in the diagnosis of genital warts has been recorded and some indication of herd immunity is being documented. The latter is observed by a significant reduction in the number of episodes of genital warts amongst heterosexual males (largely non-vaccinated) in the same clinics where the reduction amongst females was documented. In the same analyses, genital warts in male homosexuals during the interval remained constant as was the level of all other STDs(Fairley and Hocking et al. 2009). The analyses strongly suggest that the reduction in incidence of genital warts in males was a consequence of the high vaccination coverage of the female population in the same age range. A significant reduction of the cases of CIN 1+ and CIN 2+ in these populations has been also recorded within the first four years of the vaccination program (Brotherton and Fridman et al. 2011).

Very high coverage rates with Cervarix have also been achieved in the United Kingdom among the target populations aged 12-13 and the catch-up population of up to 18 years of age. A significant advantage in coverage has been generally observed in areas where vaccination is offered in the context of school based programs. Similar observations have been reported within countries (i.e., the different autonomous regions in Spain) by comparing subpopulations served by school based programs with populations served by health centre based programs. Even with an equivalently centralized subsidy of the vaccine costs (the cost of the vaccination program has to be regionally supported), compliance is far better if controlled school based programs are implemented.

A number of other examples have been reported from developing areas of the world where HPV vaccination has been introduced as part of controlled demonstration programs. One of such programs was lead by the Program for Appropriate Technology in Health (PATH) and explored strategies of vaccine introduction in four areas in Peru, Vietnam, India and Uganda. These projects have concluded amongst others that vaccine acceptance by the population is satisfactory, that a strategy of using school-based vaccination programs in urban areas is highly appropriate but combined programs of school and outreach visits is necessary in areas were the population is dispersed and school attendance is likely to be insufficient. Moreover, strategies based on campaigns in Uganda (Child Plus Days) unveiled the complexity of targeting girls based on age rather than on school grade. The former, particularly if age is restricted to single cohorts, generated a significant time loss and reduced coverage in trying to verify age.

In other populations of the developing world such as Bhutan or Panama where HPV vaccine was offered free of charge, vaccination coverage has been very satisfactory (Markowitz. 2012).

4 Issues in vaccine use and introduction

Early indications following Phase III trials were strongly driven by the priority of preventing cervical cancer. At this stage however, advances in the understanding of the spectrum of cancers related to HPV, the results of additional vaccination trials and the evolution of vaccine costs, strongly indicate that some the original preventive indications are unnecessarily self-limited.

4.1 Single gender vaccination.

HPV was first recognized as a cause of cervical neoplasia and all subsequent preventive efforts were oriented towards cervical cancer, the second most frequent cancer in women worldwide. However, research has identified the same HPV types, notably HPV 16, as the cause of a fraction of almost all genital tract cancers in men and women and more recently, of a significant fraction of cancers of the oral cavity and oropharynx. Furthermore, HPV vaccine trials in males have shown the potential of HPV vaccines to prevent genital warts (if Gardasil is used) and anal preinvasive lesions (AIN 2/3).

Previous experiences with other vaccines (i.e. rubella) showed that in certain cultural environments, female only vaccination prompted rumors and negative attitudes towards vaccination on the grounds of unjustified side effects or more extravagant proposals such as the existence of international plots to sterilize young women or other. As a result interruption or irregular coverage of all vaccines occurred and subsequent outbreaks of previously controlled infections such as polio virus occurred and spread to areas where the disease was already considered under control. Gender neutral vaccination and incorporation of the HPV vaccines into the expanded program of immunization (EPI) would bypass the problem and facilitate coverage.(Kane. 2012)

Major arguments in favor of male vaccination are: i) the expected impact on herd immunity in populations where vaccination coverage among women is low (somehow arbitrarily defined as below 70%); ii) the impact of reducing genital warts in men, especially men who have sex with men (MSM), if Gardasil is used; iii) the impact on HPV-related cancers in males; and iv) avoidance of concerns in the population on the importance and motivation for HPV vaccination, potentially triggered by the promotion of single-gender vaccination.

Some of the deterrents of the male vaccination proposal at this stage are: i) the late acquisition of the evidence of the burden of HPV related conditions in men as compared to the early focus on cervical cancer; ii) the limited evidence on the impact of HPV vaccines in men; and iii) the high price of the vaccines leading to concerns that male immunization is not cost-effective.

