HPV Today

Newsletter on Human Papillomavirus

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HPV VACCINES AND EQUITY

Vaccines are among the most successful health interventions for the prevention of infectious diseases, and HPV vaccines are a key weapon for preventing a major cancer. What are the key issues regarding their successful introduction?
This major breakthrough has to be followed up by concerted efforts aimed at an early introduction of these vaccines. Among the major challenges, particularly for developing countries, will be the cost of the vaccine. It will be important that governments and collaborating organizations identify the burden and societal cost of the diseases associated with the human papillomavirus and the financial mechanisms that will allow the sustainable introduction of these vaccines.

With regard to cervical cancer mortality clusters in developing countries, how is cervical cancer perceived in the field of vaccines and vaccination?
The field of vaccination was not able to count on this vaccine until recently, therefore its arrival in the public health armory has excited all those involved with vaccines and immunization. It is expected that once governments are able to introduce the vaccine it will be very well received in most communities.

What trials should now be performed in developing countries to facilitate the understanding and adoption of HPV vaccines?
We need to increase awareness of the diseases associated with HPV and that we now have an additional tool to help prevent them. It will also be important to identify whether this vaccine can be used in lower age groups, which would allow its incorporation into the normal childhood vaccination schedule and thereby greatly facilitate the logistics of its introduction.

(continues on page 3)

INTERVIEW WITH
CIRO DE QUADROS

No. 14 February 2008

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How do you envisage the introduction of HPV vaccines in developing countries?

It is still too early to identify the best strategy for the introduction of this vaccine in developing countries. However, it is envisaged that there should be initial catch-up campaigns aimed at vaccinating a large cohort of individuals who potentially will benefit from its use. Many developing countries have accumulated considerable experience with vaccination campaigns aimed at adolescents and adults when implementing programs for the control or elimination of diseases such as neonatal tetanus, where they vaccinated women of child-bearing age, and measles and rubella, where they vaccinated adolescents and men and women up to 35 years of age.

In developed countries, cervical cancer is an important cause of death among women in the low socioeconomic strata who do not access screening. How can we enhance access to HPV vaccines among these social groups?

Vaccines are a public health good and, as such, governments will have to ensure that all population groups are covered with the benefits of this technology to avoid the inequities that have somehow built up over the past few years with the advent of modern preventative health technologies. Governments will have to take responsibility for those individuals who do not have medical plans or insurance policies that cover vaccines and provide the means of reaching all sectors of the population.

The professional field of cancer prevention is now enlarging to include the international institutions that have expert experience in vaccines and vaccine introduction. What would be your recommendation to unite these efforts and increase efficiency?

The advent of the vaccine against HPV brings together two major health communities who have not usually worked together in the past, namely oncologists and vaccinologists. The successful control of the diseases associated with HPV will, to a large extent, depend on the level of collaboration and coordination between these groups. I am confident that this will be a success, however, because we have had numerous examples of collaboration between health groups who usually do not relate to each other in the past. For example, during the polio eradication efforts in the Americas there was a high level of collaboration between epidemiologists and neurologists and, more recently, with the efforts to eradicate rubella and congenital rubella syndrome (CRS), there was a large degree of collaboration between epidemiologists, gynecologists and obstetricians.]

FOOTNOTE: Dr. De Quadros was a key leader in the expansion of vaccine use against the traditional childhood diseases of diphtheria, tetanus, *perthusis*, measles, polio, and tuberculosis and the introduction of Hepatitis B and Heamophilus influenzae type B vaccines in the Americas. He also directed the Pan American Health Organization (PAHO) efforts that resulted in the eradication of polio and measles from the Western Hemisphere. He is now the Head of International Programs at the Albert B. Sabin Vaccine Institute in Washington (USA).

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LESSONS LEARNED FROM THE INTRODUCTION OF THE HEPATITIS B VACCINE: A MODEL FOR THE CONTROL OF CERVICAL CANCER WITH HPV VACCINES

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Viruses and bacteria are now known to be major and preventable causes of human cancer, and health providers such as pediatricians, nurses, family and general practitioners, and obstetricians and gynecologists (OBGYNs) should appreciate and actively pursue their role in preventing cancer with vaccines. HPV vaccine is the second vaccine that can prevent a major human cancer. The first was hepatitis B (Hep B) vaccine which prevents primary liver cancer and the lessons learned from the successful introduction of this vaccine have great relevance for the control of cervical and other cancers caused by HPV. We know how to control a cancer with a vaccine since we have done it with Hep B: more than 80% of countries now routinely deliver Hep B vaccine to all children through (mostly) government-funded routine immunization programs.

OBGYNs who know about HPV and cervical cancer need to learn about vaccines, and those who immunize children and adolescents need to learn about HPV and the spectrum of diseases it causes.

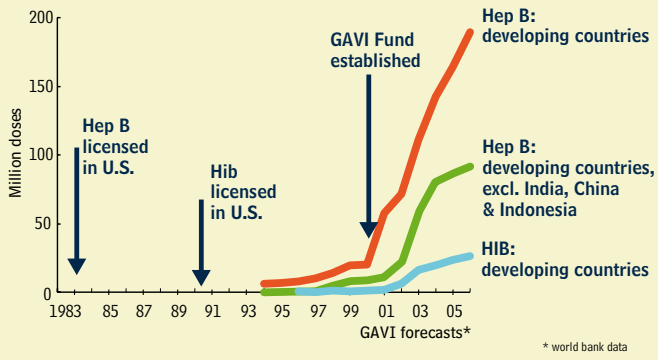
Vaccines can be used in two ways: they can be delivered by health providers to individual patients, or they can be provided as part of government-funded routine immunization programs such as infant or school-based programs. The initial delivery strategy for Hep B vaccine, which was to deliver the vaccine to largely adult "high-risk" groups, protected many individuals like health-care workers but failed to control the disease on a community basis and would have had little impact on rates of cancer. Only when the primary strategy shifted to vaccination of all infants worldwide did we effectively begin to control the disease and the subsequent cancer. Rates of Hep B carriers in immunized cohorts in the highest risk countries have fallen from 10-15% to 1-2%, transmission of the virus has almost stopped in many countries, and reductions in rates of liver cancer have been directly measured. With HPV vaccine, only routine funded delivery programs such as school-based programs targeting pre-adolescents will achieve the coverage required to have a major impact on rates of cervical cancer.

Like HPV, Hep B viral infection causes a spectrum of malignant and non-malignant diseases, and cancer occurs following decades of chronic infection.

Cancer epidemiologists believe that the "success" of the immunization program will occur when they see reductions in rates of cancer. However, public-health specialists see the problem differently and define "success" as soon as they fully immunize a person, turning a "susceptible" into an "immune" individual.

Health economists also heavily "discount" outcomes (such as preventing cancer) that occur many years following the "investment", in this case immunization. Discounting is a necessary economic tool, but it may poorly reflect our values in understanding the impact on society and the family at the loss of a father from liver cancer or a mother from cervical cancer. Newer vaccines are initially more expensive than older, more mature products, and the financing of Hep B vaccines, especially in the developing world, caused a gap of many decades between the introduction of the vaccine in the industrial world (it was introduced in 1982), and widespread availability of the vaccine in the poorest countries in the developing world, which occurred in this century. The global health community is working hard to narrow the gap, and has created programs and funds such as the Global Alliance for Vaccines and Immunization (GAVI) and Fund to help the poorest developing countries with introduction and financing issues. The fund now has about 5 billion dollars committed to helping the poorest 72 developing countries strengthen their immunization programs and health systems, and introduce newer vaccines such as HPV.

