Consultation of the Human Papillomavirus Expert Advisory Group (HEAG)
3-5 September 2007, WHO-HQ, Geneva

FINAL MEETING REPORT

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I. INTRODUCTION AND MEETING OBJECTIVES

The third meeting of the WHO HPV Expert Advisory Group (HEAG) convened with these objectives:

- To update members on recent data relevant to decisions on global HPV vaccines introduction;
- To seek members’ critique and proposed revisions to a draft Background Paper that includes evidence needed to support possible future HPV vaccine recommendations of WHO's Strategic Advisory Group of Experts (SAGE) and a possible future WHO Position Paper on vaccine use;
- To seek members’ recommendations on clinical, programmatic, economic and policy-related research relevant to WHO recommendations for HPV vaccine use;
- If evidence were deemed sufficient to support recommendations on HPV vaccine use, to discuss candidate recommendations for future deliberation by SAGE; and
- To seek members’ recommendations about information needed for decision making tools that countries could use to foster evidence-based decisions about vaccine introduction.

Dr Teresa Aguado, Initiative for Vaccine Research (IVR), WHO, welcomed meeting participants, reviewed recent events, and provided a charge to HEAG members. In April 2007, the Strategic Advisory Group of Experts (SAGE) concluded that clinical trial evidence indicated that the introduction of HPV vaccines is likely to bring benefits, particularly to developing countries with high cervical cancer mortality and limited screening programmes, but also to developed countries with existing screening programmes. SAGE also concluded that programmatic opportunities for delivering HPV vaccines exist, such as adolescent school-based programmes, national immunization days, vaccination weeks, or child health days. SAGE asked HEAG to review evidence that could be the basis for a future WHO HPV vaccine Position Paper and to identify outstanding questions about safety, efficacy and delivery for future consideration by SAGE.

Dr Aguado also noted that the terms of reference (TOR) for HEAG are being revised to be consistent with TOR for other Advisory Groups to WHO's Initiative for Vaccine Research (IVR). The current TOR state that HEAG will be responsible for establishing the WHO recommendations and guidelines related to the HPV vaccine deployment and that HEAG shall directly report to SAGE. The proposed revised TOR states that HEAG shall synthesize scientific evidence, perform analyses, and draft documents (which may include candidate recommendations for vaccine use) for consideration by SAGE in view of formulating WHO Recommendations and Guidelines for the administration of HPV vaccines. Dr Aguado noted that the next HEAG meeting in 2008 would convene under new TORs and that the HEAG membership may change in the future due to new requirements about WHO advisory committee members, new areas of required expertise, and potential or actual conflict of interest of current members. Current members will be notified about their ongoing membership within the next few months. Dr Aguado noted that some meeting participants declared actual or potential conflicts of interest and that they were not selected as workgroup facilitators or rapporteurs and that recommendations from such participants would be included in the meeting report at the discretion of WHO.
Dr Patricia Janet Garcia, HEAG member and chair of the meeting, opened the meeting by highlighting important changes since the last HEAG meeting of August 2006. Since then, the quadrivalent vaccine has been licensed in many countries and the bivalent vaccine in two. (At the time of the September 2007 meeting, the bivalent vaccine has been licensed by at least 4 countries.) Several industrialized countries have recommended the quadrivalent vaccine or recommended HPV vaccination in principal (without specifying a vaccine product) for national use and some have introduced this vaccine into immunization programmes. She reviewed the meeting agenda (see Annex), noting that oral presentations would be given on the first day to ensure that meeting participants were aware of recent data and that these new data should be considered in 4 workgroup discussions on the second day devoted to 1) Safety, efficacy, and immunogenicity; 2) Delivery, integration with screening, and monitoring and evaluation; 3) Vaccine impact, cost, cost-effectiveness, and financing; 4) Sociocultural issues, patient education, communication, and policy. Dr Garcia asked workgroup participants to review current evidence and decide if it were sufficient to start drafting candidate recommendations about use of HPV vaccines for future consideration by SAGE, a discussion that would strongly consider regional perspectives. Workgroups would report their conclusions on the afternoon of the second day and the third day. The third day would conclude with a general discussion about readiness for drafting candidate recommendations about HPV vaccines and presentations and discussion about monitoring and evaluation needs for vaccines and research and communication priorities for WHO, and a panel on building partnerships for decision-making about HPV vaccine introduction in regions led by WHO Regional Office representatives.

II. UPDATES ON RECENT DATA, EXPERIENCE, AND OPINIONS

Update on vaccine efficacy and immunogenicity (Dr Lauri Markowitz, US Centers for Disease Control and Prevention, HEAG member)

Two VLP vaccines: a quadrivalent vaccine (Merck) and a bivalent vaccine (GSK), have been assessed in phase II and large phase III efficacy trials of females subjects only. More than 20,000 women, aged 16-26 have been included in the trials for the quadrivalent vaccine and more than 27,000 women, aged 15-25, have participated in trials of the bivalent vaccine. Regions included in the trials were North and Latin America, Europe and Asia-Pacific. The vaccines have been evaluated using different study designs, but with many common features. Phase III studies for the quadrivalent vaccine and interim analyses of ongoing Phase III studies of the bivalent vaccine have been published. Published studies have presented results on various populations, including "per-protocol" and "intention to treat" populations.

Efficacy

Trials results have shown that both vaccines have a high efficacy against HPV type-related endpoints among females naïve to the relevant vaccine type:

- In the per protocol populations\(^1\): one study of the quadrivalent vaccine showed an efficacy of 98% (95% confidence interval (CI) 86-100%) for the prevention of HPV 16/18 related cervical intraepithelial neoplasia grade 2 or 3 (CIN 2/3) or adenocarcinoma in situ (AIS); another study found 100% for the prevention of condyloma (95% CI 92-100%) and vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VaIN) grade 2+ (95% CI 49-100%). Publication of results of the per protocol analysis of bivalent vaccine phase III trial data is anticipated when final endpoints are analyzed.

- In the unrestricted susceptible populations\(^2\): the quadrivalent vaccines showed an efficacy of 95% (95% CI 85-99%) and the bivalent vaccine of 90% (97.9% CI 53-99%) for the prevention of HPV 16/18 related CIN 2/3 or AIS.

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\(^1\) Per protocol population for efficacy: naïve to relevant vaccine HPV type through month 7, received all 3 vaccinations, no protocol deviation and cases counted after month 7.

\(^2\) Unrestricted susceptible populations (or total vaccinated): naïve to relevant vaccine HPV type, received at least one vaccination, cases counted day one after first dose.
In the intention to treat population\(^3\), the quadrivalent vaccine showed an efficacy of 41% (95% CI 27-53%) for the prevention of HPV 16/18 related CIN 2/3 or AIS, an efficacy of 71% (95% CI 37-88%) for the prevention of VIN or VaIN grade 2/3, and an efficacy of 78% (95% CI 71-83%) for vulvar and vaginal lesions (including genital warts).

When investigators examined subpopulations of women with evidence of past or current HPV infection, as demonstrated by HPV positive serology or PCR tests, the quadrivalent vaccine did not demonstrate any therapeutic effects such as faster clearance of HPV infection or less progression to disease related to HPV types with which women were infected at baseline. Similarly, the prophylactic bivalent vaccine has shown no evidence of therapeutic value in clearing preexisting infection.

Regarding the duration of protection, efficacy data available from phase II trials have shown that both vaccines show sustained high efficacy against persistent HPV infection through ~60 months. Data from phase II trials of the quadrivalent vaccine have shown efficacy of 100%, but confidence bounds range from <0-100\extend below zero due to small numbers of endpoints.

Preliminary data suggest partial cross protection of the bivalent vaccine against some related, non-vaccine types: efficacy for preventing persistent infection at 6 months with HPV 45 (efficacy of 59.92%, 97.9% CI 2.6-85.2%), HPV 31 (efficacy of 36.1%, 97.9% CI 0.5-59.5%), and HPV 52 (efficacy of 31.6%, 97.9% CI 3.5-51.9%). For the quadrivalent vaccine, studies are underway to evaluate cross-protection against persistent infection with HPV types 31, 33, 45, 52, and 58 and cervical, vulvar, and vaginal lesions caused by these types.

**Immunogenicity**

The main basis of protection is neutralizing antibody. The minimum protective antibody threshold is still not known and serological tests for HPV antibody are not standardized, precluding direct comparison of antibody detection across the two vaccines. Despite this, data demonstrate that both vaccines induce serum antibodies in virtually all vaccinees. Vaccine-induced antibody titres are higher than those seen after natural infection and remain higher for at least 5 years. In the quadrivalent vaccine trials, some vaccinees had lost detectable antibody to HPV 18, but this waning immunity was not associated with loss of protection against HPV 18-related clinical outcomes. In addition, a sharp, rapid increase in antibody titres against all four vaccine HPV types has been demonstrated, when a fourth vaccine dose was given after completion of the primary series of quadrivalent vaccine. This indicates a strong anamnestic response suggestive of immune memory. The bivalent vaccine’s ASO4 adjuvant induces a higher, more persistent humoral response than the same vaccine composition containing Al(OH)\(_3\). Similarly, the proprietary aluminium adjuvant used in the quadrivalent vaccine, amorphous aluminium hydroxyphosphate sulfate, induces higher and more sustained antibody than Al(OH)\(_3\).

Adolescent bridging data show that, for both vaccines, immunogenicity in young adolescents (9 or 10-15 years old) was not inferior to that in older adolescent females and adult women included in the efficacy trials. Geometric mean titres for the younger age group are about two fold higher than those of older adolescents and women. In bridging studies of the bivalent vaccine administered to women aged 25-45 years, antibody titres for HPV 16 were lower than those of younger women enrolled in the efficacy trials, but remained substantially higher than titres seen with natural infection. Immunobridging data for older women given the quadrivalent vaccine will be available in the near future.

**Remaining questions and on-going research**

For both vaccines, remaining questions include the duration of protection, the immunogenicity and safety in HIV-infected and other subpopulations, efficacy in males, and cross protection against related non-vaccine HPV

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\(^3\) Intention to treat population: all subjects regardless of baseline status, received at least one vaccination, cases counted day one after first dose.
Discussion
Clarification questions about ongoing research were asked.

Update on Safety (Dr Dina Pfeifer, Quality, Safety, and Standards, Department of Immunization, Vaccines, and Biologicals, WHO)

Dr Pfeifer reviewed safety information, safety data limitations, the report of the June 2007 meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS) (Weekly Epidemiology Report. World Health Organization. 20 JULY 2007. Nos. 28/29, 2007, 82, 255–256. http://www.who.int/wer), and data on behavioral and other potential consequences of vaccination. Data on safety have been generated through trials, but interpretation of results is somewhat difficult as the trials have included different populations, geographical locations, methods and safety endpoints. As a result, combining diverse types of data into single safety databases for each product produces results with possible biases. For both vaccines, safety data are available on more than 16,000 trial participants and post marketing surveillance data are available for the quadrivalent vaccine first licensed in the US in June 2006.

Concerning reactogenicity, injection site pain, swelling, and erythema have been reported very commonly for both vaccines and some of these signs and symptoms are similar to the profile of tetanus toxoid given to vaccinees of the same age. Compared with these symptoms, injection site pruritis and bleeding have been reported less commonly in recipients of both vaccinees. Frequently reported systemic symptoms associated with one or both vaccines include dizziness, syncope, nausea, fatigue, arthralgia, myalgia, mild fever, and headache. Some of these symptoms may be associated with mass sociogenic illness among quadrivalent vaccine recipients, particularly adolescents, a problem reported in Australia among girls who were vaccinated en masse in a confined space.

Serious adverse events following immunization (AEFI) have occurred in less than 0.1% of vaccine recipients based on trial and post marketing surveillance data, the latter restricted to the quadrivalent vaccine. They include rare reports of hypersensitivity reactions, thrombosis and embolism (especially in oral contraceptive users), Guillan Barré syndrome, seizures, autoimmune disorders such as Stevens Johnson syndrome, and death. These events have been temporally associated, but not necessarily causally associated, with vaccine administration. In trials of both vaccines, incidence of these systemic events was not significantly greater in vaccinees compared to control subjects. Some autoimmune disorders may be recorded in temporal association with HPV vaccines as the onset of some of these conditions occurs during adolescence and young adulthood.

GACVS reviewed the safety of HPV vaccines in June and December 2005 and June 2007. The 2007 meeting concluded that current evidence on the safety of HPV vaccines is reassuring, but that postmarketing surveillance is important to identify possible rare adverse effects. Interpreting rare events is challenging because high quality
data on the underlying rates of rare diseases in older girls and adolescents are very limited, partly because adolescents are rarely defined in available datasets of children or adults. GACVS urged continued surveillance for reproductive outcomes, establishing vaccine registries to follow adverse events long term, and sharing protocols for monitoring safety to allow adaptation by countries wishing to start such surveillance.

Concerning reproductive safety, Dr Pfeifer noted that although the clinical trials excluded pregnant women, some women became pregnant during the trials, yielding data on pregnancy, fetal and infant outcomes. Evaluations of the quadrivalent vaccine have indicated similar frequencies of spontaneous abortion and late fetal death before and after vaccination and rare, diverse congenital anomalies among offspring of vaccinees that are unlikely to be associated with vaccination. In addition, toxicity tests of both vaccines in rats have not shown vaccine-related malformations or negative effects on reproduction. This has resulted in classification of the quadrivalent vaccine as category B by the US FDA and category B2 by the Australian Therapeutic Goods Administration. Neither HPV vaccine is intended for use in pregnancy, but these preliminary safety data may imply that pregnancy testing before vaccination provided through public health programmes is not needed, that inadvertent vaccination during pregnancy is not a reason to terminate pregnancy, but that for females planning a pregnancy, conception should be delayed until at least one month after vaccination. Lessons learned from tetanus, rubella and OPV vaccination campaigns may be relevant to HPV vaccines. These indicate that the public may be concerned about adverse effects of vaccines on fertility, especially in light of legitimate research in the 1990s on antifertility vaccines. Dr Pfeifer noted attitudinal, cultural barriers to HPV vaccines that may be related to general opposition to vaccines, negative reactions to STI vaccines, limited public awareness of HPV, and structural and economic barriers to delivering vaccines to a new target age group.