In this rapidly evolving field, vaccination trials among males have been satisfactorily conducted and licensing by regulatory agencies has already occurred in the US and other countries. However formal introduction into routine vaccination public programs has not yet been proposed. Some male populations at high risk of HPV infections and HPV related cancers (i.e., MSM) are potential target groups for first introduction of male HPV vaccination. (MMWR 2011; Palefsky and Giuliano et al. 2011)

4. 2 Target age groups for vaccination:

The introduction of HPV vaccines into the routine immunization programs of peri-adolescent girls in most developed countries is a major first step of preventive oncology.(Global Advisory Committee on Vaccine Safety. 2009) However the target ages for vaccination offers a canopy of national alternatives with limited scientific rationale. While all regulatory offices recognize the priority to vaccinate girls before sexual behaviour starts (in the range of 9 to 14 years of age), in Europe alone, the upper limit for vaccine recommendations range from single cohorts below the age of 14 in Spain and Norway to age 18 in the UK or Belgium, to age 23 in France and to age 26 in some regions in Italy and in Greece. More interestingly, the vaccination program in Australia, with an estimated national vaccination coverage of 50% in women up to the age of 26 with Gardasil achieved an almost disappearance of genital warts and a significant reduction of CIN 2+ lesions in the 4 year interval following the introduction of the vaccination program.

Vaccination trials in women up to the age of 45 (Castellsague and Munoz et al. 2011) have also shown that vaccine efficacy is high among women that are HPV DNA negative at study entry. It is known that HPV exposure can occur at any age group as long as the person is sexually active. Therefore vaccination can offer some degree of prophylactic benefit at any age group and the major deterrent to a generalized vaccination program with a difficult to determine upper age limit is vaccine cost. The discussion becomes particularly relevant when considering the reduction of the frequency of screening events required for vaccinated women and additional cost benefit analyses will have to be conducted accordingly.

4.3 Predicted impact of vaccinating sexually adult women

Phase III HPV vaccination trials have provided efficacy estimates in different cohorts, mimicking potential users in the population at large. The preventive value of HPV vaccines is better expressed in women that are naïve to the relevant HPV types at study entry and VE decayed rapidly when vaccinated cohorts were evaluated irrespective of the HPV status at study entry and with case counting starting on the day after the first dose is delivered (usually described as Intention To Treat [ITT] or Total Vaccinated Cohort [TVC] type of analyses). Based upon these observations in the early reports of the trials (interim analyses and analyses within the first 2/3 years of follow up), VE and vaccination of adult sexually active women was considered of little interest. However, with the observation of larger number of individuals for longer periods of follow up, VE estimates for the ITT/TVC cohorts significantly increased in both vaccines trials(Garland and Hernandez-Avila et al. 2007; Herrero R and Wacholder S et al. 2011). This is explained because the CIN 2+ cases that are attributable to prevalent HPV infections or low grade lesions at study entry tend to occur in the first years of follow up and equally so in both the vaccinated and the controls groups.

However as time elapses, cases related to *de novo* HPV infections are observed and VE estimates increase significantly. Therefore, the potential for prevention of programs that target the general population at large irrespective of their HPV status at vaccination still needs to be assessed. Cost benefit analyses and related screening protocols will also have to pay attention to this observation.

4.4 Cost of the vaccines

The price of the vaccines when first introduced was significantly higher that any other widely used infant vaccines and similar to the initial prices of hepatitis B vaccines. Cost benefit analyses based on prices above 100E per dose in the private markets and similar in the public markets strongly limited the rapid introduction of the vaccine into developing countries and severely reduced vaccine indications in developed countries by restricting the target populations to one single age cohort in several of them. As expected, major efforts have been invested in lowering the price of vaccines including massive negotiations for procurement, tiered prices for emerging economies and very low prices for GAVI eligible countries. Other opportunities for price reduction in the future will probably come from ongoing studies evaluating alternative options such as two-dose regimes or different forms of packaging and delivering systems.