Introduction of Hep B and HIB vaccines into developing countries before and after the establishment of the GAVI fund



The Global Alliance for Vaccines and Immunization (GAVI) proved to be a critical instrument to channel resources for vaccination in the countries with lowest public health budgets. GAVI is currently evaluating the use of HPV vaccines as a priority in developing countries.

Most health practitioners are aware that HPV and most newer vaccines are expensive in private markets in industrial and developing countries, but many are unaware that vaccine prices can be sharply "tiered" for large scale public sector purchases. For example, Hep B vaccine still costs approximately $100 for three adult doses in private pharmacies in industrial countries, but governments in developing countries can buy large quantities of vaccine for public sector programs for

about $0.60 for three pediatric doses. This tiering effect took decades for Hep B vaccine but there are hopeful indications that this will occur much more quickly for current new vaccines.

No-one knows the duration of protection when new vaccines are introduced. Hep B vaccine surprised us with its long duration of protection, now more than 20 years, and booster doses are not yet recommended. Following Hep B vaccine introduction, hundreds of papers were written on antibody titres following immunization, models were developed predicting duration of protection based on antibody decay curves, and in some countries recommendations were made for booster doses based on these curves. However, protection against clinical disease and the carrier state lasted decades longer than detectable antibody: memory B cells induced an anamnestic antibody response upon exposure to the virus or a booster dose of vaccine, and we still do not know the duration of protection of Hep B vaccine. The relevance of this model for HPV vaccine is not yet clear, but like Hep B, HPV infection has a long incubation period and current evidence suggests that it induces B memory cells. We do not yet understand the duration of protection of HPV vaccine, but we know it is solid for at least five years.

Morbidity from vaccine preventable conditions.
Number of cases before (1920-80) and after (1999) vaccine introduction in the US

The prophylactic achievements of immunization is one of the major successes in the history of medecine. Diseases such as polio have been virtually erradicated in the majority of countries in the world. Viral induced cancers -such as liver cancer or cervical cancer- can follow a similar trend of erradication although the delays and the complexity of the public health programs pose significant novel challenges to the immunization and cancer prevention fields.

DISEASE	NUMBER OF REPORTED CASES BY VACCINATION TIME PERIOD		
	BEFORE	AFTER	CHANGE %
Diphtheria	206,939	1	-99.99
Measles	894,134	86	-99.99
Mumps	152,209	352	-99.76
Pertussis	265,269	6,031	-97.63
Polio (wild)	21,269	0	-100.0
Rubella	57,686	238	-99.58
Cong. Rubella	20,000+	3	-99.98
Tetanus+	1,560	33	-97.88
Inv.Hib (>5y)	20,000+	33	-99.83
TOTAL	1,639,066	6,777	-99.58

source: Morbidity and Mortality Weekly Report (MMWR)

Because HPV vaccine prevents cancer which is caused by a sexually transmitted infection, the messaging about this vaccine can be complex and should vary to be culturally appropriate. Hep B vaccine is also sexually transmitted (among other modes of transmission) and we dealt with this issue following vaccine introduction, especially when adolescents were targeted. With HPV most messaging should be about cancer prevention, but one vaccine also prevents genital warts, and both vaccines will be targeted to pre-adolescents, thus raising communication issues regarding sexual transmission. Sexual activity before marriage is common in industrial countries, but in traditional cultures most women are virgins at marriage and are infected by their husbands. Communication strategies about the vaccine should therefore reflect these realities. Anti-vaccine groups are also important and are very sophisticated users of the internet, and immunizers must learn how to effectively deal with the rumors emanating from those with anti-vaccine agendas.

PROPHYLACTIC HPV VACCINES

There are currently two licensed HPV prophylactic vaccines based on virus-like particles (VLPs), namely Gardasil®, which is produced in yeast, and Cervarix™, which is produced in baculovirus. Both vaccines have a common goal of preventing disease associated with the two most prevalent HPV types (-16 and -18) associated with the risk of progression in cervical cancer. In addition, Gardasil® contains VLPs for types -6 and -11, with the intention of providing protection against genital warts. Clinical trials have established that these vaccines are safe, well tolerated and highly immunogenic and that they induce neutralizing antibodies that are detectable in the genital mucosa. VLPs are generally type-specific and generate antibodies that protect against infection with the virus types included in the vaccines. The peak anti-VLP antibody responses are substantially greater than those made during seroconversion in natural infections. Independent clinical trials have proved that both Cervarix™ and Gardasil® are essentially 100% effective in preventing the infection of HPV-16 and -18, which cause around 70% of known cervical cancer cases.

There are excellent data showing the efficacy of these vaccines in the prevention of high-grade cervical intraepithelial neoplasia (CIN) when assessed in women between 15 and 26 years of age who have not previously been exposed to the HPV types in the vaccines used.

Immunogenicity bridging studies have also shown superior antibody levels following vaccination in girls (and boys) aged 9-15. This finding supports the widespread recommendation from various national agencies that the best time for the vaccines to be administered will be prior to the onset of sexual activity in young girls. Gardasil® has also been shown to be effective in preventing other HPV-16 and -18-related anogenital lesions such as vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN) as well as HPV-6/-11-related genital warts in women aged 15-25. Although one can speculate that vaccination of men should also lead to a reduction in disease rates in women, this has not yet been demonstrated. Mathematical modeling

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suggests that there is little additional reduction in cervical cancer to be gained by vaccinating males if high coverage of females can be achieved. While these vaccines are not therapeutic, some benefit would be gained against the other types in the vaccine if a recipient had been exposed, for example, to HPV-16 but not HPV-18. Vaccination in older women may also bring other benefits since the acquisition rates of HPV infection do not significantly alter in the third to fifth decades and immunization may protect against new infections or boost otherwise sub-optimal natural immunity. Since these vaccinations are unlikely to be sterilizing, and the extent of latent infection is unknown, it will be important to monitor vaccinated women of all ages carefully.

The available trial data show that protection against infection is maintained for at least five years. However, while the antibody levels induced by vaccination are considerably higher than those detected in natural infection, it is not clear what levels are sufficient to prevent infections since all vaccinees seroconvert. Apart from the different VLPs included, the two vaccines are formulated with different adjuvants (Gardasil® with aluminum hydroxyl phosphate sulphate and Cervarix™ with a proprietary agent (ASO4) composed of monophosphoryl lipid A adsorbed on to aluminum hydroxide). These adjuvants are included to boost the immune response and can influence the type and longevity of responses. Both vaccines are given as three immunizations at 0, 1 (or 2) and 6 months, but comparison of antibody titres for the different vaccines are not straightforward as the methodologies for detection are not the same. For Gardasil®, antibody responses drop to near naturally induced levels for HPV types -6, -11 and -18 while HPV-16 antibody levels are approximately 16-fold higher after five years. Fortunately, there is good immunological memory since re-boosting with Gardasil® can again elicit high levels of antibodies. By comparison, Cervarix™ produces continued high antibody HPV-16 and -18 levels that are 17- or 14-fold greater, respectively, than naturally induced levels at 4.5 years. Plasma antibody level concentration may be critical to sustained vaccine-induced protection since this is delivered at the mucosal surface by mechanisms that transudate antibodies to the cervical vaginal mucus (CVM). Importantly, naturally induced antibodies are not detectable in the CVM, which suggests that waning levels could allow breakthrough infections, although none have yet been detected. It is important to realize that vaccine-induced protection may not mimic natural infection, where innate and adaptive cell-mediated processes may be more important.