Regarding behavioural issues, Dr Pfeifer noted that public concerns that HPV vaccines might promote earlier or riskier sexual behaviour are not supported by data indicating that other sexual health interventions do not increase risky behavior (e.g., condom promotion and sex education), fear of STI does not strongly motivate abstinence, and one vaccine is unlikely to undermine sexual health values communicated by parents. She noted that ongoing cervical cancer screening is needed for vaccinated females later in life to prevent cervical precancerous lesions and prevent cancer due to oncogenic HPV types not related to current vaccines and that vaccination may alter screening behaviour or reduce incentive of developing countries to develop basic screening services. She stressed that very few countries currently have immunization programmes that deliver a 3 dose vaccine to 9-25 year olds. Absence of school-based or other types of immunization programmes for adolescents suggests that common EPI systems used to monitor vaccine safety may not be adequate to monitor HPV vaccine safety in some countries. She concluded that the safety of HPV vaccines would be better characterized as more fully immunized females are followed in trials and post-marketing surveillance and that attention should be given to adverse events related to dose and age, concomitant use with other vaccines, and HIV-infected persons.

**Discussion**

Merck and GSK representatives noted that in their vaccine trials, the mean number of sex partners before and after vaccination were not significantly different. GSK continues to follow sexual behaviour in their ongoing phase 3 trial. For both vaccines, long term safety and behavioural issues will be evaluated in phase IV studies. Merck will evaluate sexual activity in an efficacy trial of adolescents aged 9-15. Further analysis of sexual behavior was recommended, especially in developing countries. Merck indicated they are considering large demonstration projects or evaluations as part of clinical trials in developing countries. The potential impact of vaccines on behaviors also may relate to other vaccines (e.g. potential HIV vaccines).

**Update on delivery strategies and programmatic issues (Dr Vivien Tsu, Program for Appropriate Technology for Health (PATH), Temporary Advisor)**
Dr Tsu reviewed possible vaccine target groups, service delivery options, potential synergy with other health interventions for children and young adolescents, how vaccines could complement other cervical cancer control interventions, and capacity of health systems to deliver vaccine and new programmatic research. She noted that girls will likely be the primary target group aged 9-13 years old, and that to achieve the highest impact, girls should get vaccinated before sexual debut and HPV exposure. She added that priority should be given to a single cohort of this age in low-resource settings because vaccination of older adolescents and young adults (catch-up) may provide important clinical benefits but is less cost-effective and logistically more difficult. However, this strategy may be most feasible and affordable in higher resource settings. A multi-dose primary vaccine series for a pre-adolescent target group has never been addressed by the Expanded Programme on Immunization (EPI) so new mechanisms for vaccine delivery, including community involvement, will need to be developed.

PATH is conducting formative research in India, Peru, Uganda and Vietnam. Both Merck and GSK are collaborating with PATH to assess delivery options in some sites. Data collection in Peru and Uganda are complete and began in July 2007 for India and Vietnam. Research objectives include evaluating delivery options and alternate dosing schedules (quarterly, semi-annually, and annually) for the quadrivalent vaccine. Leading service delivery options are school-based programmes, national child health or immunization days, vaccination weeks, a mixed model (where school-based is supplemented by community outreach for missing girls), and health facility delivery. School-based programmes could build on high rates of primary school completion (> 50%) in all WHO regions and school-girls can also be a channel to reach out-of-school girls. In demonstration projects evaluating school-based delivery in Peru, uptake has varied by school from 20% to 100%. Child health days or vaccination weeks, which include adolescents, occur annually or semi-annually in many countries in Asia, Africa, and Latin America and could be used as a primary or "mop-up" strategy. For example, semi-annual campaigns in Uganda cover 0-14 year olds in and out of school. However, campaigns require major resources and are currently designed to delivery two doses a year, not a 3 dose vaccine over 6 months required by current HPV vaccines. Most EPI programmes have many elements needed to deliver HPV vaccines (cold chain, intramuscular injection skills, injection supplies, storage, transport, and disposal systems) but introducing HPV vaccines would require training on unique issues such as the capacity to monitor 3 dose coverage and impact on outcomes that may occur decades later. Preliminary data from demonstration projects reveal typical immunization problems (needle recapping, freezing, insufficient transport and refrigeration) as well as issues unique to HPV vaccines such as record systems for a 3-dose vaccine, monitoring for adverse events, and the capacity to watch vaccinees 15 minutes after injection to monitor syncope and dizziness.

Preliminary data from Peru in which about 2000 girls have received their first dose after receiving information from teachers have revealed a few minor adverse events, but no major adverse events; about 7% have missed the second dose. Parents are generally supportive, although study requirements for written consent have led to some refusals. Potential acceptability issues include the lack of awareness of cervical cancer burden. More public education is beneficial for both vaccine and screening acceptability. Fears about the association with sexually transmitted infections (STI) has not shown to be a problem, but rumors about possible fertility effects of HPV vaccines have arisen. Systematic analysis of and response to expressed concerns and information needs can strengthen the community and political support. Opportunities to share opinions and experience about HPV vaccines have emerged, including the web-based WHO Community of Practice about cervical cancer and HPV vaccines, expected to be launched by the end of 2007 (http://HPV-vaccines.net).

HPV vaccines provide an opportunity for synergy with other health interventions for children and young adolescents. Co-vaccination with other vaccines such as for tetanus, rubella, hepatitis B, measles catch-up and perhaps in the future, HIV vaccines, may be an option. Other health interventions such as deworming could be offered at the same time and health education and promotion messages could be given. Combining interventions may reduce the cost of each by sharing resources such as staff and transport. Many countries are already interested in addressing health of this age group, especially through schools. Finally, HPV vaccines can be a valuable component of comprehensive cervical cancer programmes. These programmes would include primary
Discussion

A concern was raised that a mixed delivery strategy would lead to different coverage levels among different target groups. It is still a question if an active community programme, including girls who do not attend school, can result in high coverage Dr Tsu noted that uptake will depend on the quality of the strategy, the existence of community workers and leaders and the motivation. It was also noted that vaccinated adolescents may be interested in inviting both in-school and out-of-school peers for vaccination. The costs of various strategies were discussed and Dr Tsu noted that the ongoing demonstration project in Peru is collecting delivery cost data.

Update on the public health impact and cost-effectiveness of HPV vaccination (Dr Sue Goldie, Harvard School of Public Health, Temporary Advisor)

Dr Goldie noted that key policy questions about HPV vaccination in the context of cervical cancer control differ in low, middle and high-income countries, and modeling and cost-effectiveness analyses can inform these questions. Selected questions in developing countries include: 1) What is the optimal cancer control programme given that screening for women and a preventive vaccine for adolescents exist?; 2) Which screening approach is optimal?; 3) How might the public health impact and cost-effectiveness vary between settings, especially in light of geographic differences in HPV type distribution?; and 4) What is the cost-effectiveness of different vaccine strategies? She stressed that these policy questions are characterized by complexity, uncertainty, and inevitable tradeoffs and that decision analysis can be used to compare expected benefits, risks, and costs of different interventions while considering model data uncertainties. She added that cost-effectiveness studies that address health value for money should not be confused with studies that assess financial impact or budget analyses that assess costs or affordability. She stated that both types of studies are important for policy decisions.

Cervical cancer prevention models have been applied to several low resource settings. Analyses focusing on cervical cancer screening strategies have shown that, in developing countries, newer screening approaches that link screening and treatment in 1-2 visits and target women aged 30-45, are most effective and cost-effective (according to GDP threshold\(^4\)) and could reduce cervical cancer mortality up to 40% given 2-3 high quality screenings over a lifetime. Some models have examined the impact of vaccination in reducing the number of infants and children orphaned by women who have died of cervical cancer in their middle years.

Dr Goldie stressed that the overall impact of HPV vaccines in terms of total averted cancer deaths would be much greater in countries with moderate incidence of cervical cancer but with a very large population of women at risk, (such as India which now accounts for 25% of cervical cancer cases worldwide) than in countries with small populations but higher cancer incidence. Therefore, she emphasized that considering the age-standardized incidence rate is not sufficient to prioritize where the vaccine would be most beneficial. She noted that the incremental cervical cancer reduction achieved by vaccinating males is minimal, compared to the costs required to vaccinate both males and females, if high coverage can be achieved in pre-adolescent girls.

To assess how cost-effective HPV 16,18 vaccination is compared to screening, more complex models have been used to capture heterogeneities between countries in HPV epidemiology, age-related and type-specific HPV prevalence in women with normal cytology, the age-related incidence of cancer, and HPV type-distribution in invasive cancer cases. Application of a model, calibrated to these types of epidemiologic data, to resource-poor...
settings without effective screening, such as Brazil, has shown that the clinical benefits of an HPV 16/18 vaccine are likely to be substantial.

Since vaccine prices are not yet known for different developing countries, the models developed to date represent vaccination costs as a composite cost per vaccinated woman that includes costs of vaccine, administration, and programmatic costs. Some, but certainly not all, of these costs are related to vaccine price. For example, wastage costs are greater for more costly vaccines. In Brazil, compared to the status quo of no vaccination and no screening, vaccination of 70% of pre-adolescent girls would be expected to result in a mean cancer reduction of 43%. In comparison, screening alone would be expected to reduce lifetime risk of cancer 22-31% depending on the screening test and strategy, and a combined strategy of pre-adolescent vaccination plus screening three times in a lifetime with cytology or HPV test would be expected to reduce cancer by 56-61%. At a cost of 25 IS per vaccinated woman, (implying a price per dose of $5-7 excluding wastage, administration, and vaccine support), vaccination alone would clearly be cost-effective in Brazil (using the GDP threshold) and the most effective strategy would be vaccination before age 12, followed by screening three times between ages 35-45. However, for countries with GDPs lower than 1000 IS, the cost per vaccinated woman may need to be as low as 8 IS (implying a price per dose of $1-2), to be both cost-effective and affordable. Dr Goldie emphasized that cost-effectiveness analyses do not provide information on affordability to the payer so that a cost-effective strategy may not be feasible if countries lack the money to invest. For example, vaccinating 70% of 11 year olds in Brazil would cost about 33 IS million compared to 70.5 IS million to provide three cytologic screens in the lifetime of a single cohort of women. She noted that analyses presented using international dollars are intended to be comparative across countries and that estimates of implied price can be expressed as international dollars or US dollars. For planning purposes, countries may want to express resources required for vaccine administration, support, delivery, and other programmatic aspects in their own currency, especially if these resources may be not be tradeable.

The Global Cervical Cancer Policy Project is a multi-year collaboration to develop models for different epidemiological settings utilizing data from >25 countries. The goal is to generate timely policy analyses for initiatives such as the GAVI investment case, the PAHO Revolving Fund, and other financing organizations. Empirically calibrated models have been developed for several countries as well as a companion model that can generate outcomes for GAVI-eligible countries that are based on less extensive epidemiologic data. Although the latter models rely on simplifying assumptions and assess only relatively simple strategies, they can estimate outcomes such as number of cases averted, deaths averted, life-expectancy gains and disability-adjusted life years. Secondary benefits such as the maternal orphans averted have been calculated to represent a fuller range of benefits. Model corroboration with more complex models is completed for 5 GAVI eligible countries.

Several uncertainties that influence model predictions. These include uncertainties about the type-specific natural history of HPV infection and immunity to natural infection, interaction between HPV types, duration of vaccine protection, vaccine cross-protection against non-vaccine HPV types, the magnitude of herd immunity; operational costs and feasibility, effectiveness of delivering 3 doses to target groups, and the efficacy of alternate schedules and two doses. As vaccine prices in prospective markets are uncertain, it remains unclear if cost-effective strategies will be affordable.

Discussion

Questions were raised about the role of HPV 6 and 11 in developing countries and associated lesions of ASCUS, CIN1, and anogenital warts. Dr Goldie noted that HPV 6 and 11-related disease has virtually no impact on mortality and a limited impact on cost-effectiveness in current models of the poorest developing countries because these countries rarely diagnose or treat these conditions, so costs are negligible. She also noted that the impact of vaccines on mortality from anogenital cancers other than cervical cancer is minimal compared to that of cervical cancer mortality, but would certainly add to the benefits. Dr Hecht noted that models should carefully
consider discounting rates, given that the interval between vaccination and prevention of incident cervical cancer is longer than the interval between screening for precancerous lesions and incident cervical cancer and this difference can make vaccination appear less effective and cost-effective because benefits are delayed. Dr Goldie agreed, and reiterated the importance of presenting results using a range of discount rates, as well as providing outcomes that are not discounted (e.g., lives saved).

**Update on secondary prevention strategies (Dr Andreas Ullrich, Non-Communicable Diseases, WHO)**

Dr Ullrich described WHO's new global plan against cancer that advises cancer prevention, cure, care and management and development of a comprehensive strategy for cervical cancer prevention as outlined in the plan’s new prevention module. Recently, WHO has developed several documents to guide cervical cancer control programmes that address secondary prevention through screening, as well as primary prevention through education and HPV vaccines. Cytology screening has been shown to be effective in reducing cervical cancer morbidity and mortality when implemented in an organized way, but organized screening with high coverage is applied in only a few high income countries. The feasibility of an organized, cytology-based screening is limited for low and middle countries; most have no screening or opportunistic screening with low to moderate coverage.