With rapidly decreasing prices, the economic limitations that modulated the age ranges covered by the public system in developed countries may change and move towards wider vaccination indications such as the one adopted by the Australian Government. These considerations are likely to be particularly important in emerging economies and other regions in the world (i.e. eastern European countries, Turkey, Mexico etc) that are now at the planning phases of their national policies for cervical cancer prevention. (Andrus and Sherris et al. 2008)

4.5 Alternative uses of HPV vaccines

Ongoing trials and demonstration programs are now evaluating two-dose vaccination regimes instead of three using either of the available vaccines. Initial results in the Costa Rica trial (Herrero R and Wacholder S et al. 2011) looked at women who received one or two doses of Cervarix instead of a standard 3 dose regimen. In this trial, even one dose showed high antibody titers, not inferior to the titers in people receiving the conventional three dose schedule. Assessment of the efficacy and duration of protection with one or two doses requires further validation in formal comparative trials that are currently underway in India, Canada and elsewhere.

Alternative schedules using longer intervals between the doses are other alternatives that are being tested in Mexico, Vietnam and in Quebec, Canada using schedules at 0, 6 and 60 months.(Kreimer and Rodriguez et al. 2011; Neuzil and Canh et al. 2011) The protocol should be able to assess the efficacy of two doses as well as the convenience and impact of a booster dose 5 years after initiation of the vaccination scheme. Short term results from the program in Mexico suggest that two doses at 0 and 6 months induce higher antibody titers than the conventional 0 and 1 or 2 months. No efficacy results are so far available from these studies. (Lazcano, E et al. personal communication)

One of the programs with Cervarix is examining the validity of administering the vaccine to infants aged 4 with a view to incorporate them into the EPI schedules.

Further studies in 0 to 1 year olds and co-administration formulations with the other EPI vaccines would represent a major advantage in terms of achieving high coverage and vaccination of males as well as females. However to date no major programs are under way to examine these options.

5 Prospects for second generation vaccines and impact on preventive strategies

Research is actively ongoing on the preparation of so-called second generation vaccines that would overcome some of the limitations of current vaccines.
The first objective of the second generation HPV vaccines will be to address the spectrum of HPV types by increasing the number of antigens. Trials of a nonavalent HPV (including HPV 6, 11, 16, 18, 45, 31, 33, 52, 58) vaccine targeting protection against the HPV types that cause 90% of cervical cancer as well as genital warts are currently in advanced Phase III trials and results are awaited in 2012.

A similar end result could be achieved (i.e VE >90%) by Cervarix if the reported impact on CIN 3+ lesions irrespective of HPV type (93.2%VE) is shown to persist over time.

Other alternatives to increase the valency of HPV vaccines is exploring L2 based constructs and cheaper high throughput production systems. These vaccines are currently in the early days and entering Phase I trials(Jagu and Karanam et al. 2009).
Figure 1 (adapted from(Bosch. 2009)) shows a speculative diagram on plausible protocols for cervical cancer prevention with broad spectrum vaccines in developing and developed countries. Details of several of the steps of the proposal will require additional clinical research for verification and recommendation.