Both vaccines have shown some cross-protection against other HPV-16 and -18-related types associated with cervical neoplasia, thereby contributing to an increased efficacy in preventing cervical neoplasia. Ongoing trials will document the precise degree of cross-protection and the influence of each vaccine on preventing high-grade CIN. This will be particularly important for the HPV-18-related type HPV-45 since this is the third most prevalent type associated with both squamous and adenocarcinoma of the cervix worldwide. Further refinements in the use of adjuvants may be pivotal in achieving antibody levels that afford useful (cross) protection and longevity. In addition, this could help to reduce the amount of immunogen required and/or the number of immunizations and have important implications for any future boost requirements and timing.

Further improvements in HPV type coverage are clearly desirable and a multivalent VLP L1 vaccine based on 11 HPV L1-type VLPs could theoretically prevent 95.7% of cervical cancer. Unfortunately, this increase in valency is also likely to increase the manufacturing complexity and cost. Given that even the existing vaccines may be too expensive for use in the developing countries where more than 80% of all cervical cancer cases occur, other approaches which may be more cost-effective need to be pursued.

We should be excited that there are now two vaccines available which have proven potential to prevent high-risk HPV-16 and -18 infection and their associated precancerous anogenital (and other) lesions.

This is a magnificent example of translational research which has required key advances from basic HPV virology/immunology, the development/validation of HPV detection methodologies, detailed analyses of clinical specimens from screening/treatment programmes, and production/testing of the first-generation vaccines with proof of their safety and efficacy. This remarkable progress has been driven by synergies between academic, clinical, and commercial interests. The challenge now is for academic funding agencies (charitable and state), health services, and politicians to realize that these advances are only the first step on the road to reducing the risk of HPV-associated anogenital and other neoplasia. The widespread introduction of vaccination in developed countries will bring benefits but there is an absolute requirement to remain diligent in follow-up of these cohorts, particularly as regards longevity of efficacy, the requirement for boost immunization, and any influence on the screening programmes. To impact the disease burden worldwide will require new vaccines with improved properties and the political will to deliver.

INTRODUCING HUMAN PAPILLOMAVIRUS VACCINES: GREAT HOPES BUT QUESTIONS REMAIN

Introduction

The first prophylactic HPV virus-like particle (VLP) vaccine against HPV types -6/-11/-16/-18 was licensed in 2006 for girls and women aged 9-26 years, and the second prophylactic HPV vaccine against HPV types -16 and -18 was licensed in 2007.

HPV vaccines: results in synthesis

1. HPV vaccines are safe, well tolerated and highly immunogenic
2. HPV vaccines are almost 100% effective against high-grade cervical vaginal and vulvar pre-cancers caused by the vaccine HPV types in unexposed women
3. the impact of the vaccines in sexually active women will be lower: These vaccines do not show therapeutic effects
4. implementation of HPV vaccination is a great opportunity but also raises many questions

The HPV viruses and cancer

Genital HPV infection and HPV-associated cervical and other anogenital cancers are significant public health problems globally. An estimated 493,000 cervical cancer cases occur each year, with 274,000 deaths, 80% of which occur in developing countries. Cervical cancer is the second most common cancer in women.

HPV is the most common sexually transmitted viral infection and the lifetime risk of HPV infection is extremely high. A large proportion of adolescents are exposed to HPV soon after sexual debut, although approximately 90% of women with new HPV infections clear the infection within two years.[1]

HPV-16 and HPV-18 are responsible for approximately 70% of all invasive cervical cancers worldwide. The attributable proportion for each one of the other high-risk (HR) HPV types in the etiology of cervical cancer is relatively small, with HPV-45 and -31 being the next most common causal types. In addition to cervical cancer, HPV also causes other female anogenital cancers, including vulvar, vaginal, and anal cancer. These cancers account for approximately 6% of all gynecological cancers (for review, see ref.[2]). No screening programs exist for vaginal and vulvar cancers. The treatment of vulvar or vaginal intraepithelial neoplasia (VIN, VaIN) is challenging, can be disfiguring, and requires long-term follow-up since disease recurrence is common. Studies based on cancer registries from Finland and Sweden have shown that women treated for cervical intraepithelial neoplasia (CIN) have a high-risk of other anogenital cancers up to 10-20 years after the initial diagnosis of CIN.[3,4]

The HPV vaccines

The first prophylactic HPV virus-like particle (VLP) vaccine against HPV types -6/-11/-16/-18 was licensed in 2006 for girls and women aged 9–26 years and the second prophylactic HPV vaccine against HPV types -16 and -18 in 2007. The key findings of studies of vaccine efficacy in preventing cervical and vulvar or vaginal disease are summarized in Table 1. Clinical phase-III trials have shown that these vaccines are almost 100% effective in preventing infection and high-grade pre-cancer associated with the HPV types included in the vaccine.[5-7] Studies have also shown that the vaccines are well tolerated, safe, and highly immunogenic when given in three doses within six months.

Trials with the HPV -6, -11, -16 & -18 vaccine (Gardasil®)

A randomized, double-blind phase-III trial of the quadrivalent HPV vaccine among 12,167 women, who were followed for an average of three years after receiving the first dose of vaccine or placebo, showed that the vaccine efficacy in women who had not been previously infected with HPV -16 or HPV -18 is 98%.[5] The vaccine efficacy was found to be 44% in an intention-to-treat population of all women, including those with or without previous infection, with a vaccine efficacy against all high-grade cervical lesions (CIN 2/3) regardless of causal HPV type of 17%. This study was performed in 13 countries and 90 study sites. The results were confirmed in a combined analysis of four randomized clinical trials with mean follow-up of three years after first dose The corresponding vaccine efficacies were 99%, 44%, and 18%. This combined analysis included 20,583 women aged 16-26 years.[6]

Protection against vulvar and vaginal precancer

The efficacy of the quadrivalent prophylactic HPV vaccine against vulvar and vaginal lesions was also found to be high.[8,9] Combined analyses of three randomized clinical trials of 18,174 women 16 to 26-years of age showed that the vaccine is 100% effective against VIN 2-3- or VaIN 2-3-associated HPV -16 or HPV -18.[9] The vaccine efficacy was found to be 71% in the intention-to-treat population, with a 49% efficacy against these high-grade vulvar or vaginal lesions irrespective of whether or not HPV DNA was detected.

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Table 1:
Randomized trials with HPV-6/-11/-16/-18 (*Gardasil*®) *or* HPV -16/-18 (*Cervarix*™) *vaccines for prevention of anogenital and cervical disease (genital warts,* CIN2/3, AIS, VIN2/3 *and* VaIN2/3): *key results*

Study	Number of participants		Age range (years)	Mean follow-up	Endpoints	Vaccine efficacy (percent, 95% CI)			
	Vaccine group	Control group[a]				Per-protocol Efficacy for vaccine-type HPV[b]	Efficacy for HPV vaccine types		Efficacy for any HPV type[f]
							Modified intention-to-treat[d]	Intention-to-treat[d]	Intention-to-treat
GARDASIL® HPV -6, -11, -16, -18: Advanced Reports									
FUTURE II, 2007(b)	10,291	10,292	16-26	2.5-3.5 years	CIN 2/3, AIS	**99 (93-100)**	NR	44 (31-55)	18 (7-29)
FUTURE I, 2007 [e]	2,241	2,258	16-24	3 years	CIN 2/3, AIS	**100 (94-100)**	NR	55 (40-66)	20 (8-31)
FUTURE I, 2007 [e]	2,261	2,279	16-24	3 years	GW, VIN 1-3, VaIN 1-3	**100 (94-100)**	NR	73 (58-83)	34 (15-49)
CERVARIX™ HPV -16, -18: Interim Report									
PATRICIA, 2007	7,788	7,838	15-25	15 months	CIN 1–3	NR	**89 (59-99)**	NR	NR
PATRICIA, 2007	7,788	7,838			CIN 2/3	NR	**90 (53-99)**	NR	NR