New screening alternatives to cytology include visual inspection with acetic acid (VIA), which can be used in a screen and treat approach. A prospective, cluster randomized study in India has shown that a single visit VIA screen and treatment with cryotherapy done by well-trained nurses and midwives is acceptable and effective in reducing cervical cancer mortality. Nationwide, operational studies on VIA screen and treat are ongoing in 6 African countries to evaluate the feasibility and efficacy of this approach.

Although HPV DNA tests have higher sensitivity than cytology for detecting high grade CIN in older women, their use in low resource settings is limited because of costly equipment and materials. A study that compared VIA, HPV testing and cytology in India found that HPV DNA tests and VIA were equally or more sensitive than cytology, but less specific for detecting CIN 2/3. New HPV test technologies have recently emerged, e.g., a new rapid test that could be used in settings where returning for test results is difficult and expediting treatment prevents losses to follow up.

HPV vaccines will complement existing primary and secondary prevention methods but questions remain about how to integrate primary prevention through HPV vaccination and secondary prevention through screening. For vaccinated girls and women, there is a continued need for screening if it exists as available vaccines only protect against two risk HPV types, responsible for ~70% of cervical cancers, the duration of protection is not known, and it will require several years before high vaccine coverage levels are achieved. Non-vaccinated women will also need screening. Appropriate screening technologies and/or algorithms must be developed for both vaccinated and non-vaccinated populations.

**Discussion**

It was noted that screening programs will need to be modified in countries that have introduced HPV vaccine and have established screening programs. Dr Denny raised a question about the low sensitivity for HPV DNA tests (about 40%) found in the Indian studies and noted that other studies, including those in Africa, have demonstrated much higher sensitivity of these tests.

**Update on data for decision making and decision tools (Dr Silvia de San Jose, Catalan Institute of Oncology, Temporary Advisor)**
The Catalan Institute of Oncology (ICO) compiles, processes and disseminates country-specific information related to HPV and cervical cancer with the goal of facilitating global, regional, and country specific decisions on cervical cancer prevention options. ICO is part of a WHO Collaborating Centre that includes the Bill and Melinda Gates Foundation, the Programme for Health Decision Science, Harvard School of Public Health, the Institut Català d’Oncologia, the International Agency for Research on Cancer, PATH, and the Department of Immunization, Vaccines and Biologicals, WHO. On July 2, 2007, the WHO/ICO HPV and Cervical Cancer Information Centre was launched (http://www.who.int/hpvcentre). This website provides summary reports and allows specific data queries for countries to examine national data and compare them with data from other countries, the region and the world. Data are available on burden of HPV related cancers, HPV burden, factors contributing to HPV-related cancers, prevention strategies, screening activities, socio-demographic characteristics, reproductive health indicators and immunization coverage for other child vaccines.

A 2006 monograph on the role of HPV vaccines and screening in cervical cancer prevention, coordinated by ICO (Bosch FW, et al eds. HPV Vaccines and Screening in the Prevention of Cervical Cancer, Vaccine 2006; 24 (Suppl 3) has now been translated into Spanish. A new compilation of the WHO/ICO Information Centre data (HPV and Cervical Cancer in the World) that includes regional sections, country-specific information synthesized on one page, methods and references is being printed. Regional monographs are also in preparation, the first one focusing on HPV and cervical cancer burden in Latin America and the Western Pacific region. ICO also assists in developing mathematical models to evaluate the impact of vaccination and screening on HPV-related disease and results will be soon incorporated in the Information Centre. Based on expert mathematical modeling advice, ICO does not expect to develop easy-to-use decision making tools.

**Discussion**
Clari‌fication questions were posed.

**Update on Support to Regulatory Authorities for HPV vaccine registration and the WHO vaccine prequalification process (Dr Liliana Chocarro, Department of Immunization, Vaccines, and Biologicals, WHO)**

**Support to regulatory authorities**
Dr Chocarro noted recent important changes in regulatory approaches. After licensure is obtained in the country of manufacture, the product must be licensed in the importing countries. Local registration relies on review by the national regulatory authority (NRA) that may consider if available clinical data are relevant to that country or similar countries and if the vaccine has been prequalified by WHO, a process to assure quality and safety.

Many developing countries have insufficient regulatory review expertise and experience to assess pre-licensure clinical data and lack capacity to monitor trials in country. There is therefore a need to strengthen regulatory capacity for the oversight of clinical trials (authorization and inspections), to assess clinical data for registration purposes, and to develop alternative pathways for regulatory review. In 2004, WHO established the Developing Country Vaccine Regulators Network (DCVRN) to strengthen procedures for evaluating clinical trial proposals and clinical trial data in developing countries. It includes representatives of RSA, India, Indonesia, Thailand, South Korea, China, Russia, Cuba and Brazil. The DCVRN holds meetings twice a year and address regulatory issues for specific vaccines. HPV vaccines were addressed in the Bangkok meeting in November 2005. Consideration was given to the fact that US FDA accepted high grade precancerous lesions (e.g., CIN 2/3) as surrogate end points for evidence for cancer prevention for registration purposes. Although WHO does not issue opinions about country registration decisions, an international panel convened by WHO also recommended these same precancerous endpoints be used for registration purposes. True effectiveness of both vaccines (protection against cervical cancer) will have to be assessed at the post marketing stage. Unlike most vaccines, outcomes for HPV vaccine (precancerous lesions, cancer) are not usually monitored by NRA as
part of post marketing surveillance (PMS) for adverse events following immunization. Monitoring vaccine impact would therefore need to be done through cancer registries, and lack of capacity and resources for this in most countries is of major concern. Links between immunization and cancer control programmes at country level have to be strengthened. Other activities of the DCVRN include developing a training curriculum and a checklist for GCP inspections.

The AFRO Vaccine Regulatory Forum (AVAREF) is a regional network of regulators that provides information to regulators of African countries and promotes communication and collaboration between NRAs and ethics committees. The September 2007 meeting will address HPV vaccines because they are deemed high priority because clinical trials or HPV vaccine introduction are under way in Africa.

Prequalification of vaccines
To assure the quality of vaccines purchases for procurement by UN agencies for large-scale public health programmes, WHO prequalifies vaccines. A pre-requisite to consider for a vaccine prequalification application is the functionality of the regulatory authority of the country responsible for the license. This is usually, but not necessarily, the country of manufacture. WHO evaluates the technical expertise of a NRA for their capacity to evaluate the quality of a candidate vaccine using established indicators with the goal that the NRA of the country of manufacture will evaluate vaccine quality on an ongoing basis. The process consists of 4 steps: 1) review of the product summary file that includes manufacturing, quality control and clinical data among other information; 2) testing of consistency of lots; 3) WHO consultation with the NRA and; 4) WHO site visits to manufacturing facilities conducted jointly with NRA. Vaccines that successfully complete this review are prequalified to supply UN agencies and are listed on WHO's official list of prequalified vaccines. Prequalification status is valid for 2-5 years, followed by reassessment. Fast track procedure used for emergency response and acute shortages do not apply to new vaccines like HPV vaccines.

Discussion
Clarification questions were posed.

HPV vaccine investment case and demand modeling (Mr Steve Brooke, PATH, Temporary Advisor)

Investment Case
An investment case is an analysis of the projected benefits, costs and challenges of a public health initiative and has become standard practice to inform major decisions about new vaccine funding. A GAVI investment case includes 3 key components. 1) A description of the proposed investment, including investment objectives, description of the problem, the proposed project, the cost and funds needed and the financial sustainability; 2) the rationale for investing, including relevance to GAVI objectives, expected incremental impact of investment, constraints and opportunities, and economic analysis; and 3) implementation of monitoring and evaluation.

Key developers and stakeholders for the HPV vaccine investment case are PATH, WHO, Harvard University, IARC, UNICEF and the World Bank. The goal is to seek review of the core analysis by stakeholders by the first quarter of 2008. If GAVI requests the investment cases, it could be submitted, published and disseminated during the second quarter of 2008.

The investment objective is to reduce the inequitable burden of cervical cancer and precancer in GAVI-eligible countries by making effective and safe HPV vaccines available to girls as rapidly as possible. The case considers all GAVI countries and assumes phased adoption and vaccination of a one-year cohort of girls aged 10-11 years old with exact age depending on country-specific parameters. The proposed delivery strategy is school-based, but additional community activities may be added where opportune. Key uncertainties with the case include
Demand Modeling
Demand modeling is a systematic approach to generate and analyze future vaccine uptake scenarios and tends to be less precise than demand forecasting. Demand modeling supports the investment case and informs dialogue around demand and supply issues. To date, 3 base case scenarios have been developed that assume a basic strategy of school-based delivery only, a mixed strategy of school-based delivery plus community campaigns in countries with primary school completion of <70%, and a maximum strategy of school-based delivery and community campaigns in all GAVI-eligible countries. 20 GAVI countries have been selected for more detailed secondary data validation. Critical knowledge gaps in the near term (< 5 years) include global and local funding, vaccine price and supply and in the longer term (> 5 years), uptake of other new vaccines, and community acceptance. In the longer term, critical gaps include duration of vaccine protection and availability of second generation vaccines.

Discussion
Participants discussed the stakeholders of the HPV investment case and one participant suggested that UNICEF might be an important and interested stakeholder. Another concern raised was the limitation of the investment case to GAVI-eligible countries and the need for finding appropriate approaches for middle income countries. Some HPV vaccine demonstration projects are under way in non-GAVI eligible countries (e.g., Peru) and these and other middle income countries may need financial help to introduce HPV vaccines. Mr Brooke stressed that current models can also be applied to middle and high income countries. Over time, projections will be generated and disseminated. Participants asked why the core model considered only a 1 year cohort of girls and proposed future consideration of adolescent health interventions that would include HPV vaccines. Mr Brooke responded that although the model could include multi year cohorts and catch up populations, a 1 year cohort was deemed most feasible and expected to have the highest impact and that the model will include a larger intervention package that will include cancer screening, and possibly other adolescent health interventions. One participant noted that vaccine demand to date has been enormous in some markets and asked about vaccine supply to which Mr Brooke noted that work is needed to estimate supply scenarios. Representatives from WHO Regional offices also noted the need for vaccine financing support for non-GAVI eligible countries in their region. In addition, packaging costs for the vaccine, supply forecasting, target age groups and integration with other adolescent health programs were raised as additional considerations required in vaccine financing models.

Update on WHO, regional, and country perspectives and policies on HPV vaccines (Dr Kathleen Irwin, Initiative for Vaccine Research, WHO)

Dr Irwin described perspectives and policy pathways for new vaccines at WHO and in countries and characteristics of recent WHO vaccine recommendations that may be relevant to HPV vaccines. WHO's recommendations about vaccines rely heavily on recommendations of SAGE, WHO's principal advisory group on immunization policy and practices. SAGE also advises WHO on global policies and strategies and progress of the Global Immunization Vision and Strategy (GIVS) that includes a goal to increase adolescent immunization. SAGE recommendations are influenced by HEAG, the Global Advisory Committee on Vaccine Safety (GACVS), the New and Underutilized Vaccine Initiative (NUVI), WHO Regional offices, WHO Regional Immunization Technical Advisory Groups, World Health Assembly statements and resolutions, and other regional and country opinions. SAGE holds two meetings annually.

If SAGE recommended use of HPV vaccines in the future, a WHO Position Paper related to those recommendations would be drafted. The recommendation and Position Paper would be submitted to the Director General, WHO, who in turn, would review and finalize a WHO recommendation, and disseminate the
HPV vaccines were discussed at a major session at the April 2007 SAGE meeting. SAGE concluded that clinical trials indicate that vaccine introduction would greatly benefit countries with high cervical cancer mortality with limited screening as well as countries with established screening programs. They noted that developing delivery methods for the target age group, building capacity for education and communication, and monitoring vaccines after introduction will be crucial but challenging. SAGE advised HEAG 1) to review the evidence needed to inform future discussions about HPV vaccines and a possible future HPV Position Paper and to identify outstanding questions about vaccine safety, efficacy, and delivery, and 2) to monitor results of safety and efficacy in HIV-infected persons, simplified schedules, delivery methods, and cost-effectiveness in low and middle income countries.

Since April, HPV vaccines and cervical cancer were addressed in several meetings. In May 2007, the World Health Assembly unanimously approved the WHO Executive Board Progress on Report on Cervical Cancer that advised integrating HPV vaccines into existing immunization, cancer control, reproductive, sexual, and adolescent health programmes. In June 2007, GACVS concluded that current evidence on HPV vaccine safety is reassuring, but noted that injection site reactions are fairly common, and that data on safety in pregnancy and rare adverse events are limited. A June 2007 session on HPV vaccines in the meeting of the New and Underutilized Vaccine Initiative raised questions about integrating vaccination and screening programmes, challenges of delivering the vaccine to adolescents, and whether infant or young child dosing was feasible.

A major goal of the September 2007 HEAG meeting is to determine if available data are adequate to start drafting candidate recommendations about HPV vaccine use for future consideration by SAGE. If yes, the process of drafting the recommendations could start at the meeting and if not, participants will be asked to identify information that is essential before drafting candidate recommendations. Feedback of this HEAG meeting will be given to SAGE at their 30 minute session on HPV vaccines in November 2007. As this will not be sufficient to debate candidate recommendations, a longer session would be needed at a future SAGE meeting.