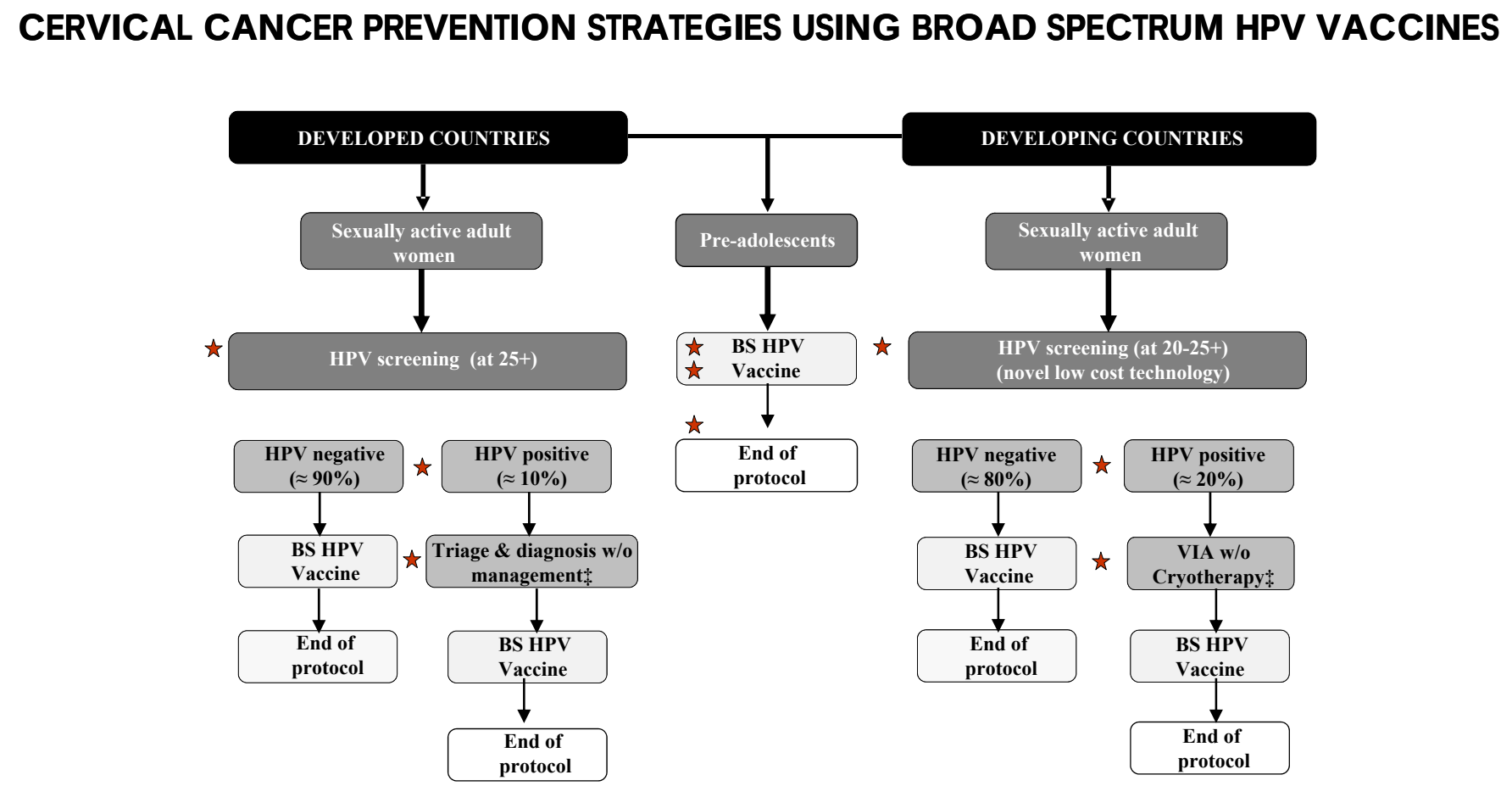
[Figure 1] adapted from(Bosch. 2009).

According to the scheme, HPV vaccination of women could be proposed as broad as feasible in terms of age groups while retaining the emphasis on young pre-sexual initiation girls who would not need further screening. Needless to say, some safety evaluations of the proposal would be necessary in focused clinical trials early in the process.

Vaccinated sexually active young women (i.e. before the ages of 25/30 but years after sexual initiation) could be offered a single event HPV screening when reaching the age of 25 or 30. The screen would identify the group of women that were already HPV-positive before vaccination and remained persistently infected who would then be followed.

Women at ages 30 to 45 + could be offered broad spectrum HPV vaccines at the time that a single HPV screen is offered. In the screening event, women found HPV negative (80 to 90% of the target population) will complete the HPV BS vaccination program with no further screening requirements over their lifetime. For women that turned out to be HPV positive, diagnostic and follow-up procedures (colposcopy / biopsy / surgery) could be activated in parallel with completion of the vaccination

Figure 1



BS= Broad spectrum; HPV=Human Papillomavirus; VIA= Visual inspection with acet ic acid

‡ = Details of such protocols would require additional clinical research; ★ = Vaccination event

Adapted from (Bosch 2009)

scheme. Following treatment of the CIN 2+ cases identified, HPV screening could be further used once/twice in their lifetime as a proof of cure and a safety net.
Whatever the final format of the protocols, broad spectrum vaccines have the potential to i) alleviate the health services demand of the repeated screening protocols currently in use ii) influence the cost benefit analyses in favor of generalized vaccination and iii) trigger a significant reduction in cervical cancer mortality over a medium term, well before the long term benefits of the generalized adolescent HPV vaccination are clearly visible.