[a] In HPV 6/11/16/18 vaccine trials, control group received placebo; in HPV-16/18 vaccine trials, control group received a hepatitis A vaccine.
[b] Efficacy in participants who received all three doses of vaccine or placebo, had no major protocol violations, were seronegative and HPV-DNA negative for vaccine-type HPV up to one month after third dose, and may have been infected with non-vaccine-type HPV or have an abnormal Pap test at baseline.
[c] Efficacy in participants who received at least one vaccine dose, who were seronegative and HPV-DNA negative for vaccine-type HPV at month 0, and who may have been infected with non-vaccine-type HPV or have had a low-grade abnormal Pap test at baseline.
[d] Efficacy in participants who received at least one vaccine dose and had at least one follow-up visit after first dose, and who may have had infection or disease associated with non-vaccine-type before vaccination.
[e] Separate analyses of efficacy for prevention of cervical disease and anogenital disease.
[f] Pooled analysis of three clinical trials.
[g] 97.9% Confidence Intervals.
References: Future II[5,6], Future I[8]; Patricia[7]
CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in-situ; GW: genital warts; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia; NR: not reported.

Trials with the HPV -16 and -18 vaccine adjuvanted with ASo4

An interim analysis of another large international phase-III study of an ASo4-adjuvanted HPV-16/-18 VLP prophylactic vaccine including 18,644 women aged 15-25 years showed a vaccine efficacy of 90.4% against CIN 2/3 after a mean interval of 15 months since the first dose.[7] The study population included women who had prevalent oncogenic HPV infections, often with several HPV types, as well as low-grade cytological abnormalities at study entry. A large proportion of end-point cases with high-grade CIN had several oncogenic HPV types. Additional exploratory analysis were performed to address the causality of specific HPV types in the lesion, taking into account preceding HPV infection and HPV gene expression and these analyses showed protection of 100% against -16 or -18 CIN2+. This vaccine also demonstrated cross-protection against incident infection with HPV -45, HPV -31, and HPV -52, which is in line with the results of previous phase-II trials.[10] This phase-III trial is still ongoing.

The vaccine efficacy in the intention-to-treat analyses of all -16 and -18 related end-point cases was of 44% and of all endpoints regardless of the HPV type (thus related to any other HPV type) is only of 17%. The reason why vaccine efficacy is, at most, modest in the entire vaccinated cohort is the apparent lack of efficacy among subjects with previous exposure to the HPV types included in the vaccine. So far it is difficult to infer both the effectiveness of vaccination and the role of non-vaccine HPV types in the overall rates of precancerous lesions.

It has been estimated that 129 women would need to be vaccinated in order to prevent one case of high-grade CIN during an average of three years.[11]

The availability of an HPV cancer vaccine has elicited enormous enthusiasm in the medical community and

beyond. However, the efficacy of the vaccine development is limited by several factors. First of all, not all cervical, vaginal, or vulvar cancers are caused by HPV -16 or HPV -18. Therefore, for full benefit it appears necessary to vaccinate young women before they are infected with these two HPV types. Furthermore, whether the efficacy against high-grade pre-cancer can be extended to prevention of true cancers and prevention of cancer-related deaths remains unanswered. Other issues requiring continued follow up of the vaccinated cohorts include the proposals of male vaccination and evaluation of herd immunity, the long term duration of the protection and the long term safety of the vaccines. Although the vaccines have been studied in 33 countries and one is already licensed in more than 80 countries, post-marketing safety surveillance is of paramount importance. At least 20 US States are currently considering laws to make HPV vaccination mandatory for pre-teen girls[12] and have created some ethical, religious and political concerns.[13,14]

In summary, the efficacy of the two prophylactic HPV vaccines against high-grade cervical, vaginal, and vulvar pre-cancers approaches 100%, in women not exposed to the vaccine HPV types before vaccination and to the fraction of pre-cancers associated with the vaccine HPV types. The results suggest that both vaccines demonstrate almost similar efficacy. The data available so far provide sufficient evidence to support policy recommendations for the introduction of the HPV vaccine. Implementing HPV vaccines is a great opportunity but also a great challenge, and mandatory HPV vaccination raises many questions and more answers are needed.

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CURRENT STATUS OF HPV VACCINATION RECOMMENDATIONS

HPV vaccines were first approved for clinical use only about 18 months ago, but already many countries have developed national recommendations for their use. The primary target population for vaccination in most countries is pre-adolescent girls. However, a number of countries also include provisions for "catch-up" vaccination of adolescent girls and, in some countries, young sexually active women. In this review I will describe the currently available recommendations for use of the HPV vaccine as of October 2007.

European Countries

Thirteen European countries (Austria, Belgium, Denmark, France, Germany, Greece, Italy, Luxemburg, Norway, Spain, Sweden, Switzerland, and the U.K) have national recommendations for use of the HPV vaccine. These recommendations are outlined in Figure 1.[1] Italy has one of the most restrictive recommendations, with universal vaccination recommended for only 12-year-old females, although the vaccine is provided free of charge by the state.[2] The Spanish Public Health Commission recommends vaccination of a cohort within the age range of 11-14-year-old females.[3] Other countries such as Luxemburg and Norway target a similar age group for universal vaccination (12 and 11-12-year-olds, respectively), but allow for catch-up vaccination in females up to age 16 in Norway and age 18 in Luxemburg.[1] In Denmark, the Danish National Board of Health recommends using a vaccine that protects against genital warts and vaccinating all girls around age 12.[3] It also recommends a two-year "catch-up" vaccination period for 13-15-year-old females. This is very similar to the program announced by the government immunization program in the U.K., which recommends universal vaccination of 12-13-year-old girls and provides for a two-year "catch-up" vaccination period for females up to age 18.[4] Switzerland's Swiss Federal Office of Public Health recommends universal vaccination of 11-14-year-old girls with the quadrivalent vaccine to prevent both cervical disease and genital warts and "catch-up" vaccination for females aged 15-19 for a five-year time period.[5] It is recommended that vaccination of females 20 years and older be considered on an individual basis in Switzerland. The High Counsel on Health in Belgium recommends universal vaccination of females between 10 and 13 years of age and states that "catch-up" vaccination of 14-15-year-old females could be recommended based on the outcome of a

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health economics evaluation.[1] Austria recommends vaccination of females between the ages of 9 and 15 years (preferably delivered prior to the onset of sexual intercourse) as well as the vaccination of males of the same age (provided the quadrivalent vaccine that prevents infection with HPV-6 and -11 is utilized). Sweden's National Pharmaceutical Benefits Scheme recommends vaccination of all girls between 13 and 17 years of age with the quadrivalent vaccine.[1] In Germany, the recommendation is universal vaccination of girls between 12 and 17 years of age and states that older females can still benefit from vaccination.[2] France has a recommendation for universal vaccination of 14-year-old girls using the quadrivalent vaccine, and recommends vaccination for females between 15 and 23 years of age provided they are not sexually active or have only initiated sexual intercourse within the last year. Sixty five percent of the cost of the vaccine is paid for by the state.[6,7]

Australia, Canada, and the United States

The Australian National Immunization Program is providing universal vaccination of all 12-year-old girls through a school-based vaccination program but is only reimbursing the cost of the quadrivalent vaccine even though the bivalent vaccine is also approved for use in Australia.[8] The national program is also allowing for a two-year "catch-up" period for the vaccination of girls aged between 13 and 18 years through school-based programs and females aged between 18 and 26 years through general practitioners. There is a very high rate of participation in the "catch-up" vaccination program in this country because of an extensive public awareness campaign on the benefits of vaccination. Vaccination of 9-26-year-old females using the quadrivalent vaccine is recommended by the National Advisory Committee on Immunization in Canada.[9] The Advisory Committee on Immunization Practices (ACIP) has recommended routine vaccination of 11-12-year-old females in the US States as well as vaccination of females between 13 and 26 years of age if they have not been previously vaccinated, irrespective of whether or not they have initiated sexual activity.[10] Because the bivalent vaccine is not yet approved for use in the US States, this recommendation is currently limited to the quadrivalent vaccine.