WHO uses published and non-published data to support vaccine recommendations, takes a global perspective (even though recommendations may be regional), and prioritize issues in middle and low income countries and public sector programmes. WHO avoids product-specific recommendations, but “generic” recommendations note product differences. Recent WHO recommendations have emphasized integration with other disease control methods, vaccine impact, feasibility, and affordability, and the role of cost-effectiveness in decision-making. Some past recommendations have advised a primary series even when the need for boosters remains uncertain and recommended vaccines even when local data useful for decision making were uncertain or pending. Consequences of WHO recommendations on vaccine use include engagement of organizations that finance and procure vaccines for low and middle income countries such as GAVI, UNICEF, PAHO Revolving Fund and other international and national organizations. For this reason, the prequalification process is undertaken in parallel with development of recommendations on use. Once vaccines are recommended and approved for GAVI funding it may take years before they are available at subsidized prices in GAVI-eligible countries.

Country decisions about vaccine introduction are influenced by recommendations of WHO, regions, similar countries and commercial and non-commercial advocacy. Before the meeting, the quadrivalent vaccine was licensed in more than 80 countries and the bivalent vaccine in at least 2. Several industrialized countries already recommended the quadrivalent vaccine or recommended HPV vaccination in principal (without specifying a vaccine product) for national use and some have introduced this vaccine into immunization programmes. Regional meetings on cervical cancer and HPV vaccines were held in 2007 for SEARO, WPRO and EURO regions. The PAHO meeting is scheduled for November 2007 and planning for meetings in EMRO, and AFRO
Discussion

Clarification questions were posed.

HPV vaccine research and decision-making tools for HPV vaccine introduction led by WHO (Dr Nathalie Broutet, Reproductive Health and Research, WHO)

Dr Broutet described the aims of the WHO/UNFPA HPV and Cervical Cancer Work plan 1) to reduce HPV-related mortality and morbidity, particularly cervical cancer, through appropriate interventions including HPV vaccines, and 2) to guide policy and programme design for vaccine introduction, within the context of other interventions used in cancer control and sexual and reproductive health programmes.

The Workplan has 3 research-related objectives. The first is to conduct country-level research to inform global policy and country-level HPV vaccine introduction decisions. Three projects are linked to this objective: 1- WHO's Department of Reproductive Health and Research (RHR) has established the HPV Vaccine Community of Practice (http://HPV-vaccines.net), an online, global network of stakeholders to share information, experiences, and opinions about HPV vaccines. HPV experts will facilitate on-line discussions, summarize major themes, and correct misinformation. The site will also provide a forum for on-line surveys of health care professionals to assess education and research needs, developing protocols for research on vaccine acceptability and delivery, providing technical assistance to programmes and researchers, and evaluating and disseminating tools for vaccine introduction.

2- A research proposal to study delivery strategies of HPV vaccine for adolescents in school and health settings. The study will compare strategies with and without a sexual and reproductive health counseling package or other health services (e.g., antihelminthics). It will assess feasibility of interventions; vaccine uptake, acceptability, and adherence to recommended schedule; delivery costs and resource utilization, and other outcomes.

3- An evaluation of new HPV rapid tests as a possible screening tests for use in low resource field settings, including screen and treat approaches. The first rapid HPV test, an adaptation of the Digene Hybrid Capture 2 test, detects high risk HPV types developed through a partnership with PATH and Digene is expected to be available in 2008 at a cost of ~5 $ for developing countries.

The second research objective is to facilitate informed decisions for HPV vaccine introduction at the country level. A decision-making tool is being considered to assist countries in conducting situation analyses that consider health policies, health priorities, HPV-related disease burden, current strategies to prevent HPV-related disease, current immunization policies, programmatic capacity, potential impact of vaccines, and data on vaccine efficacy, safety and quality relevant to that country. Developers are proposing a modular structure that may include check lists, flow charts, software, budgeting tools, and generic protocols for acceptability research.

The third research objective is to ensure that clinical research needed for country introduction of HPV vaccines be performed. Work under consideration includes:

1. Evaluations of the value of rapid HPV tests alone and compared to VIA for clinical practice and monitoring vaccine impact, if field evaluations of rapid HPV tests are promising.

2- Applied research that is unlikely to be led by the private sector. For example, trials of a 2 dose schedule or alternative 3 dose schedules, the efficacy of vaccinating girls less than age 9.
3- An evaluation of whether new adolescent interventions such as male circumcision for HIV prevention might facilitate HPV vaccine introduction. Both vaccine producers have indicated progress on or interest in sponsoring some of these studies. Some work would benefit from partnering between WHO, its partners, industry and research institutions.

**Discussion**

One participant noted that using the Community of Practice was an interesting opportunity for research and that special attention should be paid to delivery issues in adolescents. It was also noted that phase IV and other studies conducted by industry will produce useful information and that it would be helpful to identify research priorities that industry could incorporate into their protocols. For example, research on earlier age of vaccination, and appropriate type-specific HPV tests companies would need advice on the most appropriate age groups and genotypes. Industry representatives also noted that researchers could examine industry clinical databases on screening tests, STI, colposcopy results, and behaviours to expedite publication of findings. Also noted was that studies from non-research settings (e.g. behavioural data) should complement trial data.

Questions were raised about the value of rapid HPV tests for monitoring vaccine impact because they do not allow for genotyping. It was noted that rapid HPV tests could be useful if followed by type-specific tests which are not yet commercially available. It was also noted that WHO Laboratory Network includes 9 labs that can perform HPV antibody DNA testing and genotyping and provide training and technical support to countries conducting research and/or assess impact of vaccination. PATH noted they have issued a request for proposal for small grants for countries for supporting country work, especially for fieldwork based on generic protocols.

**Options for monitoring vaccine coverage and impact on clinical outcomes**

Dr Franceschi noted that monitoring of HPV vaccination programmes can be done using a combination of good design, appropriate populations, proper clinical samples, and reliable tests. Monitoring should consider unique features of HPV disease, including the fact that the disease (cervical cancer) occurs long after infection, that the minimum level of antibodies required for protection is not known, that HPV DNA tests are expensive and use specimens collected by pelvic examination, and serology tests are not highly sensitive nor standardized. Moreover, HIV-infected women are more likely to be infected with multiple HPV types which complicates vaccine efficacy studies and monitoring approaches.

She noted that monitoring of HPV vaccination programmes should ideally measure level and duration of protection in vaccinated persons enrolled in clinical trials or through post-marketing surveillance, population vaccine coverage, safety, HPV DNA prevalence in sexually active young women, rates of genital warts (e.g., through ad hoc registries in high-resource countries), cytological/histological abnormalities detected through cervical cancer screening, and trends in cervical cancer incidence and mortality. She noted that such a comprehensive approach may be feasible in only a few countries.

Some, but not all, of this information, can also be collected in developing countries. All countries should monitor population vaccine coverage and number of doses delivered through routine national immunization programme surveys or personal vaccination cards. A measure of "drop off" after delivery of the 1st dose should be a key monitoring indicator. All countries should monitor safety through national passive surveillance systems for reporting side effects, if available, or monitoring safety data from other countries. Monitoring of antibody level among vaccinated persons in trial participants and special serosurveys are essential to inform duration of immune response, need for boosters, minimum protective antibody levels, potential for alternative schedules, and desirable characteristics of 2nd generation vaccines. HPV DNA prevalence in sexually active women before the target age for screening programmes can be assessed in adolescent health clinics that provide contraceptive
and STI services and conduct pelvic examinations. This might be feasible in Africa but may be difficult in some countries, notably Asian countries where strong stigma about pre-marital sexual relationships may make it difficult to enroll unmarried women. Monitoring cytological/histological abnormalities could be done through organized screening programmes with high screening coverage, such as found in a few industrialized countries, and in the many countries where screening does not exist, including developing countries, through sentinel surveillance. The final stage of monitoring should be cancer morbidity and mortality which would require cancer registries or special studies. Monitoring of cytologic or histologic specimens would allow HPV typing to assess the proportion decline in lesions due to vaccine-related HPV types and the possibility of HPV type replacement.

The WHO HPV Laboratory Network will be crucial for standardizing HPV antibody assays, DNA tests, sample collection and transport methods, and laboratory procedures necessary to evaluate vaccine impact. In the future, it may be easier and more acceptable to use self-collected vaginal cells or dried blood spots for large scale monitoring of HPV DNA or serology, respectively. HPV DNA testing may be more useful than antibody tests because the minimum level of protective antibody is not known. For monitoring purposes, HPV DNA tests that are too sensitive may not give meaningful results if they detect transient, clinically-unimportant infection. The current high price of HPV tests is a barrier to use them for monitoring vaccine impact. The interest of diagnostic companies in developing new HPV tests such as the Hybrid Capture type 16,18, 45 probe test, line blot genotype test, and Luminex multiplex genotype test, may facilitate use of HPV tests for monitoring purposes.

Discussion

The objectives of monitoring and evaluation should be clearly defined, as some activities may be a one time exercise (e.g. establishing the levels of protective antibodies) while others must be done on an ongoing basis (e.g., assessing the cold chain). However, evaluating protective antibody levels is also necessary to validate trial findings when special populations are vaccinated (e.g. those affected by malaria, HIV, or malnutrition) and to evaluate the quality of vaccine delivery (e.g. breakthroughs due to cold chain problems). As the minimum level of protective antibody and mechanism of protection are not known and future vaccine products (e.g., orally delivered products) may have different capacity to produce antibody in serum and genital secretions, it might be necessary to examine HPV antibodies in genital secretions. Detection of antibodies is further hampered by the absence of commercially available serological tests. Both serologic and HPV DNA tests may require processing by centralized laboratories to ensure quality. To monitor coverage (and drop out rate after 1st dose), countries could use existing EPI surveillance systems, cluster surveys, or DHS surveys. These may rely on personal vaccination cards as card retention rate is improving in countries where cards are required for school admission.

Cervical cancer communication for diverse audiences (Mr Scott Wittet, PATH, Temporary Advisor)

Mr Wittet noted that communication challenges vary by group. Parents, teens and communities have limited knowledge of cancer and its relation with viruses. Many issues are confusing: high infection rates versus low cancer rates, partial efficacy of the vaccine, long delay to symptomatic disease, why only girls are targeted, etc. Moreover, there is considerable misinformation about cancer. A recent survey found that 35% of Canadian women who are familiar with HPV believed that HPV causes ovarian cancer. In at least one developing country, some women believe soiled feminine pads cause cancer.

For parents, teens, and the public, key messages should include the rationale for vaccination, how to access services, information about vaccine cost, how to handle side-effects and respond to misinformation or rumors. HPV vaccine education also offers opportunities to educate about other adolescent health and cancer issues.

For providers and policymakers, communication needs may include information about different HPV types and other scientific and medical issues, the long delay to visible impact, and some kind of response to unanswered
For health care providers, key communication needs include information on disease burden and the public health rationale for vaccination strategies, why cervical cancer is a priority, vaccine characteristics and use, new system requirements and cost, how to communicate with patients and deal with rumors and misinformation. Educating providers is especially important because most parents make decisions about immunizing their children largely based on provider recommendations rather than an understanding of vaccine benefits or mechanism of action.

Communication needs for programme managers include disease burden and the public health rationale for strategies, clinical changes and challenges, new logistics, procurement, record-keeping systems, and the impact on other health services or opportunities (such as other new vaccines under consideration).

If WHO aims to encourage well-informed decisions about cervical cancer prevention in countries, communication objectives might include stimulating discussion and providing data at global, national and regional levels; encouraging vaccine production and financing; mobilizing communities to demand vaccination; and inspiring providers to provide quality services. Mr Wittet described WHO materials about HPV vaccines and noted that the WHO could be improved by directing users to more updated information and a single, cross-linked "home page" for cervical cancer. He also discussed how partners can help users find WHO materials, such as by promoting them on other websites such as www.rho.org.

Discussion

Meeting participants indicated that WHO’s competitive advantage is communicating with policy makers and distilling and standardizing information from different sources. The new HPV and Cervical Cancer Community of Practice will reach people working in HPV and cervical cancer and could be a channel for WHO information. However, care will be taken that summaries of messages from this site, if disseminated by WHO, are not inconsistent with other WHO messages to avoid confusion among audiences.

Other partners also have an important role in communication, including UNFPA and their affiliated family planning clinics and antenatal clinics. These providers could advise on HPV and cervical cancer screening and could be trained to educate or counsel patients about HPV issues. Family planning clinics may also be good venues to provide young people with vaccine or information about vaccines. For UICC (International Cancer Control Union), HPV vaccines are an organizational priority and interest of member organizations is increasing. The World Cancer Day in 2009, sponsored by UICC, may focus on HPV vaccines. Similar promotional activities are sponsored by the European Cervical Cancer Association and information is available at their website (www.ecca.org). There is also a need to get more information at peripheral levels of health care where providers have difficulty accessing recent information.

III: PANEL DISCUSSION BY REPRESENTATIVES OF WHO REGIONAL OFFICES ABOUT PARTNERSHIPS BETWEEN PROGRAMMATIC STAKEHOLDERS IN HPV VACCINES (Drs Richard Mihigo (African Regional Office, AFRO), Merle Lewis (American Regional Office, AMRO), Hinda Ahmed (Eastern Mediterranean Regional Office, EMRO), Andrei Lobanov (European Regional Office, EURO), Ranjith
AMRO
At regional level, priorities are set by the annual Directing Council of PAHO, which next meets in October 2007. Every 2 years, a Technical Advisory Group on Immunization meets with the national Immunization focal points of all countries to discuss country progress, experiences and challenges, financing issues, and future initiatives, etc. At the country level, decision making regarding vaccine introduction has become difficult as many new (and more costly) vaccines are now available. PAHO is therefore, working with researchers to develop simple tools to collect epidemiologic and economic burden data and to calculate vaccine cost-effectiveness, so that countries would have the data to make decisions about priorities for new vaccine introduction, including HPV vaccines.

