Report of the Consultation on Human Papillomavirus Vaccines

World Health Organization, Geneva, April 2005

Table of contents

Executive summary **3**
1. Introduction **5**
2. Presentations **6**
The causative role of HPV in anogenital and other cancers *(Prof. Harald zur Hausen)* 6
The global epidemiology of HPV and cervical cancer *(Dr Nubia Muñoz)*
and proposals for further data collection *(Dr Sylvia Franceschi)* 8
Update on HPV vaccine trials *(Dr Elaine Esber and Dr Gary Dubin)* 13
Cost effectiveness of HPV vaccines *(Dr Sue Goldie and Dr Evan Myers)* 16
Programmatic issues regarding HPV vaccine introduction *(Dr Ciro de Quadros*) 19
3. Discussions **21**
Attitudes to HPV vaccines 21
Information gaps regarding HPV and HPV vaccines 23
4. Update on work by PATH and WHO in the field of HPV and HPV vaccines **25**
PATH *(Dr Jacqueline Sherris)* 25
WHO *(Dr Teresa Aguado, Dr Nathalie Broutet)* 25
4. Recommendations from the HPV meeting **28**
5. References **30**
Annex 1: Agenda **32**
Annex 2: List of participants **33**

Executive summary

Cervical cancer affects approximately 1.4 million women worldwide and claims an estimated 239 000 lives each year. Over 99% of cervical cancer cases result from genital infection with human papillomavirus (HPV). The disease represents a major health inequity, as 80% of those with cervical cancer live in developing countries. The peak incidence of HPV infection occurs in adolescents and young women, while cervical cancer typically follows 20–30 years later. Currently, the best way to prevent cervical cancer is through regular gynaecological screening and treatment of precancerous lesions. In developing countries, however, this method has had only a limited impact due to the cost and complexity of properly screening and treating women.

Vaccines against HPV infections are likely to be a cost-effective and practicable means to reduce incidence of cervical cancer. Two candidate HPV vaccines, both protecting against new and persistent infections with the most common cancer-causing HPV types (HPV 16 and 18), and one also protecting against genital warts (including, in addition, HPV types 6 and 11), are in phase III clinical trials among women aged 16 to 25. Marketing applications for these products will be submitted to regulatory agencies in 2005–2006 for licensure. If licensed, the likely target age will be adolescents and young women.

In this consultation, current knowledge on the epidemiology of HPV and cervical cancer, HPV vaccine trials and the predicted cost–effectiveness of HPV vaccine were reviewed and plans for further data collection in these areas were presented. Programmatic issues related to future HPV vaccine introduction were discussed, and the outstanding information requirements for making evidence-based policy decisions were identified. The main outstanding gaps include:

- evaluation of vaccine safety and efficacy (immunogenicity and prevention of persistent HPV infection) in Africa, particularly populations with high HIV prevalence;

- evaluation of the immune response to vaccine at school entry (when contact with girls would be much easier than in later years) and in infancy – e.g. at age 9–12 months, together with measles vaccine or measles, mumps and rubella (MMR) vaccine;

- evaluation of simultaneous administration of HPV vaccine with other vaccines such as tetanus toxoid (TT), measles, mumps and rubella vaccines;

- development of toolkits with applied research and surveillance methodologies, to enable countries to conduct local assessments of:

  - knowledge and attitudes of health professionals, teachers, community leaders, parents and adolescents regarding HPV, cervical cancer and HPV vaccines;

  - coverage and quality of adolescent health services; and

  - methods for monitoring and evaluating HPV vaccination programmes.

WHO will work in consultation with expert advisors to develop guidelines to assist countries to integrate HPV vaccination into their immunization, cancer control, reproductive health and adolescent health programmes.

1. Introduction

Cervical cancer is the leading cause of cancer mortality among women in developing countries. There are estimated to be approximately 500 000 new cases of cancer, leading to about 239 000 deaths each year (*World Health Report*, 2004). Over 99% of cervical cancer cases are linked to genital infection with human papillomavirus, which is the most common viral infection of the reproductive tract worldwide and infects an estimated 660 million people. While HPV infection resolves spontaneously in the majority of people, it can develop into chronic infection and, in some women, cervical cancer. The disease represents a major health inequity, as 80% of cervical cancer victims live in developing countries. The peak incidence of HPV infection occurs in adolescents and young women, while cervical cancer typically follows 20–30 years later. Industrialized countries have greatly reduced deaths from cervical cancer through screening programmes that allow early detection and treatment. These programmes are expensive and difficult to implement in low-income countries.