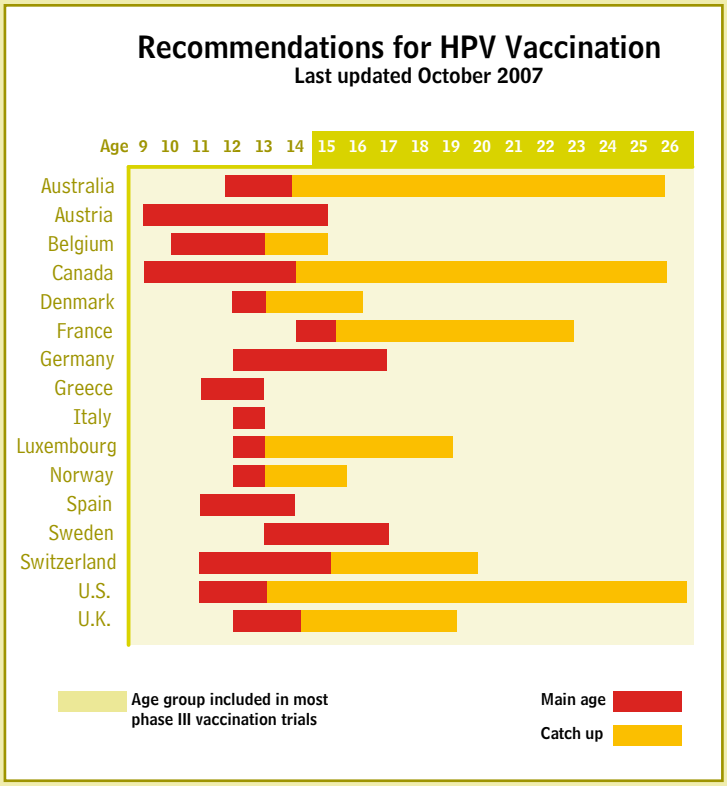

Figure 1

References: **1.** Human Papillomavirus Vaccine Gardasil® Becomes The First Vaccine To Be Reimbursed Within The Pharmaceutical Benefits Scheme In Sweden. http://wwwmedicalnewstodaycom/articles/71172php 2007. **2.** Germany, Italy back Merck's HPV vaccine for girls. http://wwwreuterscom/article/governmentFilingsNews/idUSL2653863420070326 2007. **3.** Two more European countries recommend free HPV vaccination for pre-adolescent girls to prevent cervical cancer. http://google-sinacom/2007/10/16/two-more-european-countries-recommend-free-human-papillomavirus-vaccination-for-pre-adolescent-girls-to-prevent-cervical-cancer/ 2007. **4.** HPV vaccine recommended for NHS immunization programme. http://wwwgnngovuk/environment/fullDetailasp?ReleaseID=325799&NewsAreaID=2 (Friday October 26, 2007) 2007. **5.** Swiss back cervical cancer shot, UK decision soon. http://wwwreuterscom/article/health-SP/idUSL1871371420070618 2007. **6.** In France, delicate questions over Gardasil®. http://moneycnncom/2007/07/11/news/companies/gardasil/indexhtm 2007. **7.** France. S-MsGgpsi. 2007. http://wwwreuterscom/article/companyNewsAndPR/idUSL1174470620070711. **8.** Preventing cervical cancer. http://wwwhealthgovau/cervicalcancer 2007. **9.** Human Papillomavirus (HPV). http://wwwhc-scgcca/iyh-vsv/diseases-maladies/hpv-vph_ehtml 2007. **10.** Markowitz LE *et al.* Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007;56(RR-2):1-24.

LONG-TERM FOLLOW-UP OF (COMMUNITY RANDOMIZED) VACCINATION TRIALS FACILITATES THE IMPLEMENTATION OF HUMAN PAPILLOMAVIRUS VACCINATION

Safe and efficacious vaccines against HPV do exist

The first vaccines against HPV types -16 and -18 have excellent vaccine efficacy against HPV-16/-18 infections and associated high-grade intraepithelial lesions[1,2] and adverse effects are the same in the vaccine and control arms.

Long-term follow-up

The Nordic countries have an essentially similar health-care infrastructure with comprehensive health registers that use unique personal identification numbers as well as organised cervical screening programs and associated biobanking systems. A virtually complete registry-based follow-up of all HPV vaccination trial participants over many years is therefore possible, which will yield data on the impact of HPV vaccination on invasive cancers, cervical screening usage and its results, health-care consumption and possible late adverse effects. It will also enable the retrieval of samples for HPV typing as well as more detailed analyses, for example in investigations of possible reasons behind vaccine breakthrough cases.

The different ongoing Nordic long-term follow-up efforts involve about 40,000 young women (22,000 of whom have been enrolled in Finland).[3] As the phase III HPV vaccination trials started many years before the HPV vaccination implementation, the Nordic long-term follow-up trials are expected to serve as a "sentinel cohort".

Estimating the impact of implementing HPV vaccination in populations

As health-care infrastructure and economics and the epidemic spread of HPV are different in different countries, the optimal implementation strategies to use may also differ between different countries. Vaccination trials up to phase III measure results on an individual level; what the vaccine uptake in populations will be and what the effect of herd immunity will be cannot be determined. Eradication of rubella only after both girls and boys were vaccinated in the Nordic countries is a good example of the strength of herd immunity.[4,5] In common sexually transmitted infections like HPV infections, the effect of herd immunity is even stronger because of the assortative nature of sexual behaviour.

A mathematical model based on comprehensive data on the sexual behaviour of the Finns and the occurrence of HPV-16 infections during the last 20 years indicates that eradication of HPV should be possible, particularly if both girls and boys are vaccinated. The 70% vaccine coverage already achieved helps to protect the new birth cohorts from HPV-16 infection,[6] and eradication of HPV-16 infection is seen with 90% population coverage (typical for Nordic vaccination programmes).