In relation to improving the regulatory environment for HPV vaccine introduction, PAHO’s Technology and Health Services Assessment Unit, in collaboration with the Immunization Unit convened a meeting in 2006 with 10 country NRAs to review clinical HPV vaccine dossiers.

Under the guidance of the regional immunization unit, an internal HPV vaccine partnership has been established with stakeholders from units on HIV/AIDS, public information, adolescent health, chronic health, chronic diseases, immunization, procurement, gender and ethnicity, reproductive health, health technology assessment, and health policy and health systems. This partnership has been responsible for the formulation of a regional strategic action plan for the prevention of cervical cancer. An external HPV vaccine partnership has also been created with several organizations, including the US Centers for Disease Control (CDC), PATH, the US National Cancer Institute, the American Cancer Society, UICC, WHO and some countries in the region. The Caribbean region has indicated that, based on technical data, an interest in introducing HPV vaccines and strengthening their cervical cancer prevention programmes.

In relation to the public sector financing of HPV vaccines, countries have used the PAHO Revolving Fund to procure vaccines for their national schedules. Consolidation of orders and bulk purchasing allows for negotiation of reduced vaccine prices. Vaccines are available to all countries at a single price. However, as the prices of new vaccines increase and financial sustainability is more challenging, countries have been asked to consider strategies for expanding fiscal space in their national budgets to support immunization.

In relation to delivery strategies, the PAHO region has extensive experience with childhood and adult immunization, vaccine delivery through schools, community outreach, and adolescent clinics and these can all serve as potential strategies or venues for HPV vaccine delivery.

EMRO
In this region, no HPV vaccine activities have been started. In the regional office, the reproductive health, chronic disease and immunization units are beginning discussions and are planning to invite country representatives to consider decision making about vaccine introduction if vaccines are licensed. The knowledge and the status of vaccines in the region vary greatly. In some countries, the vaccine has already been licensed, in others research is ongoing, and in others, knowledge of vaccines is very limited. A challenge for HPV vaccine introduction is competing priorities, e.g., challenges in achieving high coverage of routine childhood vaccines such as rubella and measles. Moreover, poverty (6 countries supported by GAVI) and low school attendance rate (with only 60% of girls attending school in some countries) will make financing and delivery difficult.

SEARO
This region consists of 11 countries, of which 9 are GAVI eligible. With support from GAVI, all countries have introduced hepatitis B vaccine except for Timor-Leste. Introduction of infant HepB vaccination in India is being
The Regional Office immunization unit is working closely with reproductive health and non-communicable diseases units to sensitize countries about cervical cancer and HPV. Current priority activities include developing surveillance systems to define HPV epidemiology and disease burden and to explore options for sustainable introduction of HPV vaccines. Even with minimal copayments for new GAVI-subsidized vaccines, this could be very burdensome for developing countries. Given current HPV vaccine prices, immediate introduction is likely to be a major challenge.

**WPRO**

In the WPRO region, key stakeholders for HPV vaccines are represented in the Reproductive Health Cluster and the Non-communicable Diseases Cluster in the Division of Building Healthy Communities and Populations’ (DHP) and in the Expanded Programme on Immunization (EPI) Cluster in the Division of Combating Communicable Diseases (DCC). The other relevant stakeholder is the Child and Adolescent Health Cluster in DHP. Cervical cancer is currently not very visible in Cluster work plans. Rather, reducing maternal mortality, treating sexually transmitted infections, and promoting healthy behaviors are top priorities. There is no centralized information on status of screening or treatment programs. HPV vaccines are being discussed in different EPI forums along with other new vaccines. HPV vaccines have been licensed in several Western Pacific countries and Australia became the first country to introduce an ongoing school-based, government funded HPV vaccination programme that includes pre-adolescents and a two year catch strategy for females aged 18-26. The current regional workplan goal is to create awareness and visibility of HPV and cervical cancer among stakeholders. This will require collaboration between clusters and within countries, although the current high vaccine cost makes it challenging to initiate consultations.

**EURO**

This region has the largest number of Member States, and includes very wealthy and very poor countries, including 8 countries eligible for GAVI support. The region has very successful experience with the introduction of new vaccines (e.g. for HepB). A WHO Regional meeting on strengthening cervical cancer prevention was held in May 2007 and included a session on HPV vaccines. During the meeting it was emphasized that cervical cancer prevention should consider a wide range of prevention tools and that cervical cancer screening is an important tool that needs to be strengthened in many countries. Collaboration and partnership within the Regional office have been very important in the preparation of this meeting and will be continued to provide effective comprehensive support to countries. The Regional Office is preparing a strategic document on HPV vaccine introduction. A draft of this document was presented at the meeting of the European Technical Advisory Group of Experts (ETAGE) and is currently being finalized. By September 2007, 35 countries in Europe had licensed the quadrivalent vaccine and 8 had made technical and/or policy decisions about vaccine introduction.

**AFRO**

In this region, HPV and cervical cancer have not received attention until recently. In February 2007, during a special session in the regional meeting in Maputo, research papers on HPV were presented. The AFRO office was asked to conduct a survey on the ongoing studies in the region. For the region, it is important to develop a comprehensive strategy on cancer prevention, and cervical cancer would be an important component. The last AFRO Regional Committee discussed on how to define a strategy for cervical cancer and concluded that strengthening capacity of NRA to review licensing applications and for monitoring clinical trials in African would be an important first step. HPV will be discussed at several future fora and there is a need for other units to be involved in this. Challenges and opportunities do exist; one of them is that the majority of the countries of
the region are eligible for support by GAVI, although the required country contribution for co-financing HPV vaccines will be an issue. Another challenge is the potential shortage of personnel needed to deliver vaccines. This will require training and education for health care workers in the region. Lastly, there have been some challenges in school-based vaccination campaigns targeted only to girls, an issue relevant to HPV vaccines.

IV. CHARGE TO WORKGROUPS

Four workgroups were convened to address various. (See Annex for workgroup members.)

- Workgroup 1: Safety, efficacy and immunogenicity of the quadrivalent and bivalent vaccines
- Workgroup 2: Delivery, integration with screening, and monitoring and surveillance
- Workgroup 3: Impact, cost, cost-effectiveness and financing
- Workgroup 4: Socio-cultural issues, patient education, communication and policy coordination.

Each workgroup was asked

- To suggest revisions to a draft Background Paper that was sent to meeting participants before the meeting. This draft summarized evidence that would be needed to debate recommendations about HPV vaccine use in the future. It included sections on the virus, immunology of HPV infection, risk factors for HPV infection and HPV related disease, burden of disease caused by HPV, WHO guidelines on prevention and control of cervical cancer and anogenital warts, characteristics of HPV vaccines (including use of virus like particles, immunogenicity, clinical efficacy, duration of protection, vaccination schedule, dose and administration, co-administration with other vaccines and medications, safety and adverse events, contraindications and precautions), vaccine impact, options for introduction, the influence of vaccine acceptability and coverage on vaccine impact, impact of vaccine on disease prevention, cost effectiveness, vaccine financing, monitoring and surveillance, education and communication, and future research needs. Workgroups were asked to identify errors of fact, omissions of information essential to WHO policy about vaccine use that should be added, unnecessary sections to be deleted, incorrectly interpreted data corrected, and additional tables and figures to summarize data.

- To determine if data were adequate to start drafting candidate recommendations for future consideration by SAGE and, if adequate, to start draft candidate recommendations on relevant topics.

- If data were sufficient to start drafting candidate recommendations, to determine if a product-specific recommendation on HPV vaccines would be warranted.

- If data are sufficient to draft candidate recommendations, to identify high priority research issues.

- If data are not sufficient to draft candidate recommendations, to identify research that is essential before drafting candidate recommendations.

- To identify types of information countries should assess before considering vaccine introduction and determine if this information is available in most countries, and if not, if countries could use information from countries with similar demographic, epidemiologic, or health characteristics.

V. PROPOSED REVISIONS TO DRAFT BACKGROUND PAPER

Many revisions were proposed in workgroups and general discussions. (see Annex).

VI. PRELIMINARY CANDIDATE RECOMMENDATIONS

Each workgroup was asked if data were sufficient to start drafting candidate recommendations for future consideration by SAGE. Workgroup members were not asked if data were sufficient to support a SAGE recommendation on HPV vaccines as this would be premature and beyond the scope of the charge to HEAG. All workgroups stated that data were sufficient to start drafting candidate recommendations for future consideration by SAGE and proposed preliminary candidate recommendations and supporting information. Workgroup 1, charged to address efficacy, immunogenicity, and safety, was unanimous in this opinion. This
group declined to draft detailed recommendations at the meeting but requested that WHO draft more detailed candidate recommendations and circulate them for comments after the meeting. Each workgroup presented candidate recommendations for discussion by all meeting participants. This was followed by a general discussion of candidate recommendations from which persons judged by WHO to have an actual or potential conflict of interest were excused. Before this discussion, Dr Irwin reviewed WHO’s recent recommendations on pneumococcal vaccines, noting parallels with potential recommendations about HPV vaccines. However, the consensus from this general discussion, listed below, did not differ from the consensus about candidate recommendations from workgroup discussions. The detailed list below includes information that might be proposed to SAGE as 1) elements of HPV vaccine recommendations; 2) information to be included in a Position Paper to support such recommendations or 3) other support documents such as information to decision makers and programme managers. Thus, only selected items from this list may be submitted to SAGE for consideration.

**General issues**
- A global recommendation is justified.
- Africa should not be excluded from recommendations as disease burden is well established. (Group 1)
- The overall burden of disease for cervical cancer is probably under-reported in some countries, so caution against specifying recommendations for high-burden regions, countries or groups. (Group 1)
- WHO should develop a single recommendation that addresses both vaccines that should note differences in vaccines related to product characteristics, efficacy, immunogenicity, disease prevention indications (e.g., cancer, warts), safety, cost-effectiveness, and time horizon for observing vaccine benefits (e.g., prevention of warts will be observed before prevention of cancer due to shorter latent period). Countries should consider these differences when choosing vaccines for their unique needs, e.g., this may depend on the value placed on the clinical and economic benefits of vaccines that protect against HPV 6 and 11-associated anogenital warts and low grade or borderline cytologic abnormalities (and the relatively shorter timeline for return on investment for these conditions as compared to HPV 16, 18-related precancerous lesions and cancers).

**Safety**
- No major safety problems have been identified to date (Group 1)
- Safety should be evaluated in long term follow up of trial participants and post-marketing surveillance

**Efficacy and impact on reducing disease burden**
- Based on the currently available data and the current model predictions, HPV 16, 18 vaccines are expected to significantly reduce cervical cancer incidence and attributable mortality if high vaccine coverage is achieved, vaccine is delivered to girls shortly before sexual debut, and duration of protection lasts 10+ years. (Group 3)
- Females in countries without access to screening and females in countries where screening exists but are unlikely to be screened later in life stand to benefit most from HPV 16, 18 vaccines. (Group 3)
- High coverage among girls with the quadrivalent vaccine with VLPs for HPV 6 and 11 are expected to significantly reduce incidence of genital warts in females and males. (Group 3)

**Target population**
- Pre-adolescent girls (before the onset of sexual activity) should be the primary target population for vaccine introduction. (Group 1)
- Prioritization should be to achieve high coverage in young girls before considering a catch-up programme or vaccinating boys. (Group 3)
- Catch up populations and males should be considered as a secondary target population as resources permit in accordance with cost-effectiveness studies. (Group 1)
Vaccination programmes should prioritize vaccinating females who, later in life, would be least likely to be screened. (Group 3)

**Contraindications:**
- Persons with known allergic, hypersensitivity, or other adverse reactions to vaccine components or previous doses of HPV vaccine should not be vaccinated. (Group 1)

**Special subgroups**
- Vaccines are not contraindicated for immunocompromised individuals, however immunogenicity and efficacy are unknown. (Group 1)
- Pregnant women should not be vaccinated, if pregnancy status known. There is no need to terminate pregnancy if pregnant women if a pregnant woman is inadvertently vaccinated. (Group 1)
- Research is ongoing for special sub-groups, e.g, males, HIV-infected persons. (Group 1)

**Dose and Administration**
- Safety and immunogenicity of the quadrivalent vaccine are not impacted by co-administration with Hep B vaccines; other studies of co-administration with other vaccines ongoing. (Group 1)
- Vaccines can be co-administered in accordance with national vaccination schedules and guidelines. (Group 1)
- 3 dose schedule is recommended. Data that might support alternate dosing schedules are not yet available but are being collected. (Group 1)
- Duration of protection is expected to be sustained, but need for boosters must be determined from long term follow-up studies in selected countries. (Group 1)

**Delivery options**
- Delivery options will likely differ for primary target population and catch-up or other populations but may include school based programmes, community outreach, adolescent health services, primary health care services, and other service providers (e.g., gynecologists). (Group 2)
- Factors to consider when devising delivery strategies include primary school attendance rate for girls to assess feasibility of school-based programmes, existence of community outreach for other vaccines or interventions to assess feasibility of reaching out-of-school youth, and existing screening programmes and their coverage. (Group 2)
- Partnerships between health programmes are needed to develop delivery strategies in countries and at regional and international level. (Group 2)