Vaccines against HPV infections have the potential to be a more practical and cost–effective way to reduce the incidence of cervical cancer. Two candidate HPV vaccines, both protecting against the most common cancer-causing HPV types (HPV 16 and 18), and one also protecting against genital warts (including in addition, types 6 and 11) are currently undergoing large phase III clinical trials among women aged 16 to 25. In anticipation of the licensure of HPV vaccines within the next 2–3 years, the World Health Organization convened this consultation on 14–15 April 2005, to review available data and planned work on the epidemiology of HPV and cervical cancer; the efficacy, acceptability and cost–effectiveness of HPV vaccines; and the potential to integrate HPV vaccination with existing immunization programmes. The consultation aimed to identify gaps in the information needed to make recommendations regarding future use of HPV vaccines. Following the consultation, WHO will create an expert advisory group that will assist WHO and its Member States in generating guidelines for accelerating the safe and effective use of HPV vaccines to reduce the incidence of HPV vaccine-preventable cervical cancer and precancerous lesions. A short meeting of potential participants of the group was held on 15 April, following the open consultation and update on HPV vaccines. The main recommendations from the closed session are included in this report.

The consultation was opened by Ms Joy Phumaphi, Assistant Director-General, Family and Child Health cluster, WHO, who welcomed the participants to the meeting. Ms Phumaphi highlighted the exciting prospects for HPV vaccines as an additional tool to prevent cervical cancer. The impact may be especially high in areas where it has not been feasible to implement an effective screening and early treatment programme. At the same time, several challenges must be met. Screening programmes will still be useful for detection of existing cancers, precancerous lesions and new cases that would arise despite vaccine use, since types other than those included in the vaccine also cause cervical cancer. The future systematic use of HPV vaccines in developing countries may depend on data on the local epidemiology of HPV and cervical cancer, bridging studies of vaccine effectiveness and acceptability, financial resources, and the feasibility of vaccinating adolescents. Ms Phumaphi lamented the lack of inclusion of sites in sub-Saharan Africa in vaccine trials to date, and emphasized the need to understand the effects of vaccines in areas of high HIV prevalence.

2. Presentations

The causative role of HPV in anogenital and other cancers *(Prof. Harald zur Hausen)*

106 genotypes of human pathogenic papillomaviruses have been identified, and their genomes are fully sequenced. Available data indicate that there are more than 100 additional genotypes, showing the heterogeneity of this virus family. According to phylogenetic classification, the high-risk types fall into two “clades”, which are species separated into groups of near neighbours on the phylogenetic tree.

The causative role of certain HPV types in cancer was reviewed in an evaluation at the International Agency for Research on Cancer (IARC) in February 2005 (Table 1). The consensus was that there is sufficient evidence for carcinogenicity of the anogenital tract for types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 (the "high-risk" types of HPV). Some case–control studies also point to a role of HPVs 26, 68, 73 and 82 in cervical cancer, but they are found relatively rarely. There is possible carcinogenicity of HPV 6 and 11, which although not being associated with cervical cancer, are consistently detected in the rare Buschke-Löwenstein tumours converting into verrucous carcinomas of the vulva. In the skin, some types of HPV Genus β are possibly carcinogenic to humans. HPV 5 and 8 are considered as carcinogenic for patients with epidermodysplasia verruciformis. No major role has been found for HPV in oesophageal cancer.