The ultimate design: Cluster-randomized implementation trials

The National Public Health Institute in Finland has started a community randomized trial in the 33 biggest cities, which also have the highest occurrence of genital HPV infections. During 2007/2008 14- and 15-year-old adolescents will be vaccinated against HPV types -16 and -18. During 2008/2009 13- and 14-year-olds will also be vaccinated ("catch-down" strategy). From 2012 onwards the prevalence reduction of HPV-16/-18 and high-risk (HR) HPVs will be evaluated among 18-year-olds in conjunction with chlamydia screening by comparing communities vaccinating girls against HPV with those

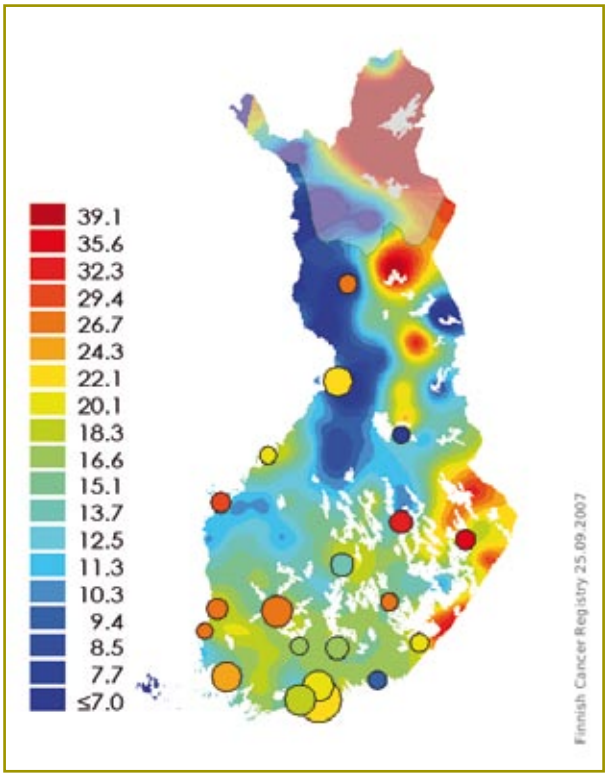

Figure 1:
Seroprevalence of HPV-16 antibodies in a representative sample of the population of Finland examined in 1998-2002. Colour code represent percent of women seropositive and circles represent sites where Phase IV vaccination trials are organized (excluding Helsinki metropolitan area).

Matti Lehtinen[1] and Joakim Dillner[2]

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vaccinating both boys and girls against HPV and those communities vaccinating only against hepatitis B virus (HBV). At the age of 18, cross-over vaccination will also be organized to provide the participants with all the health benefits.

It will also be possible to monitor if replacement of HPV-16/-18 with new HR HPV types not included in the vaccine is occurring. Because of the ongoing implementation trial much greater proportions of the early adolescents will be protected against HPV and HBV infections than would be the case if there had been only opportunistic vaccination. On the other hand, the community randomized trial enables an optimally stringent evaluation of the effectiveness of HPV vaccination for its implementation into the national vaccination program, which would not otherwise be possible.

HPV surveillance programs

However, even carefully planned and implemented programs need monitoring to assess whether they actually work in practise for achieving the goals set (e.g. eradication of HPV). Such monitoring should preferably be performed in a manner that is internationally comparable, thereby allowing the success of different programs in different countries to be compared.

Several Nordic countries will be using similar methodology for monitoring vaccine impact in populations to that being used for long-term follow-up of the phase III vaccination trials, i.e. registry linkage studies to assess the effect on invasive cancers, cervical screening usage and its results, health-care consumption and possible late adverse effects as well as to enable the retrieval of samples for HPV typing. A key component of this is HPV vaccination registration based on personal identifiers and informed consent for future linkages and HPV testing.

Conclusions

HPV vaccination is one of the most powerful tools currently available for cancer prevention. It is therefore of utmost importance that there is a strong emphasis on translational research that optimises the scientific knowledge base of how HPV vaccination programs should most efficiently be implemented, continuously monitored and optimised. Internationally standardised HPV surveillance efforts and ambitious programs to chart the overall health consequences of HPV vaccination using registry linkages and exploitation of the use of scientific designs in the implementation will be major tools to advance the knowledge of how HPV vaccines should be used to obtain the optimal effects.

The key components of all HPV vaccine program monitoring that needs HPV testing are:

1. Condyloma reporting statistics including HPV typing of reported cases. As the incubation time for condylomas is short (about 3 months), disappearance of condylomas will be the first clinical endpoint for evaluation of whether an HPV vaccination program has indeed stopped the circulation of HPV
2. Testing and typing for oncogenic HPV in sexually active teenage groups. This can be done, for example, by HPV testing at designated "sentinel" venereology/sexual health clinics. Both Sweden and Finland will be exploring the use of anonymised HPV testing concomitantly with routine Chlamydia screening
3. HPV testing in the first round of population-based cervical screening; and finally
4. HPV typing of cases of cervical cancer and other major HPV-associated diseases

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THE DAMAGE CAUSED BY RUMOURS AND ANTI-VACCINATION GROUPS

Introduction

At the beginning of the 21st century, vaccines have increasingly become victims of their own success. Occasionally vaccine controversies arise and have always resulted in a major decrease of vaccine uptake,[1–3] therefore with the ongoing introduction of HPV vaccination a number of lessons from the past should be taken into consideration: a careful, phased introduction of HPV vaccines, careful marketing strategies, the compilation of evidence-based data in the target population on coincidental associations are required to pro-actively avoid or rapidly counter possible vaccine scares.[4]

Major risks are taken by trying to speed up the introduction of the vaccine, putting at stake the confidence and trust of the public, not only towards HPV immunisation but towards vaccination in general.

Knowledge of the infectious disease

The burden of disease and the threats caused by vaccine-preventable diseases are, to a certain extent, much less visible as a consequence of the success of vaccination programmes. The times when hospital wards were filled with children unable to breath autonomously due to poliomyelitis paralysis are something that no parents and very few of the current health-care providers have experienced, although they were a sad reality only 50 years ago. Infections like hepatitis B and human papillomavirus are essentially invisible and are characterized by a rather unknown link with a pathology that occurs many years later! Clearly, if an individual (or health-care worker) is not aware of the real disease menace the benefits of vaccination are perceived as limited and rumours can easily tip the benefit/risk balance towards rejection. Studies regarding parental attitudes towards HPV immunisation show a lack of knowledge regarding HPV and its role in cervical cancer.[5,6]

Anti-vaccination groups

The introduction of HPV immunisation must be done in a context where organised resistance towards (childhood) vaccines already exists and misleading information is distributed via the Internet. The globalisation of the information exchange regarding safety scares is a new dimension that should be addressed and requires a coordinated response (e.g. the Vaccine Safety Net Project of the World Health Organization [WHO] Global Advisory Committee on Vaccine Safety).

Anti-vaccination groups and their sympathisers are well-organized, extremely diverse and include: parents or individuals who have experienced a (possibly coincidental) adverse event following immunization; persons with religious or philosophical objections to vaccination; adherents to "natural" or alternative medicine; individuals convinced of conspiracy theories; individuals opposed to government intervention in personal health issues; lawyers and other individuals with financial or political agendas; scientists reporting hypotheses to the media as fact; and opinionated media.[7] Anti-vaccination groups have in common that they focus on the (unsubstantiated) damage caused by vaccination and promote the refusal of vaccination. Medical doctors are often the source of the stories about alleged side-effects and diseases of unknown origin are very often linked with immunization (diabetes, autism, neurological disorders, chronic fatigue syndrome, alopecia, …).

Perceptions of the HPV vaccine

The fact that HPV infections are transmitted sexually and that HPV vaccines are recommended to be administered before sexual debut makes some parents believe it will encourage promiscuity, and both parents and providers see this as a hurdle towards acceptance of the immunisation. A survey among US States paediatricians (performed before licensure of the HPV vaccine) regarding intention to recommend the HPV vaccine showed that fewer than half of them anticipated giving the HPV vaccine to younger (10–12-year-old) female patients. In addition, 60% thought that the parents would be concerned that HPV vaccination may encourage risky sexual behaviour.[8] Immunization is regarded by many of us as something related to infancy. In the near future, however, adolescents will increasingly be targeted for specific immunization programmes: catch-up (e.g. measles vaccination), booster (diphtheria-tetanus-pertussis vaccination) or the start of an adolescent vaccination programme like HPV vaccination.