**Integration of vaccines within cervical cancer prevention programmes**
- HPV vaccines and screening are complementary in cervical cancer prevention. HPV vaccines are a primary prevention tool for cervical cancer and do not eliminate the need for screening. (Group 2)
- Vaccinated girls should continued to be screened (later in life), if screening is available, to protect them from oncogenic, non-vaccine-related HPV types (Group 3). However, screening approaches may be modified in the future.
- Screening should continue for non-vaccinated women. (Group 3)
- In countries with effective screening programs, screening strategies should be assessed and potentially modified after HPV vaccines are introduced. (Group 3)
- For countries without screening, if the vaccine is to be introduced, it should be complemented by at least limited screening when vaccinees reach mid-life, when feasible (Groups 2, 3)
- Countries should form interdisciplinary teams to harmonize development of policies, strategies, and communication messages. (Group 4)
Teams should include experts in immunization, cancer control, reproductive and sexual health, child health, adolescent health, education, etc. (Group 4)

**Patient education and communication**
- Recommendation that tailored communication strategies should be designed to address concerns of different groups, cultural, socioeconomic and individual factors (Group 2)
- Educational strategies should be developed that are specific for each of the following audiences: adolescents, parents/guardians, community leaders, educators, health care providers, programme managers, policy makers, and the public. (Group 4)
- Educational efforts should stress the role of vaccines within comprehensive cancer control programme. (Group 4)
- When educational strategies are developed, consideration should be given to incorporating information about sexuality, reproductive health, and other adolescent and women’s health issues. (Group 4)
- Education and communication strategies should recruit leaders (professional groups, religious leaders, community leaders, women’s groups) to develop and endorse strategies. (Group 4)
- Consider appropriate and effective communication channels for marginalized audiences.
- Consider access, service strategies, and preferred communication channels.
- Counteract misinformation (Group 4)
- Use interdisciplinary teams to foster collaboration and harmonization of policies and messages
- Coordinate educational messages across the private and the public sectors whenever possible. (Group 4)
- Engage with media and the entertainment industry to promote responsible media coverage. (Group 4)
- Based on existing evidence and target audience, key messages *may include*:
  1) Basic information about HPV infection
  2) Basic information about HPV vaccine: efficacy, safety, duration of protection, number of doses, where and how to access it
  3) Importance of continued cervical cancer screening in vaccinated females, if screening exists
  4) Reinforce healthy sexual decision-making behaviors when vaccinating.
  5) Emphasize that vaccination does not impact fertility.
  6) Emphasize that a vaccine against cancer is not a vaccine against *all* cancers or all STI.
  7) Information about potential vaccine benefits for boys and men that is appropriate to local context of vaccine licensure status for males.

**Monitoring**
- Post-marketing surveillance should be undertaken in selected countries. (Group 1)
- Lack of monitoring systems or capacity should not delay vaccine introduction.
- As a minimum, all countries should monitor vaccine safety and coverage.
- Sentinel surveillance on other outcomes (e.g., HPV prevalence, precancerous lesions, cancer) should be conducted when feasible.

**Cost-effectiveness, cost, affordability, and financing**
- In developing countries without screening, HPV vaccination of preadolescent females is likely to be cost effective provided that cost of vaccine delivery is similar to or possibly lower than many other GAVI-subsidized vaccines and that duration of protection is at least 10 years. (Group 3)
- Attention needs to be given to internal and external financing opportunities. (Group 3)
- There is a need to mobilize resources with GAVI, and other funding organizations that can assist low and middle income countries. (Group 3)
- Countries should plan to finance administration and delivery to sustain high coverage. (Group 3)
- Vaccine price is a key driver of cost effectiveness, and therefore needs to be significantly lower than current developed country pricing. Mechanisms are needed to accelerate this process. (Group 3)
Discussion about candidate recommendations

General issues:
Dr Garcia noted that candidate recommendations should raise the issue of competing health priorities and should acknowledge that cervical cancer prevention may not be a high priority for some counties. Dr Irwin noted that this may be the first time when two vaccines that might be considered for a combined recommendation have substantially different clinical indications. One participant added that a general recommendation for both vaccines would be appropriate if it addresses HPV-related diseases and is not restricted to diseases related only to HPV 16 and 18, the benefit common to both vaccines. One participant advised that a general recommendation that notes differences between the two vaccines should address differences in cost-effectiveness of the quadrivalent and bivalent vaccines in different settings. In settings where resources are invested in screening, diagnosing, following, and treating HPV 6 and 11-related conditions (anogenital warts, ASCUS and LSIL cytology results, CIN1), the benefits and health care savings expected from vaccinating against HPV 6 and 11 would be somewhat greater than in settings where these conditions are not managed. However, cost savings related to HPV 6 and 11 would be far less than those related to HPV 16 and 18.

Dr Merle Lewis advised that WHO should make a general recommendations about vaccines that protect against HPV 16,18-related disease, noting the differences between the two products, and advise countries to decide which vaccine(s) is suitable for their clinical and epidemiologic and financial context and preferences. Dr SanJose added that any differences between the two vaccines in cross-protection against non-vaccine types and the level of evidence supporting each vaccines should also be included.

Efficacy and impact on reducing disease burden
Dr Irwin asked if models had considered unintended consequences of vaccination on behavior (e.g., increasing risky sexual behaviors or deferring screening) and Dr Goldie noted that this has been considered and under some assumptions, models predict that if vaccinees have low screening rates later in life, cancer rates could increase. Dr Tsu said that this potential unintended consequence may be one reason why countries may choose to introduce vaccines but not to introduce screening, especially when new screening programmes would require staff and special training. She added that PATH is collecting data on possible negative behavioral consequences of vaccination. Dr Garcia asked Dr Goldie about the definition of "high vaccine coverage" in her model assumptions and noted that consideration should be given to which subpopulations are vaccinated (in terms of cancer risk and future screening opportunities) and that high coverage is important from a health equity point of view. Dr Goldie responded that coverage is not the most essential driver of cost-effectiveness, but is important.

One participant stated that a recommendation that stresses that a substantial impact is dependent on duration of protection of 10+ years will discourage vaccine introduction and advised merely stating this as a model assumption. Another participant noted that countries will be reluctant to invest in a whole new delivery system if there is uncertainty about the need for boosters which would entail added expense and complexity, especially in most countries where recalling patients would be difficult. Dr Rees added that if modeling results on vaccine impact are presented as uncertain, or more uncertain than with other recommended vaccines, SAGE will be less likely to recommend HPV vaccines. Dr Irwin noted that WHO has recommended other vaccines (Hib) when duration of protection was uncertain. Dr Rani noted that if protection last only 10 years, vaccines will not protect females from acquiring HPV during the highest risk period in late teens and early 20s; impact will be limited and will merely increase the mean age of HPV acquisition to a later age. Dr Franceschi responded that vaccinating girls would likely have a major impact because cervical cancer risk is associated with early age at sexual activity and that delaying infection in early adolescence may offer important protection. Other participants said that WHO should not delay recommending vaccines until data on impact on cancer incidence are available, some 40 year hence.
Target age group
On participant asked how the pre-adolescent target age group should be defined and a Workgroup 1 participant proposed that it should be determined by data on mean age of sexual debut in country and the lowest age specified by licensing requirements. The lowest age for which vaccine is currently licensed in any country is age 9. For this reason, the general terms “pre-adolescents” and “adolescents” are used instead of a specific age ranges. A WHO staff member indicated that WHO defines adolescents as persons 10-19 years old. Another participant recommended that African populations should not be excluded as potential target populations because trials have not yet been done in Africa. It was noted that estimates of the burden of disease in Africa are based on just a few countries and that countries lacking data may be resistant to considering vaccines. Dr SanJose noted that the WHO/ICO Information Centre includes regional data from Africa and meeting participants agreed that countries could consider regional data to estimate burden of disease if country data were lacking. Given the geographic overlap of the HIV epidemic and cervical cancer epidemic, especially in Africa, Dr Rees advised that candidate recommendations should detail issues for HIV-infected persons in a special section.

Delivery options
It would be helpful to include more information about school-based delivery and note advantages and disadvantages of this and other delivery strategies. Dr Garland noted that in Australia where HepB was delivered in both school based programmes and in primary health care settings, coverage was much higher in school based programmes. One participant stressed the importance of collaborating with educators and Education Ministries if school-based programmes are considered.

One participant cautioned about using the phrase “adolescent health services” because WHO does not advocate setting up different services for adolescents, but rather to make general primary care services “friendly” to youth. One participant advised more discussion of elements of basic services package for young and older adolescents.

Dr Ndumbe noted that HPV vaccines provide an opportunity to introduce a broader range of adolescent health and cancer prevention services, to move towards a goal of total health. He noted that a recent report indicated that 12% of deaths in Africa are due to cancer and a large proportion of these are due to cervical cancer. Women are dying and countries should be more responsible to take actions to improve health. He added that WHO should provide countries the technical assistance and HEAG should formulate recommendations to WHO on how countries and ministries can support such actions.

Dr Ndumbe cautioned that most African countries face enormous shortages of high quality health care workers and this will need to be addressed as part of HPV vaccine introduction, especially given special skills these workers might need. He also noted that very few school based programmes that vaccinate only girls have survived and recommended doing studies of vaccine acceptability in countries such as Nigeria that have resisted other vaccines due to concerns about adverse effects on fertility.

Co-administration with other vaccines
It is important to note that research on co-administration with other vaccines is ongoing and avoid implying that HPV vaccines co-administered with other vaccines would be safe or effective when data are lacking.

Integration with screening
Dr Rees asked if vaccines should be introduced only if effective screening programmes are introduced. Dr Garcia noted that many developing countries do not have screening or have ineffective screening. Dr Garland noted that at the SEARO/WPRO cervical cancer and HPV meeting, many countries were concerned about introducing the vaccine without screening and recommended that screening be enhanced in these countries. Dr
Merle Lewis noted that a previous HEAG meeting concluded that it would not be unethical to introduce HPV vaccines in countries without screening programmes (e.g., in Haiti). Dr Goldie indicated that models have shown that vaccination alone can have significant impact and be cost-effective under many model assumptions. Vaccination combined with limited screening (e.g., 2-3 times per lifetime) is more costly, but has higher impact than vaccination alone and may be considered cost-effective in some settings. One participant advised that WHO should recommend that countries need to make their own decisions about whether vaccination should be integrated with screening, and if so, how that should be done and that WHO should encourage introduction of effective screening programmes that could benefit vaccinated and non-vaccinated women. Dr Davies stressed that emphasis should be given to comprehensive cervical cancer control programmes and that countries need to evaluate their own situation and recognize that vaccination is not a magic bullet. Dr Rees added that opinions in countries about the value of vaccine vs. screening vary greatly and given the health care workforce crisis in many regions, especially Africa, it is important that vaccination efforts do not steal workforce from effective screening services or otherwise undermine these programmes.

**Monitoring**

Dr Garcia noted that monitoring vaccine impact is very important but that monitoring of new infections is very expensive. She recommended consulting documents describing monitoring for HepB vaccine impact and use of DHS surveys. Dr Lewis agreed that more discussion on valuable endpoints is needed with recommendations for monitoring for counties with different capacity and resources. Some countries can conduct surveillance using linked cancer and vaccine registries while in other countries, only one time case control studies of CIN3 lesions may be feasible. She noted an example of surveillance in Latin America, a survey of HPV prevalence in primiparous women that was recently published in the PAHO Bulletin. Drs. Ndumbe and Davies asked if GAVI would be prepared to support HPV vaccine monitoring or cancer screening as part of a HPV vaccine initiative. Dr Rees added that the recommendation should include a recommendation for monitoring vaccine quality.

**Patient education and communication**

Dr Rees mentioned that the workgroups had made no specific recommendations about the “branding” of HPV vaccines and to what extent sexual issues should be addressed and this would have a major bearing on messages and with what other interventions HPV vaccines might be “packaged.” She noted that it is easier to present HPV vaccines as cancer vaccine than STI vaccines to preadolescents (e.g. 11-12 year olds) and that communication strategies are needed to help people understand vaccine benefits. She stressed that communication messages about the quadrivalent vaccine should include wart prevention, when appropriate and noted that, from her perspective as a clinician in a South African referral centre that sees many patients with severe, recurrent anogenital warts, wart prevention benefits of the quadrivalent vaccine would be valuable. Dr Markowitz noted that in the US the main message about this vaccine is cancer prevention, with the warts prevention message being secondary. Dr Garcia noted that in Peru, the average age of onset of sexual activity is 16 years in females so talking about sex to 10-11 years old vaccinees may not be acceptable to communities. However, this resistance may be balanced by general high acceptance of vaccines. Dr Broutet advised that HPV vaccination provides an important opportunity to educate about sexual health in a culturally- and age-appropriate way, e.g. younger girls could be educated about puberty and menstruation while teens could be educated about STI. Dr Merle Lewis stressed that messages should be developed in collaboration with many stakeholders, including civil society, brought to the table early in the process. Dr Markowitz stressed that messages about vaccine use for boys and men should be relevant to vaccine licensing context as vaccines are not licensed for males in most countries. Dr Garcia noted that globalization of media prompts questions about why some countries have licensed vaccines in boys, resulting in a need to indicate potential vaccine benefits in males, as a minimum. Dr Kahn advised that messages should include a warning that HPV vaccines do not protect against non-HPV related cancers or other sexually transmitted infections (STI). Several participants stressed that messages need to be tailored to the cultural context and developmental stage of vaccine recipients and yet little is known about how to best do this in most countries. The UNFPA representative advised that advocacy, information, and
counter-misinformation activities about HPV vaccines should be offered in clinical encounters with youth and women, such as in clinics providing family planning, antenatal and postnatal care, and sexual and reproductive services, including "youth friendly" clinical services. He added that even if pregnant women should not be offered vaccine, pregnant women could be educated about HPV vaccine because they are good listeners and may be opinion leaders in families and communities.