Developing countries would follow a similar protocol, while using an adapted HPV testing system (i.e., the Care HPV test^{TM}, Qiagen Gaithersburg, Inc., MD, USA) and triage protocol for women testing HPV positive(Blumenthal and Lauterbach et al. 2005; Sankaranarayanan and Gaffikin et al. 2005). The HPV DNA test adapted for use in developing populations achieved significant features of simplicity (average lab technicians can be trained to use them) technical demands (do not require electricity or running water) and output (sampling and testing can be achieved in significant numbers over one shift period) thus allowing for strategies of testing and treating within the duration of the preventive event.

In brief, the use of BS HPV vaccines should significantly reduce or terminate the requirement for continuous screening among vaccinated adolescents and dramatically simplify the strategy for cervical cancer prevention in sexually active adult women in both developed and developing countries. They will help closing the equity gap in cervical cancer prevention between developed and developing populations.

6. Screening implications of generalized HPV vaccination

6.1 developed populations

It has been repeatedly shown that under the best technical conditions, using the Pap smear as the primary screening test, paired with colposcopy and biopsy as the diagnostic tools, the achievable reduction in cervical cancer incidence and mortality is in the range of 50 to 80 % in countries with centrally organized efforts. In countries with opportunistic screening the impact in cervical cancer reductions is generally lower. Likewise, it could be speculated that the reduction in cervical cancer incidence would be in the 80-85 +% range using HPV tests as the primary screening option with some additional triage test (cytology, HPV typing, p16+Ki 67 stains) to guide management. Even in well screened populations in Sweden or within a private insurance plan in California, some cervical cancer cases occur and these are attributed to either lack of participation to the screening program (56 - 64 % of the cases), false negative results of the Pap smear (32 - 24 % of the cases) or lack of follow up of women found at high risk in the cytology results (13 -11 % of the cases).(Andrae and Kemetli et al. 2008; Leyden and Manos et al. 2005) These seem to be nowadays the population limits of Pap smear based screening programs.

Developed countries have now the opportunity to benefit from HPV related technologies by implementing strategic combinations of population based HPV

vaccination with a second generation screening technology program for the prevention of cervical cancer. Vaccinated populations will experience a dramatic reduction in the incidence of CIN 2+ due to HPV 16 and 18 (over 60% of the CIN 2+ cases) and consequently the validity of the Pap smear as primary screening test will suffer.
A reduction by half of the underlying prevalence of the conditions of interest (CIN2+) will imply a significant loss in predictive value.(Franco and Cuzick et al. 2006; Franco and Mahmud et al. 2009) Populations such as the Australian or the British that are currently vaccinating women that will soon enter the recommended screening age groups are appropriate scenarios to test at a large scale the validity of HPV based tests as primary screening tools and will serve as guidance for future planning in other countries.

Additional public health and clinical research will help define the details of the most effective and cost-effective combinations of mass vaccination and second generation screening and triage protocols. However it can now be speculated that in defined developed populations with good preventive care services and adequate attention to immigrant populations, cervical cancer can be drastically reduced to achieve the level of disease elimination within a reasonable time frame.

6.2 developing populations

With few exceptions, developing populations have irregularly benefited from the conventional pap smear based screening strategy and numerous reviews have documented the reasons for the failure. Many of these are structural and social, thus requiring significant improvement of the public health services to achieve the results described for developed populations. This being the case, cervical cancer remains the third leading cancer in women worldwide and the number one or second cancer in women in 82 % of the 127 developing nations. Moreover, because in these countries cervical cancer strikes at young ages and significantly so among young women (i.e.<45 years of age) cervical cancer is a major component of the number of years of life lost to cancer.

In recent years, low technology tests for secondary prevention of cervical cancer in developing countries have been proposed and evaluated, such as direct visual inspection of the cervix with or without acetic acid [visual inspection with acetic acid (VIA)]. The validity of the test is limited, requires careful training and supervision of the observers and has generated inconsistent results in different settings. These methods are usually included in “see and treat” or “screen and treat” programs in order to minimize attrition in the follow-up of screened women. However the number of false positives and over treatments is considerable and its use has not been generally endorsed(Cuzick and Arbyn et al. 2008).

In contrast to the limited success of pap-smear based screening programs, developing countries have achieved outstanding results in vaccinating the infant and pediatric age groups. Vaccination in the Expanded Program of Immunization (EPI) is very high in virtually all developing populations, thanks to a great extent to international organizations and donors such as the World Health Organization (WHO), GAVI (formerly The Global Alliance for Vaccines and Immunisation), the United Nations Children's Fund (UNICEF), the Bill & Melinda Gates Foundation and others. Eradication of small pox was archived and elimination or significant control of polio, measles and other infectious diseases has been successful in most developing nations.