Focus group discussions in Denmark with adolescents and their parents have revealed that parents in particular needed a great deal of reassurance and confidence that a vaccine has been adequately tested and does not lead to serious adverse reactions. The fact that HPV is sexually transmitted had no significance for the Danish parents and young people in this study.[9]

Lessons learnt

Many lessons on how to deal with rumours that can damage the implementation and effectiveness of immunisation can be learnt for past experiences. Direct, proactive and clear communication based on credible evidence and readily available scientific data is essential to avoid or counter a vaccine crisis. Disease epidemiology and disease burden should be determined prior to the start of a vaccination programme in order to base the decision whether to recommend and use the vaccine on an objective benefit/risk balance and cost-effectiveness data. All data on effectiveness,

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possible side-effects and risks of a vaccine should be clearly communicated in order to maintain the trust and confidence of the public. As recommended by regulatory authorities and performed for all recently introduced vaccines, monitoring of the safety and efficacy should continue once the product is on the market. Finally, changes in immunisation policy and recommendations should be evidence-based and not induced by vaccination scares.[1]

An additional incentive for a careful, well-considered and gentle implementation of HPV vaccination programmes is a fair and transparent communication by authorities as well as manufacturers and health-care providers. These new HPV vaccines are not miraculous bullets—they are indeed very innovative and promising but they also have their limitations. Any exaggeration of their effectiveness will therefore serve only to enhance confusion and misunderstanding among the general public and health-care providers.

Clearly, the public, health-care providers, authorities and manufacturers should be made aware that such HPV vaccination programmes fit well into an integrated comprehensive cervical cancer control programme.

The WHO Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, was set up by the World Health Organization in 1999 to provide a reliable and independent assessment of vaccine safety issues. In the light of the current introduction of HPV vaccination programmes, there is very likely to be an increased focus on the vaccination of adolescents. The GACVS recognises that countries moving towards introducing vaccines aimed at adolescents and young adults should endeavour to secure population-specific and age-specific baseline rates of health conditions in the relevant age-groups.[10–12]

Scientific data that is essential to be able to distinguish causality from coincidence.

The first data to predict vaccine scares following HPV immunization have already been gathered. A cohort study to define possible coincidental associations with autoimmune diseases was carried out in the United States.

The results show that, due to sheer coincidence, if HPV immunization had been used with 80% coverage, 3 per 100,000 adolescents girls would have required emergency care for asthma or allergy within 24 hours and 2 per 100,000 for diabetes within 1 week of an injection. Hospitalizations for autoimmune diseases would have occurred within 6 weeks of an injection in 10 per 100,000 adolescent girls. If a catch-up program reaching only 40% of young adult women had been implemented, 28 per 100,000 patients requiring hospitalization for the recent onset or exacerbation of thyroiditis would have been within 6 weeks of an injection.[4]

It is obvious that this scientific evidence will help to prevent and counter unfounded safety accusations. These data might also be useful evidence in court.

Vaccines are no toothpaste

Aggressive immunization policies and marketing strategies will damage the confidence of the public. The rather aggressive marketing of the HPV vaccine in the United States, which tried to promote mandatory vaccination in several United States, was rapidly abandoned when conflicts of interest between the vaccine manufacture and politicians were revealed.[13] These events clearly damage the vaccine, the vaccination programmes and prevention in general. As recently argued by A. Raffels in the *British Medical Journal* "launching a programme prematurely could result in low uptake of vaccine, low uptake of screening, considerable public confusion, scaremongering about side-effects and no extra effect on disease rates".[14]

Although adverse events after immunization do exist, vaccination to prevent death and suffering from infectious diseases is without a doubt one of the greatest successes in public health. Maintaining and enhancing public trust in the safety and benefits of vaccination is crucial and it is the duty of every government, manufacturer, scientist, and health-care worker to help in this process.

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PREVENTION OF CERVICAL CANCER IN THE XXI CENTURY: LET'S PUT OUR TOOLS TO WORK

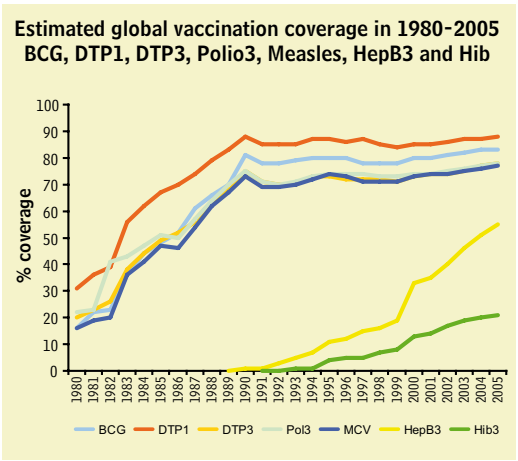
In high, middle and low income countries, the burden of cervical cancer is greatest among women of low socio-economic status or limited access to health care. Nearly 80% of cervical cancer occurs among women in developing countries, but risk also remains high in subgroups in wealthy industrialized countries who lack access to screening, prompt diagnosis, and effective treatment.

Several established and new interventions have the potential to reduce the global burden of cervical cancer, but have not been extensively or strategically applied to the highest risk populations. These include sexual risk reduction counselling, condom promotion, screening with cytology and HPV testing, visual cervical inspection, diagnosis with colposcopically-directed biopsies, various treatment modalities, and palliative care for late stage disease.

If applied more widely, this set of tools could accelerate the goal of the World Health Organization (WHO) to reduce the global burden of cancer and the gender, regional, and socioeconomic disparities unique to cervical cancer.

HPV vaccines are the newest primary prevention tool. As of October 2007, more than 80 countries had licensed the quadrivalent vaccine and more than 30 had licensed the bivalent vaccine. In several industrialized countries, HPV vaccines have been licensed and recommended for use on the basis of their high efficacy against persistent HPV infection and precancerous cervical lesions, and in the case of the quadrivalent vaccine, efficacy against external genital warts; the safety record based on available data; and cost effectiveness, especially for reducing costs of screening and follow up of abnormal screening tests. In settings where effective vaccination programs may be more feasible and sustainable than cancer screening programs, HPV vaccines may become a cornerstone of cervical cancer prevention once they become broadly affordable and accessible. However, HPV vaccines are currently too costly for public sector use in countries with the highest cervical cancer burden and action is needed to increase affordability. Because few countries have well-developed infrastructure to deliver a 3-dose vaccines to the preadolescent target group, vaccine delivery will require new approaches.

Vaccination of infants has achieved a great impact in disease reduction even in developing countries and populations of difficult access and limited resources. Vaccination coverage with three doses of DTP *or polio ranges in the* 70-90% *with rates of* 60% *in low income countries. The prospects of* HPV *vaccination programs in developing countries are thus optimistically viewed by most public health scientists.* BGC: *Bacillus Calmette-Guérin*; DTP: *Diphtheria-tetanus-pertusis*; Hep*B*: *Hepatitis* B; *Hib*: *Haemophilus Influenzae* B.