Cost, cost-effectiveness, affordability, and financing
Dr Rees stressed that the cost of vaccine wastage can be very important if many girls get only one dose and this does not confer protection. Vaccine wastage, potential or actual, will be important for assessing cost effectiveness. Dr Merle Lewis noted that the cost of monitoring and surveillance should be considered when countries budget for vaccine introduction and it could be costly. Dr Goldie noted that putting HPV vaccine affordability in terms of percent of total public expenditures, expenditure for health, or expenditures for vaccines could be informative for countries. Dr Hyer stressed that vaccination with the quadrivalent vaccine yields early impact and direct, indirect or intangible economic returns because protection against HPV 6 and 11 infection reduces incidence of anogenital warts and ASCUS and CIN1 related to these types and that these outcomes develop more rapidly after HPV exposure than higher grade CIN or cancer associated with HPV 16 and 18. Dr Barr strongly emphasized Merck’s strong commitment to tiered pricing that would make vaccines affordable in middle and low income countries and maximize public health impact. Dr Jenkins emphasized that GSK has a long-standing commitment to providing vaccines to developing countries at appropriate prices. Dr Goldie indicated that her models assume tiered pricing with prices ranging from 2 to 75$ per vaccinated girl. Dr SanJose recommended that models consider 2 year age cohorts (e.g., 11-12) to complement models looking at one year cohorts because age of vaccination is a key driver of cost effectiveness. Workgroup 3 concluded that country-specific cost effectiveness models are very difficult to develop, and recommended that countries should adapt existing models with their own data when possible, rather than create their own models. Dr Merle Lewis noted that PAHO is supporting development of simple cost effectiveness tools using country-specific data. Some participants advised that recommendations should include a section that describes results of cost effectiveness studies and a summary of conditions and assumptions needed to make vaccination cost effective. One participant asked if WHO would make recommendations about vaccine price and Dr Irwin indicated that WHO does not get involved in price decisions. Mr Brooke clarified that tiered pricing may be negotiated by UN procurement agencies (e.g., UNICEF, PAHO) and that WHO is not involved. However, Dr Irwin noted that in April 2007, SAGE advised WHO to develop a resource mobilization plan for HPV vaccines and to take action to accelerate affordability of vaccines. This SAGE recommendation was supported by HEAG meeting participants. Dr Ndumbe stated that the vaccine should be recommended because it is effective and the economic issues are secondary to a recommendation, but that price will be critical to programme implementation.

VII. RECOMMENDATIONS ON HIGH PRIORITY RESEARCH

Each workgroup was asked to determine if any research was essential before candidate recommendations could be drafted for consideration by SAGE. All workgroups concluded that no research was essential but recommended research topics that were high priority and that WHO should attempt to accelerate this work. Some workgroups also noted if research on these topics was under way or planned. This list summarizes recommendations for research and commentary for topics advised by workgroups and in general discussion.

- Viral characteristics or immunology
  - Latency and reactivation (Difficult to study) (group 1)
  - Evaluation of high prevalence or even additional peaks of HPV infection among older women in some low and middle-resource countries (e.g., due to reactivation or new infection (group 1)
  - Genetic predisposition to poor immune response to vaccines (group 1)

- Burden of disease caused by vaccine-related HPV types
Better information on burden of disease, especially in developing countries, pre- and post-vaccine introduction (studies ongoing) (group 1)
- Burden of genital warts in developing countries (group 1)
- Burden of disease outside genital tract (group 1)
- Burden of disease in HIV-infected populations (group 1)

Vaccine immunogenicity, clinical efficacy, schedule, administration
- Efficacy in children/infants, < 5 and < 1 year old (Merck studies ongoing) (group 1)
- Efficacy of alternative schedules (2 versus 3 doses; early first dose) (group 1, 2, 3)
- Immunogenicity in different populations, including persons affected with HIV, malaria, parasitic diseases, auto-immune diseases, malnutrition, smoking, allergies and hypersensitivity (several studies ongoing, Merck studies showed no impact of smoking on efficacy) (group 1)
- Efficacy of second generation vaccines, including oral vaccines (group 1)
- Safety, immunogenicity and efficacy in males (Merck study ongoing, ending in ‘08, GSK study in Finland evaluating safety and immunogenicity and impact of vaccinating males on HPV prevalence in females) (group 1)
- Duration of protection (Both Merck and GSK have follow-up studies of phase 2 and 3 trial populations, GSK has a phase 4 study in Europe, Merck is evaluating this in Scandinavia and other country-specific studies) (group 1, 3)
- Co-administration with other vaccines and medication (ongoing data collection) (group 1)

Safety, adverse effects, contraindications
- Safety in pregnancy (pregnancy registries ongoing) (group 1)
- Evaluation of adverse events following immunization (AEFI) reporting (group 1)
- Safety in different populations affected by HIV, malaria, parasitic diseases, auto-immune diseases, malnutrition, known vaccine allergies and hypersensitivity (group 1)

Operational issues
- Options for vaccine packed volume and packaging (GAVI addressing presentation and packaging, these data are critical to cost models) (group 1)
- Options for multidose vial with preservative, subject to WHO’s multi-dose policy (permitting use of unused doses for < 30 days) (group 1)
- Trade offs between wastage (e.g., multivials) vs. volume (single dose cold chain requirements)
- Methods to optimize vaccine stability (group 1)
- Use beyond cold chain (group 1)
- Predictors or and cost of wastage and “drop off” after 1st dose (Some research in developed countries, but needed in developing countries, major impact on cost studies) (groups 2, 3)

Delivery strategies
- Effectiveness of various delivery options (Some options being studies by PATH) (group 2)
- Potential to vaccinate infants, including data on safety and immunogenicity alone or in combination with other vaccines (group 2)
- Evaluation of a mother-daughter strategy: screen mothers and invite their daughters to be vaccinated (and vice versa) (group 2)
- Predictors of noncompliance with full primary vaccination series (group 4)
- Cost of different delivery modes (group 3)

Vaccine acceptability and coverage and related educational needs
- Acceptability of vaccinating boys and impact on uptake in females (group 4) (Research on educational needs, acceptability in low and middle income countries where vaccine not yet licenses is ongoing or being planned.)
- Relative advantages of vaccinating boys vs. information/awareness raising (group 2, 4)
- Educational needs and vaccine acceptability before vaccines licensed and adopted (region- and country-specific, especially in low- and middle-income countries) (group 4)
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- Actual vaccine uptake and predictors of uptake in countries after vaccine licensing including factors that influence public sector programmes (region- and country-specific) (group 4)
- Predictors of vaccine licensure and introduction decisions in countries (Research on predictors of vaccine uptake in countries where vaccines are licensed is planned or ongoing.)
  
  o Vaccines as part of a cervical cancer programme
    - Methods to integrate vaccination and screening across relevant age groups and combinations of vaccine and screening at different ages and settings that maximize impact and cost-effectiveness (Being modeled in high, middle and low income countries) (group 2)
    - Impact of vaccination on sexual and Pap screening behaviors (Existing data from industry can be analyzed and published, but other sources are needed from non-trial populations) (group 4)
  
  o Monitoring
    - Impact of vaccines on HPV type replacement (Being evaluated in Nordic countries)
    - Adaptation of monitoring methods used in research settings to programme settings (group 2)
  
  o Communication
    - Assessment of education needs of various audiences (group 4) (Development and testing of messages and evaluation of message effectiveness is planned or ongoing.)
    - Developing and testing messages, evaluation of their effectiveness, notably the emphasis of cancer and/or STI messages (Ongoing in PATH demonstration projects) (group 4)

Discussion

One participant asked what are constraints for manufacturers to include other HPV type-specific antigens in second generation vaccines and what WHO would recommend if other type-specific HPV antigens can be included. One participant noted that rich experience on delivering and uptake of other vaccines should be reviewed before launching new research on delivering HPV vaccines. Dr Markowitz noted that message testing research in the US demonstrates that HPV vaccine messages need to be extremely simple. Dr Rees advised that WHO recommendations should stress the need for developing simple messages about vaccines and screening before introduction and WHO should develop a tool to guide low and middle income countries in developing such messages. If message testing becomes too complex, it will be a barrier to vaccine introduction. PATH is evaluating some messages in demonstration projects. Dr Rosenthal advised that studies should not be to create demand for vaccine in males where vaccines are not licensed for males, but to determine if governments may be more inclined to introduce vaccine if it were also available to boys.

VIII. RECOMMENDATIONS ON DATA NEEDED FOR COUNTRY DECISION MAKING ABOUT HPV VACCINE INTRODUCTION

All 4 workgroups were asked to identify data needed by countries, whether those data were available for most countries, and if data were not available, if data from other countries could be used. Their assessments are summarized below. Workgroup 2 indicated that delivery strategies should be tailored to each country’s infrastructure for delivery through schools, community outreach, and health systems, but that lessons learned from other countries could be informative. Workgroup 3 indicated that vaccine impact, cost-effectiveness, cost, affordability, and financing will vary by country but that “prototype models” from epidemiologically similar countries could be informative, or adapted to a country’s unique circumstances if data and resources permit. Workgroup 4 noted that educational messages for patients, parents, providers, programme managers, and policy makers must be carefully adapted to be appropriate to the audience’s information needs, age, and cultural issues.

<table>
<thead>
<tr>
<th>Workgroup</th>
<th>Topic</th>
<th>Available in most countries</th>
<th>Can countries use data of other countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Safety, efficacy, and immunogenicity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Burden of disease, including avertable %</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Country-specific costs to achieve sustained, high coverage

Country-specific cost-effectiveness

Tested education messages tailored to audience

Discussion
Dr Rees stressed that data on burden of disease should be considered, even if only basic data on burden are known. Dr Franceschi noted that burden of disease data are very scanty in some areas, such as parts of China and Central Asia. It was noted that estimates of the burden of disease in Africa are based on just a few countries and that countries lacking data may be resistant to considering vaccines. Dr SanJose noted that the WHO/ICO Information Centre includes regional data from Africa. There was an apparent consensus among meeting participants that African countries could use regional disease burden data if country data were lacking.

IX. OTHER RECOMMENDATIONS FOR WHO

Workgroups and participants of general sessions made several other recommendations to WHO, including

- WHO should draft detailed candidate recommendations based on preliminary recommendations discussed at meeting and circulate to HEAG for comments after the meeting.
- Advise industry on what other HPV type-specific antigens should be included in second generation HPV vaccines based on global type distribution and virulence.
- Convene a special meeting on methods to monitor and evaluate vaccine impact and safety. This should produce recommendations on outcome indicators and methodology, including methodology for HPV DNA, typing, and serology testing being done in the WHO HPV Laboratory Network. It should address denominators used for indicators, minimal monitoring requirements for developing countries, issues that should be assessed through sentinel surveillance, and linkage of vaccine, cytology, and cancer registries.
- Support development of basic costing and budgeting tools that countries could use to estimate costs of vaccine introduction at various coverage levels over sustained periods.
- WHO’s cervical cancer screening guidelines should be reevaluated in light of new data on the role of visual inspection and HPV DNA testing as screening tools in low income settings.

X. RECOMMENDATIONS ON NEXT STEPS

Dr Irwin proposed that Dr Garcia report conclusions of the HEAG meeting at the November 2007 SAGE meeting and that the HEAG meeting report should be submitted to SAGE members before the meeting. She proposed Dr Garcia’s oral report include the status of vaccines licensure and recommendations worldwide and opinions of regions about vaccines. She should stress that the meeting yielded a strong consensus by HEAG that the current evidence (collated in the draft Background Paper and presentations) was now sufficient to start the process of drafting candidate recommendations for consideration by SAGE as early as April 2008 but this would require a major time slot. Dr Irwin proposed that Dr Garcia should propose a process to refine candidate recommendations based on input from experts and regions over the months ahead, perhaps with a writing committee. Dr Garcia should also note that the HEAG made valuable suggestions to the draft Background Paper and that it will be revised over the next few months. This Background Paper could provide the basis for future SAGE debate about HPV vaccine recommendations and if recommended, a WHO Position Paper.

Dr Irwin noted that the draft meeting report would be sent to meeting participants for comment before being finalized and submitted to SAGE in October. She also asked participants to send additional suggestions for
revising the Background Paper and noted revisions would also include newly available data and may require special workgroups to revise some sections. She indicated WHO would continue to collate and disseminate country recommendations about HPV vaccines, as well as country and regional opinions and experience about vaccines and screening. She noted that HEAG membership may be modified in the future due to new expertise needed or conflicts of interests. She thanked the Gates Foundation for providing support for meeting planning, Dr Garcia for chairing this meeting, the excellent presenters and workgroup facilitators and rapporteurs, Dr Claeys, the meeting rapporteur, WHO technical staff, and staff of IVR.
ANNEX

PROPOSED REVISIONS TO DRAFT BACKGROUND PAPER

Efficacy and immunogenicity, and safety (Workgroup 1)

- Start each section with summary bullets about highlights.
- Highlight that immune response following natural infection is not well understood.
- Note that comparing antibody response following vaccination with antibody response following natural infection provides only limited information because there is no known immunologic correlate of protection from HPV infection and the level of antibody response to natural infection does not confer protection from infection in many studies.
- Include information on HPV types and with which diseases they are associated.
- Note distinctions of epidemiology of HPV related disease in immunocompromised populations.
- Update tables with main efficacy results of recently published trials.
- Add a section on immunocompromised subgroups and their HPV-related disease burden.
- Add a paragraph on cross protection using data expected from industry shortly.
- Revise section on intent-to-treat, clarifying 3 different groups (total population with vaccine-related endpoints; total population with all HPV endpoints, susceptible population with all HPV endpoints).
- Update oral statements and package insert data with published data to eliminate duplication.
- Note that bridging data should include other groups in whom efficacy studies may not be ethical (e.g., children).
- Note lack of data on long-term duration of protection, but note that if protection is lost, it could be extended with booster doses.
- Note operational issues, including storage, packing characteristics and volume, and wastage.