Therefore, vaccination against HPV seems a relevant option as well as a realistic one to address cervical cancer prevention. Like in developed countries, adult sexually active women, in extensive populations in developing countries could benefit from the already available novel form of HPV DNA screening test, technologically adapted to be used in low development level scenarios(Andrus and Sherris et al. 2008; Qiao and Sellors et al. 2008; Sankaranarayanan and Bhatla et al. 2008; Sankaranarayanan and Nene et al. 2009; (World health organization. 2009).

7 Opportunities for research and progress

Academic research has made tremendous advancements in providing the understanding of the causes of cervical cancer and generating the technology to prevent it both at the primary and secondary levels. Anticipated developments in the years to come can be summarized as follows:

7.1 Etiology: completion of studies linking and quantifying the impact of HPV infections in the etiology of ano-genital cancer and cancer of the head and neck.
7.2 Screening. Screening programs in the public system are likely to gradually adopt HPV tests as the primary screening tool. The related clinical protocols will require additional studies to define the management of HPV + women with normal cytology. HPV-DNA testing technologies adapted to developing countries (i.e. Care HPV test) will be gradually tested and introduced in developing countries.
7.3 HPV vaccines. Research on novel HPV vaccines to be developed will continue both in the direction of increasing the valence of the vaccines and/or by including therapeutic components in the vaccine products.
7.4 Adoption of HPV vaccines. Continued developments in vaccine development should evolve in parallel to (and learn from) the implementation experiences. Efforts to introduce HPV vaccines in all countries should be strongly encouraged and it would be unjustified to delay it on the grounds of the promise of better vaccines on the horizon.
7.5 Integrated cervical cancer control. Logistical research and modeling studies will help define the most adequate strategies to address comprehensive cancer prevention strategies in extensive areas and populations where no preventive options are available nowadays.
7.6 Disease awareness and medical education. These will aim at 1) increasing the low level of awareness on the impact of cervical cancer worldwide and particularly in developing countries ii) address issues of cervical cancer as a single gender disease and the stigma of being linked to a sexually transmitted infection (STI) and iii) counteract the negative publicity on vaccines and HPV vaccination in the media .
7.3 Social consensus on cervical cancer prevention. Political efforts are now needed towards introducing the concepts of cervical cancer elimination and eradication and help reaching the stage at which the public health community at large embarks on the required worldwide effort.

Conclusion

Technologies to dramatically reduce the impact of cervical and other HPV related cancers are now available. HPV vaccines and HPV based screening tests might represent the technical requirements to begin closing the equity gap in cervical cancer prevention between developed and developing countries.

Notes

The author would like to express sincere thanks to Cris Rajo and Ion Espuña in the preparation of the manuscript.

The study has been partially supported by Spanish public grants from the Instituto de Salud Carlos III (grants FIS PI030240, FIS PI061246, RCESP C03/09, RTICESP C03/10, RTIC RD06/0020/0095 and CIBERESP), from the Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR 2005SGR 00695 and 2009SGR126), from the Marató de TV3 Foundation (051530), and from GlaxoSmithKline Biologicals, Sanofi Pasteur MSD & Merck & Co, Inc., who had no role in the preparation of this manuscript.

Conflict of interest disclosure:
FXB has received travel and consultancy fees from MSD, GSK, Qiagen and SPMSD. Through the Catalan Institute of Oncology he has administered research and educational grants from GSK, MSD, and SPMSD.

References

Andrae, B., Kemetli, L., Sparen, P., Silfverdal, L., Strander, B., Ryd, W. et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. J.Natl.Cancer Inst. 2008. 100(9):622-629.

Andrus, J. K., Sherris, J., Fitzsimmons, J. W., Kane, M. A., and Aguado, M. T. Introduction of human papillomavirus vaccines into developing countries - international strategies for funding and procurement. Vaccine. 2008. 26 Suppl 10K87-K92.

Blumenthal, P. D., Lauterbach, M., Sellors, J. W., and Sankaranarayanan, R. Training for cervical cancer prevention programs in low-resource settings: focus on visual inspection with acetic acid and cryotherapy. Int.J.Gynaecol.Obstet. 2005. 89 Suppl 2S30-S37.