Source: WHO/UNICEF coverage estimates, 1980-2005, as of August 2006. 192 WHO Member States. Date of slide: 5 September 2006

Secondary prevention has benefited from a number of developments including the implementation of liquid-based cytology and HPV testing to triage patients with abnormal cytology results or as an adjunct to cytologic screening in women over age 30. Recently, important trials in several countries have found that HPV tests as a primary screening tests have superior sensitivity and predictive value with relatively small loss of specificity as compared with cytology. Rapid HPV tests that could be performed in remote clinical settings lacking laboratories and would avoid the need to recall patients for follow up are being evaluated in field trials in several countries. Several novel biomarkers are also being evaluated as possible screening tests.

Visual cervical inspection with acetic acid is a promising new screening option for low resource settings where screening with cytology or HPV testing may not be feasible. A recent study in India found that use of a "screen and treat" approach using visual cervical inspection followed by cryotherapy of lesions identified by trained nurses and midwives significantly reduced cancer incidence and mortality, particularly among women aged 30-39.[1] Patient acceptance of this approach was also high. Similar trials are under way in Africa and Latin America. Additionally, several studies have evaluated use of cryotherapy and Loop Electrosurgical Excision Procedure (LEEP) by mid-level personnel, an option for settings facing chronic physician shortages. Finally, World Health Organization (WHO) recently included morphine on its essential medicine list, a step that will should encourage more use of palliative care for late stage disease in countries where cervical cancer often means a slow and painful death.

Informed by models of public health impact and cost effectiveness, many experts have proposed new cervical prevention programs for middle and low income countries that would include HPV vaccination of preadolescent girls followed by HPV test-based screening 3-4 times over a lifetime starting in their thirties.

WHO and many other organizations are encouraging countries to make evidence-based decisions about the best combination of prevention and control strategies based on their burden of disease, health care infrastructure, extent of existing interventions, and other factors.

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From a public health perspective, strides in cervical cancer prevention could reduce troubling gender and social disparities in health. From an individual perspective, cervical cancer prevention can preserve the vitally and lives of women who may be crucial family breadwinners, heads of households and mothers, grandmothers and caretakers who are essential to the health and education of children and the well being of families, local communities and economies. Health policy makers, program managers, and health professionals can put this impressive box of tools to work to improve the lives of women and their communities and use scare health resources more effectively.

Reference: 1. Sankaranarayanan R *et al.* Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet 2007;370: 398-406

WHO RESOURCES ABOUT CERVICAL CANCER PREVENTION AND HPV VACCINES

- Preparing for the introduction of HPV vaccines: Policy and programme guidance for countries (2006). Available in English, Spanish, French, Chinese, Russian, and Arabic.
http://www.who.int/reproductive-health/publications/hpvvaccines/
- Human papillomavirus and HPV vaccines: Technical information for policy-makers and health professionals (2007). Available in English now, and soon in Spanish, French, Chinese, Russian and Arabic.
http://www.who.int/vaccines-documents/DocsPDF07/866.pdf
- Guidelines to Assure the Quality, Safety, and Efficacy of Recombinant Human Papillomavirus Virus-Like Particle Vaccines. World Health Organization (WHO) Expert Committee on Biological Standardization, 2007."
http://www.who.int/biologicals/publications/trs/areas/vaccines/human_papillomavirus/en/index.html
- Comprehensive Cervical Cancer Control: A guide to essential practice.
Available in English, French, and Spanish.
http://www.who.int/reproductive-health/publications/cervical_cancer_gep/index.htm
- Cancer Control: knowledge into action. WHO Guidelines for Effective Programmes (includes a module on prevention that addresses HPV vaccines)
http://www.who.int/cancer/modules/en/index.html
- WHO/ICO Information Centre for HPV and Cervical Cancer. This website includes information useful to countries that have introduced or are considering introducing HPV vaccines. It includes global, country-, and region-specific data on cervical cancer incidence and mortality, incidence of precancerous lesions, HPV prevalence and type distribution, demographic and sexual characteristics, screening program data, and immunization data.
http://www.who.int/hpvcentre

Additional resources:

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BIVALENT VACCINE

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INTERNATIONAL AGENDA

London, United Kingdom

7th - 8th April 2008

Innovations and Progress in Healthcare for Women International Meeting

Venue: Queen Elizabeth II Conference Centre
E-mail: IPHW08@confab-consulting.co.uk
Web: www.womenshealth.uk.com

Las Vegas, Nevada, USA

14th - 16th April 2008

Premier Conference on Vaccine Development

Venue: Mandalay Bay Resort & Casino, Las Vegas, NV
E-mail: vbernardino@iirusa.com
Web: www.iirusa.com/vaccines/eventhome/39154.xml

Washington, USA

21st - 24th April 2008

World Vaccine Congress

Venue: Hyatt Regency Crystal City
E-mail: neil.darkes@terrapinn.com
Web: www.terrapinn.com/2008/wvc_DC/index.stm

Sonsonate, El Salvador

21st - 25th April 2008

XXVI Congreso Centroamericano de Ginecología y Obstetricia FECASOG 2008

Venue: Hotel Decameron
E-mail: informacion@fecasog2008.com
Web: www.fecasog2008.com

New Orleans, Louisiana, USA

3rd - 7th May 2008

American College of Obstetricians and Gynecologists (ACOG) Annual Meeting

Venue: New Orleans Morial Convention Center
E-mail: acm@acog.org
Web: www.acog.org/acm/

Barcelona, Spain

17th - 22nd May 2008

3rd Intercontinental Congress of Pathology

Venue: Palau de Congressos de Catalunya
E-mail: soniamolero@academia.cat
Web: www.3rdintercontinentalcongresspathology.org

Viareggio,Italy

22nd - 24th May 2008

IX International Workshop on Lower Genital Tract Pathology

HPV-Related Disease in the Vaccine Era: Time to Retire?

Venue: Centro Congressi Principe di Piemonte Viareggio
E-mail: c.imola.adriacongrex.it
Web: www.adriacongrex.it/hpv2008

Singapore, Singapore

2nd - 5th June 2008

World Vaccines Congress Asia

Venue: Grand Hyatt
E-mail: colin.zheng@terrapinn.com
Web: www.terrapinn.com/2008/wvcasia/

Helsingør, Denmark

4th - 6th June 2008

International Cancer Screening Network - Beinnial Meeting

Venue: Lo-Skolen Conference
E-mail: KSedgwick@novaresearch.com
Web: www.cancermeetings.org/ICSN/

Rovaniemi, Finland

15th - 18th June 2008

34th European Congress of Cytology

Venue: University of Lapland
E-mail: congress@ulapland.fi
Web: www.cytology2008.fi

Maryland, USA

17th - 18th July 2008

Next Generation Vaccines

Venue: Gaylord National Hotel in National Harbor
E-mail: gbroughton@ibcusa.com
Web: www.ibclifesciences.com/vaccines/overview.xml

Kunming, China

20th - 26th July 2008

BIT's 1st Annual World Summit of Antivirals-2008

Combating Severe Viral Infections

Venue: Kunming & Xizang (Tibet), China
E-mail: helen@bitlifescineces.com
Web: www.bitlifesciences.com/wsa2008

Amsterdam, The Netherlands

8th - 11th October 2008

17th Annual Congress of the European Society for Gynaecological Endoscopy

Venue: Passenger Terminal Amsterdam
E-mail: sabine.gisler@meeting-com.ch
Web: www.esge.org/future_congresses.htm

Mälmo, Sweden

8th - 14th May 2009

25th International Papillomavirus Conference and Clinical Workshop

Venue: Mälmo Exhibition and Convention Center
E-mail: info@destinationoresund.com
Web: www.hpv2009.org

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