Delivery, integration with screening, monitoring and surveillance (Workgroup 2)

- Preamble should note that vaccines are being introduced in high income countries and that most information available is from these countries and why trials were done in these countries.
- Add key information from developing countries more frequently, e.g. experience in Latin American delivering rubella and measles vaccines to older children.
- Put more text data into tables and omit some details in text.
- Clarify distinction between what current research demonstrates and what existing country guidelines on HPV vaccine use recommend.
- In the Introduction, stress why cervical cancer is an important issue, how it compares with other health problems, and why it may merit investment in prevention. Consider a table comparing cervical cancer with other health issues.
- State more clearly that it is likely that HPV vaccines will provide long term protection but that cervical cancer screening will remain necessary for vaccinated and non-vaccinated women.
- Note that targeting vaccination to adolescents raises the concept of adolescent health care and HPV vaccines provide an argument for platform for adolescent health services or packages.
- As target populations in some countries may include 10 year olds, need to clarify meaning of adolescents and pre-adolescents and specific age ranges. Note that WHO defines adolescents as 10-19 years olds, but appropriate information/counseling for 10 year olds may differ greatly from that for older teens.
- Avoid the phrase "adolescent health services" to avoid implying establishing separate services for adolescents. The phrase "youth friendly services" is preferable.
Provide more information on school-based delivery and the advantages and disadvantages of various strategies. For example, in Australia, delivering Hep B vaccination through schools yielded much higher coverage than delivery through primary health centres.

Note potential challenge of school-based programmes that only target girls and note value of studies of female-only vaccines in countries such as Nigeria where misconceptions around vaccination have been strong. Some of these issues are being addressed in PATH demonstration projects.

Provide more information on possible packages of services for younger and older adolescents. The package may vary by age, but include sexual health education, vaccine boosters (e.g., tetanus toxoid), and other health interventions.

As target population in some countries may include persons at high risk for HIV infection, add special section on burden and characteristics of HPV-related disease in HIV-infected persons and information on vaccine characteristics in this subpopulation.

Summarize potential delivery strategies in a table.

Summarize vaccine acceptability findings in a table.

Highlight acceptability concerns that may impact uptake and acceptability, e.g., gender issues, informed consent, public perception of vaccine safety.

Add information on how vaccine supply and cost influence acceptability.

Highlight need for countries to consider competing health priorities for public health benefits and vaccine financing. Include discussion of how this relates to shortage and poor training of health care providers and how human resources for vaccine introduction could be achieved, especially in Africa.

Note that lack of human resources may also be a reason why countries may want to introducing vaccines instead of cancer screening and treatment if immunization may be easier to implement and is less influenced by different social groups than these other interventions.

Refer to WHO guidelines for vaccine introduction and summarize in box.

For monitoring and evaluation section, note what activities can be done at population level, through sentinel surveillance, or through research activities. Note costs of monitoring activities.

More recommendations on indicators of vaccine programmes and impact, how they can be used and list in table. Note different recommended levels of monitoring activity based on country capacity, and that only a few countries can monitor long term incidence or link cancer registries with vaccination registries. Note that the WHO HPV Laboratory Network is developing some outcome indicators and methodology related to HPV types and immunogenicity but is not defining essential indicators.

Note challenges regarding monitoring of CIN3 lesions, costs of monitoring, and finding representative populations for HPV surveys (e.g., women at first delivery, first pregnancy) should be noted. Here, the December issue of the PAHO Bulletin may be useful.

Note relevance of experience monitoring HepB vaccination and potential to use DHS surveys.

Vaccine impact, cost, cost-effectiveness and financing (Workgroup 3)

Change organization as follows: Introduction, Tools used to estimate impact and cost-effectiveness, Health impact, Non-health impact, Costs, Cost-effectiveness, Affordability and Financing. Include discussion of uncertainly in models for each section and consolidate in summary paragraph.

Section on health impact should stress that models assume that pre-adolescent girls are primary target group and note other key assumptions:

- Include outcomes modeled for vaccine use alone plus vaccine plus 2-3 lifetime screening.
- Outcomes should include impact on 1) cervical cancer, noting that most analyses focus on squamous cell, and add section on impact on adenocarcinoma; 2) noncervical cancer outcomes (head and neck, etc); and 3) genital warts.
- Present data on models considering immunizing older, catch up female populations and males. Note differences in impact of vaccinating pre-adolescent vs. older “catch up” populations.
Include impact on vaginal, vulvar, penile, and anal precancers and cancers, anogenital warts, respiratory papillomatosis, and other outcomes due to vaccine-related HPV types, not just cervical cancer. Stress that current data may underestimate actual burden of these diseases.

Section on non-health outcomes should include averted outcomes and treatment costs and note adverse effects of losing a mother on a household means and stability

- Section on costs should note costs related to 3 doses, wastage, administration, vaccine support, programmatic and infrastructure development for new delivery platforms, monitoring and surveillance.
- Stress that administration cost can be substantial as vaccination programmes for pre-adolescent girls do not exist in most countries.
- Cost-effectiveness analysis (CEA) section should be separated into developed and developing countries.
  - Section on developing countries should summarize completed and ongoing work, describe assumptions, and summarize results.
  - Cost effectiveness metrics should be presented in standard format, such as CE ratio expressed as percentage of GDP, noting different standards for assessing cost-effectiveness based on GDP or other commonly used standards.
  - Highlight key drivers of CEA: price, cost per vaccinated woman and duration of immunity
  - Note differences in vaccine impact and cost-effectiveness of vaccinating pre-adolescent vs. older “catch up” populations.
  - Interpret CEA results in context, for example, by noting that vaccine costs considered in many models are much lower (2-7$) than current prices in developed countries and that analytical work to date has shown that prices in developing countries must be much lower if vaccination is to be cost-effective.
  - Section on CEA in developed countries should summarize published literature and note points of consistency between models.
  - Note that older CEA models did not include always genital warts as outcomes and that newer models accounting for HPV 6 and 11 show added impact and cost effectiveness and herd immunity effects. In contrast to cohort models, dynamic models that consider herd immunity show stronger effects of strategies involving male vaccination.
  - Highlight key drivers for CEA: the current screening programme (the choice of comparator is critical), vaccine price and duration of protection and secondary drivers.
  - Note importance of newer studies that include a broader range of outcomes (e.g., adenocarcinoma, other cancers)
  - Note that tools for C/E analysis are very difficult to develop, so it may be more practical for countries to use or tailor existing models than recreate their own models.
  - Stress that WHO should develop tools to calculate overall costs, including delivery costs.

- On section on affordability and finance, stress distinction with cost effectiveness.
- Highlight importance of vaccine price but note price may be lower in future.
  - Add brief comparative study between cost per fully vaccinated child in EPI programme versus potential cost of vaccinating preadolescent girl with HPV vaccine.
  - Stress role of affordability and financing mechanisms in country decision making
  - Stress implications of affordability on equity, and disparities between countries (giving attention to middle income countries not eligible for GAVI support) and disparities within countries.
  - Express vaccine affordability as percent of GDP spent on health vs. total public expenditures, total public expenditures for health, and total public expenditures for vaccines
  - Stress that affordability relates to vaccine price and delivery costs. Even if price is lower, high delivery costs may make vaccination unaffordable.
- Note that while current vaccine prices are high, companies have announced plans to offer tiered pricing for developing countries but price ranges have not been announced.
Socio-cultural issues, patient education, communication and policy coordination
(Workgroup 4)

- Restructure sections and subsections in a parallel way and provide similar information to improve clarity and usability according to this example. For example, regarding parental acceptability
  - Parental acceptability is important
  - Most parents are supportive of vaccination
  - Minority of parents have concerns (delineate concerns)
  - Factors associated with decision to vaccinate one’s child

- Add tables or bulleted lists on acceptability, education and communication, and key messages to clarify key points and shorten text.

- Highlight importance of cultural considerations and the need for different strategies by country or region.

- Highlight the importance of placing communication about HPV vaccines into the context of comprehensive cervical cancer control programs, and in some cases, sexuality education.

- Exercise caution about creating demand for vaccines via recommendations, educational and communication strategies, if the vaccine is not licensed, available, accessible, and affordable. This may include messages to males.

- Emphasize the importance of partnerships and including and relevant stakeholders early on.

- Note how packaging and messaging around vaccine may differ if vaccine is promoted as a cancer and/or STI vaccine and how this might vary by age of vaccine candidate. For example, in some countries, an STI message may be less appropriate, relevant, or acceptable to 11-12 years olds who will not start sexual activity for many years than for 14-15 year olds who have started or may soon start activity.

- Note that because vaccination is well regarded in many countries (e.g., Peru) HPV vaccination provides the opportunity to address sexual health in an age-appropriate way, ranging from basic concepts like puberty, sexual behaviour, menstruation to sexual intercourse.

- Stress the importance of good communication with parents so that they can make informed decisions about vaccinating their daughters.
Consultation of the Human Papillomavirus Expert Advisory Group (HEAG)
3-5 September 2007, WHO-HQ, Geneva, Salle C
Final List of Participants

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Ms Deborah Myers, GlaxoSmithKline Biologicals, Rixensart, Belgium
World Health Organization
Consultation of the Human Papillomavirus Expert Advisory Group (HEAG)
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Final Agenda

Monday, 3 September (Day 1)

12:30-13:00  Registration

13:00-13:15  Welcome and review of meeting objectives  Teresa Aguado

13:15-13:30  Charge to group  Patricia Janet Garcia

13:30-14:00  Update: vaccine efficacy and immunogenicity
Including status of ongoing and planned studies  Lauri Markowitz

14:00-14:30  Update: safety, including report of WHO Global advisory Committee on Vaccine Safety  Dina Pfeifer

14:30-15:00  Update: delivery strategies and programmatic issues
(including integration with screening programmes)  Vivien Tsu

15:00-15:20  Coffee break

15:20-15:50  Update: cost effectiveness and vaccine impact,
with and without screening as a complementary intervention  Sue Goldie

15:50-16:10  Update: secondary prevention strategies, including cytology, HPV testing, and visual inspection  Andreas Ullrich

16:10-16:40  Update: data for decision making and decision tools  Silvia de SanJose

16:40-17:00  Update: vaccine licensure status, support to National Regulatory Authorities, and prequalification process  Liliana Chocarro

17:00-17:20  Update: HPV vaccine investment case and demand forecasting  Steve Brooke

17:20-17:50  Update: WHO, Regional, and country perspectives on HPV vaccines  Katy Irwin

17:50-18:00  Workgroup assignments, and charge to workgroups assignment of facilitators and rapporteurs  Teresa Aguado and Jennifer Tsui

18:00  Closure for the day and reception  WHO cafeteria

19:00-19:30  Meeting for WHO HPV Small workgroup and workgroup facilitators and rapporteurs  Katy Irwin
Tuesday, 4 September (Day 2)

8:30 **Report directly to workgroup rooms**
Review of charge to workgroups

8:45-10:15 Workgroup 1: Safety, efficacy, and immunogenicity
Salle C
Lauri Markowitz

Workgroup 2: Deliver strategies, integration with screening, and monitoring and evaluation
Salle D
Denise Haefliger

Workgroup 3: Impact, cost, cost-effectiveness, and financing
Room X7
Steve Brooke

Workgroup 4: Sociocultural issues, patient education, communication, and policy
Room X10
Scott Wittet

10:15-10:45 **Coffee Break**

10:45-12:15 Workgroups continue

12:15-13:45 **Lunch**

Reports of Workgroups

13:45-15:00 Report of Workgroup 3:
Sue Goldie

- Recommendations to revise relevant sections of background paper
- Recommendations for relevant research and data for decision-making
- Discussion

15:00-16:30 Report of Workgroup 1:
Robin Biellik

- Recommendations to revise relevant sections of background paper
- Recommendations for relevant research and data for decision-making
- Discussion

16:30-17:00 **Coffee Break**

17:00-18:00 Report of Workgroup 2:
Patricia Claeys

- Recommendations to revise relevant sections of background paper
- Recommendations for relevant research and data for decision-making
- Discussion

18:00-18:15 Review of Day 3 agenda
Katy Irwin

18:15 **Closure for day**
Wednesday September 5 (Day 3)

8:30 Assembly - Salle C

Reports of Workgroups (continued) Proposed rapporteurs

8:35-9:15 Report of Workgroup 4: Jessica Kahn

Recommendations to revise relevant sections of background paper
Recommendations for relevant research and data for decision-making
Discussion

9:15-10:40 Is evidence adequate to support candidate recommendations for deliberation by SAGE? Patricia Janet Garcia
Discussion of candidate recommendations

10:40-11:00 Coffee Break

11:00-11:45 Decision-making tools for HPV vaccine introduction Teresa Aguado
Essential elements and outputs
Strategies to accelerate tool development and use

11:45-12:30 Additional research priorities for WHO Nathalie Broutet
Strategies to accelerate and coordinate high priority research

12:30-13:45 Lunch

13:45-14:30 Options for monitoring vaccine coverage and impact on clinical outcomes Silvia Franceschi

14:30-15:00 Communication priorities and products for WHO Scott Wittet
Key messages, audiences, channels and partners

15:00-15:30 Building partnerships between immunization, cancer control, reproductive, and child and adolescent health programmes in countries. WHO Regional Office Representatives panel discussion

15:30-15:50 Coffee Break and CD distribution

15:50-16:15 Summary of recommendations, action steps and timelines Katy Irwin

16:15-16:30 Closure of meeting Patricia Janet Garcia
## HEAG Work Group Composition

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<td>Facilitator</td>
<td>Dr Markowitz</td>
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<td>Dr Frazer</td>
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