Bosch, F. X. Broad-spectrum human papillomavirus vaccines: new horizons but one step at a time. J.Natl.Cancer Inst. 2009. 101(11):771-773.

Bosch, F. X., Manos, M. M., Munoz, N., Sherman, M., Jansen, A. M., Peto, J. et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J.Natl.Cancer Inst. 1995. 87(11):796-802.

Bosch, F., de Sanjosé, S., and Castellsagué, X. Evaluating the potential benefits of universal worldwide human papillomavirus vaccination. Therapy. 2008. 5(3):305-312.

Bouvard, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., El Ghissassi, F. et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009. 10(4):321-322.

Brotherton, J. M., Fridman, M., May, C. L., Chappell, G., Saville, A. M., and Gertig, D. M. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet. 2011. 377(9783):2085-2092.

Castellsague, X., Munoz, N., Pitisuttithum, P., Ferris, D., Monsonego, J., Ault, K. 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. 2011. 105(1):28-37.

Centers for Disease Control and Prevention. Reports of health concerns following HPV vaccination. Centers for Disease Control and Prevention. 2009

Chaturvedi, A. K., Engels, E. A., Pfeiffer, R. M., Hernandez, B. Y., Xiao, W., Kim, E. et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J.Clin.Oncol. 2011. 29(32):4294-4301.

Cuzick, J., Arbyn, M., Sankaranarayanan, R., Tsu, V., Ronco, G., Mayrand, M. H. et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. Vaccine. 2008. 26 Suppl 10K29-K41.

de Sanjose, S., Quint, W. G., Alemany, L., Geraets, D. T., Klaustermeier, J. E., Lloveras, B. et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010. 11(11):1048-1056.

De Vuyst, H., Clifford, G. M., Nascimento, M. C., Madeleine, M. M., and Franceschi, S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int.J.Cancer. 2009. 124(7):1626-1636.

D'Souza, G., Fakhry, C., Sugar, E. A., Seaberg, E. C., Weber, K., Minkoff, H. L. et al. Six-month natural history of oral versus cervical human papillomavirus infection. Int.J.Cancer. 2007. 121(1):143-150.

European Center for Disease Prevention and Control (ECDC). Guidance for the introduction of HPV vaccines European countries. http://edcdeuropa.eu/pdf/HPV_report.pdf. 2008

Fairley, C. K., Hocking, J. S., Gurrin, L. C., Chen, M. Y., Donovan, B., and Bradshaw, C. S. Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination programme for young women. Sex Transm.Infect. 2009. 85(7):499-502.

Forman D. Burden of HPV infections & related disease. Vaccine. 2012. In the Press

Franco, E. L., Cuzick, J., Hildesheim, A., and de Sanjose, S. Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination. Vaccine. 2006. 24 Suppl 3S3/171-S3/177.

Franco, E. L., Mahmud, S. M., Tota, J., Ferenczy, A., and Coutlee, F. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change. Arch.Med.Res. 2009. 40(6):478-485.

Garland, S. M., Hernandez-Avila, M., Wheeler, C. M., Perez, G., Harper, D. M., Leodolter, S. et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N.Engl.J.Med. 2007. 356(19):1928-1943.

Gillison, M. L. HPV and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine. 2012. In the Press

Gillison, M. L., Koch, W. M., Capone, R. B., Spafford, M., Westra, W. H., Wu, L. et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J.Natl.Cancer Inst. 2000. 92(9):709-720.

Global Advisory Committee on Vaccine Safety, 17-18 December 2008. Wkly.Epidemiol.Rec. 2009. 84(5):37-40.

Heck, J. E., Berthiller, J., Vaccarella, S., Winn, D. M., Smith, E. M., Shan'gina, O. et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int.J.Epidemiol. 2010. 39(1):166-181.

Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer R et al. Prevention of Persistent Human Papillomavirus Infection by an HPV16/18 Vaccine: A Community-Based Randomized Clinical Trial in Guanacaste, Costa Rica. Cancer Discovery. 2011. 1(5):408-419.

International Agency for Research on Cancer (IARC). IARC monograph series. IARC monograph. 2007. 90

Jagu, S., Karanam, B., Gambhira, R., Chivukula, S. V., Chaganti, R. J., Lowy, D. R. et al. Concatenated multitype L2 fusion proteins as candidate prophylactic pan-human papillomavirus vaccines. J.Natl.Cancer Inst. 2009. 101(11):782-792.