Table 1: Papillomavirus types involved in different human cancers

Type of Cancer	Papillomavirus types involved	Percentage of cases HPV-positive
Cervical	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 (26, 68, 73, 82)	>95
Vulval: Basaloid Warty Keratinizing	16, 18 16, 18 16	>50 >50 <10
Penile: Basaloid Warty Keratinizing	16, 18 16, 18 16	>50 >50 <10
Vaginal	16, 18	>50
Anal	16, 18	>70
Oral cavity and tonsils	16, 18, 33	~25
Nail bed	16	~75

Cofactors for the development of cancer include smoking tobacco and increasing parity. The role of nutrition and the inflammatory sexually transmitted infections (STIs), chlamydia and genital herpes, is debated. A systematic review of cervical cancer and the use of hormonal contraceptives found an increase in risk with increasing duration of use, but more data are needed on the extent to which the observed associations remain after use of hormonal contraceptives has ceased (Smith et al., 2003). There is no convincing evidence that condom use reduces the risk of HPV infection. Some studies show a reduction in risk for genital warts, moderate or high-grade cervical intra-epithelial neoplasias

(CIN 2 or 3), or cervical cancer, but data on protection against these endpoints are not consistent (Manhart & Koutsky, 2002). Circumcision may be associated with reduced transmission.

The evidence for high-risk HPV being the primary cause of cervical cancer is exceptionally strong and includes the following (zur Hausen, 1999): viral genes (E6/E7) are present and uniformly active in cervical cancer cells; the E6/E7 genes possess growth-promoting and transforming activity; the malignant phenotype of cervical cancer cells depends on the expression of these viral oncogenes, and epidemiological prospective and case–control studies identify high-risk HPV as the major risk factor for cervical cancer.

Discussion focused on whether there was cross immunity between viral types and whether, on resolution of initial infection, the virus was fully cleared by the immune system in those who did not maintain a chronic infection. The views expressed were that there was immunological clearance of the virus. The virus could persist if the immune system was incompetent. There is no evidence of cross-immunity between L1 antigens, but the L2 antigen might provide relatively low group-specific cross-type protection.

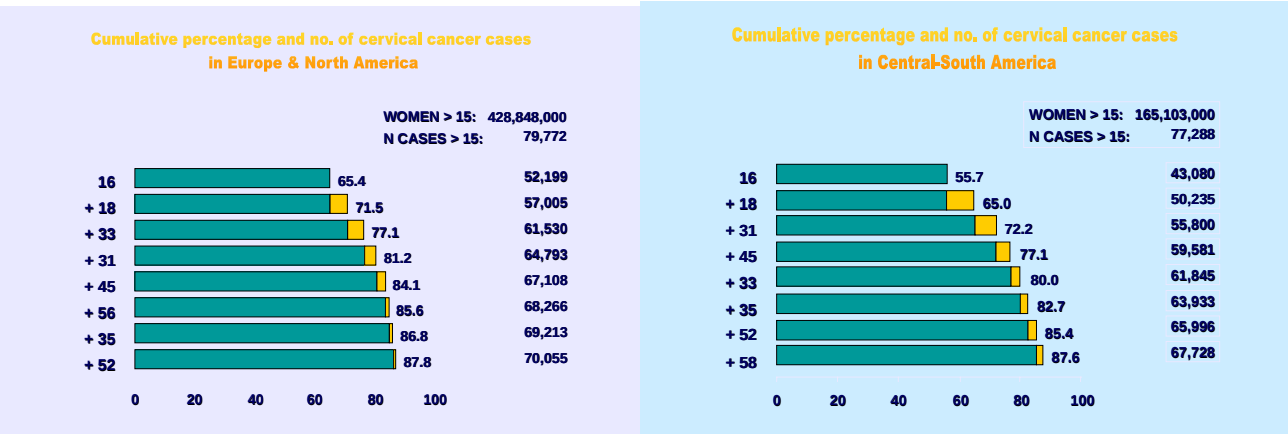
The global epidemiology of HPV and cervical cancer *(Dr Nubia Muñoz)* and proposals for further data collection *(Dr Sylvia Franceschi)*

There are an estimated 409 400 new cases of cervical cancer in developing and 83 400 cases in developed countries annually. The highest incidence rates are observed in sub-Saharan Africa and Latin America. Incidence rates are now low in developed countries, but this pattern is relatively recent. Before the introduction of screening programmes in the 1960s and 1970s, the incidence in developed countries was similar to developing countries today. India, with over 130 000 new cases estimated to occur in 2002, accounted for approximately 25% of the world's burden of cervical cancer.