Kane, M. Implementation of HPV Immunization in the Developing World. Vaccine. 2012. In the Press

Kreimer, A. R., Rodriguez, A. C., Hildesheim, A., Herrero, R., Porras, C., Schiffman, M. et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J.Natl.Cancer Inst. 2011. 103(19):1444-1451.

Leyden, W. A., Manos, M. M., Geiger, A. M., Weinmann, S., Mouchawar, J., Bischoff, K. et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. J.Natl.Cancer Inst. 2005. 97(9):675-683.

Markowitz, L. E. HPV Vaccine Introduction - The First Five Years. Vaccine. 2012. In the Press

Markowitz, L. E., Dunne, E. F., Saraiya, M., Lawson, H. W., Chesson, H., and Unger, E. R. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm.Rep. 2007. 56(RR-2):1-24.

Miralles-Guri, C., Bruni, L., Cubilla, A. L., Castellsague, X., Bosch, F. X., and de Sanjose, S. Human papillomavirus prevalence and type distribution in penile carcinoma. J.Clin.Pathol. 2009. 62(10):870-878.

Munoz, N., Bosch, F. X., Castellsague, X., Diaz, M., de Sanjose, S., Hammouda, D. et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int.J.Cancer. 2004. 111(2):278-285.

Nasman, A., Attner, P., Hammarstedt, L., Du, J., Eriksson, M., Giraud, G. et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int.J.Cancer. 2009. 125(2):362-366.

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

Palefsky, J. M., Giuliano, A. R., Goldstone, S., Moreira, E. D., Jr., Aranda, C., Jessen, H. et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N.Engl.J.Med. 2011. 365(17):1576-1585.

Qiao, Y. L., Sellors, J. W., Eder, P. S., Bao, Y. P., Lim, J. M., Zhao, F. H. et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. Lancet Oncol. 2008. 9(10):929-936.

Ragin, C. C. and Taioli, E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. Int.J.Cancer. 2007. 121(8):1813-1820.

Recommendations on the use of quadrivalent human papillomavirus vaccine in males--Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb.Mortal.Wkly.Rep. 2011. 60(50):1705-1708.

Rintala, M., Grenman, S., Puranen, M., and Syrjanen, S. Natural history of oral papillomavirus infections in spouses: a prospective Finnish HPV Family Study. J.Clin.Virol. 2006. 35(1):89-94.

Sankaranarayanan, R., Bhatla, N., Gravitt, P. E., Basu, P., Esmy, P. O., Ashrafunnessa, K. S. et al. Human papillomavirus infection and cervical cancer prevention in India, Bangladesh, Sri Lanka and Nepal. Vaccine. 2008. 26 Suppl 12M43-M52.

Sankaranarayanan, R., Gaffikin, L., Jacob, M., Sellors, J., and Robles, S. A critical assessment of screening methods for cervical neoplasia. Int.J.Gynaecol.Obstet. 2005. 89 Suppl 2S4-S12.

Sankaranarayanan, R., Nene, B. M., Shastri, S. S., Jayant, K., Muwonge, R., Budukh, A. M. et al. HPV screening for cervical cancer in rural India. N.Engl.J.Med. 2009. 360(14):1385-1394.

Schiller, J. T. A review of Clinical Trials of Human Papillomavirus Prophylactic vaccines. Vaccine. 2012. In the Press

Schiller, J. T., Castellsague, X., Villa, L. L., and Hildesheim, A. An update of prophylactic human papillomavirus L1 virus-like particle vaccine clinical trial results. Vaccine. 2008. 26 Suppl 10K53-K61.

Smith, J. S., Lindsay, L., Hoots, B., Keys, J., Franceschi, S., Winer, R. et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int.J.Cancer. 2007. 121(3):621-632.

Wheeler, C. M., Hunt, W. C., Joste, N. E., Key, C. R., Quint, W. G., and Castle, P. E. Human papillomavirus genotype distributions: implications for vaccination and cancer screening in the United States. J.Natl.Cancer Inst. 2009. 101(7):475-487.

World Health Organization. Meeting of the Immunization Strategic Advisory Group of Experts. Weekly Epidemiological Record. 2009