There are substantial global data on the prevalence of cervical cancer and its precursors, and on the distribution of HPV types among patients with cancer or precursor lesions. These data derive from a total of over 3600 women with incident, histologically confirmed cervical cancer, in two IARC multi-centre studies. The International Biological Study on Cervical Cancer recruited women with cervical cancer in 22 countries, and multi-centre case–control studies recruited women with cervical cancer in 10 countries in Africa, the Americas, Asia and Europe. PCR-based methods were used for the detection and typing of HPV DNA in cells from tumour biopsies and/or cervical Pap smears. Results from these studies have shown that HPV is a necessary cause of cervical cancer and that high parity, long-term use of oral contraceptives and tobacco smoking are important cofactors.

The five most common HPV types in squamous cell cervical carcinoma vary to some extent by region, as illustrated in Figures 1a and 1b (see Muñoz et al., 2004a, for full details). In all regions, types 16 and 18 are the most common, together accounting for 73.5% of cancers in Asia, about 65% in Africa and central/south America, and 71.5% in Europe and the United States. The next most common genotypes include types 45 in Africa and Asia; 31 in Latin America, 33 in Europe and North America and 58 and 52 in Asia.

Figure 1: Cumulative percentage and numbers of cervical cancer cases attributed to the most frequent HPV genotypes, in women aged 15 years and older, in (a) Europe and North America and (b) Central–South America

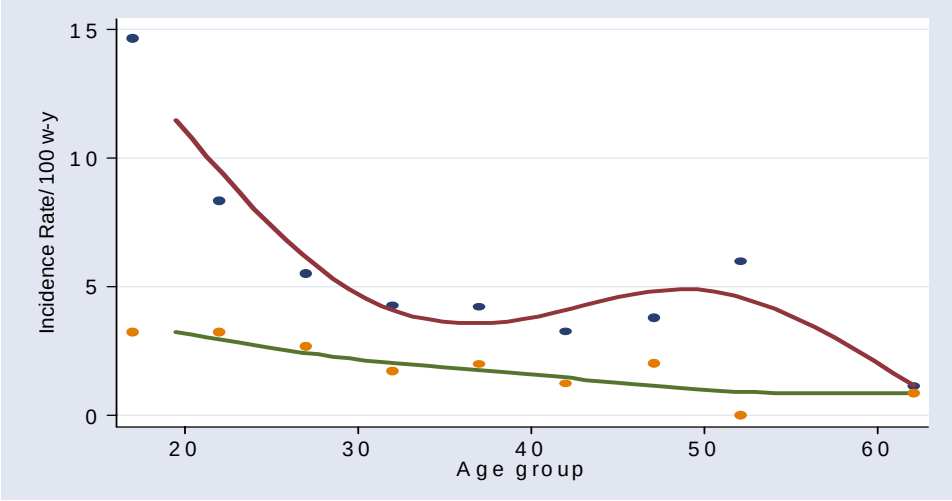


Source: Reproduced with permission of John Wiley & Sons from Figure 1d and 1b of Muñoz et al. (2004a).
© 2004 Wiley-Liss, Inc., A Wiley Company

IARC is also collecting data on the distribution of HPV types in women with normal cervical cytology, through cross-sectional surveys in 15 countries. Low-risk, intermediate-risk and high-risk areas are represented, and each survey includes approximately 1000 women, with 100 women per 5-year age group between 15 and 65+ years. A standardized risk factor questionnaire is administered. Overall HPV prevalence varies 20-fold, from 1.4% in Barcelona, Spain, and 1.6% in Hanoi, Viet Nam, to 25.6% in Nigeria; and, in general, it correlates well with the incidence of cervical cancer.

More than 50% of sexually active women become infected by anogenital "high-risk" types at some time, of which about 40% are HPV 16 and 18. In a cohort study of Colombian women, the age-specific incidence of infection with high-risk types was found to be highest in the late teens and 20s, with a second peak in middle age (Muñoz et al., 2004b; see Figure 2 below). Persistent infection with the same high-risk type is considered to be a predictor for moderate or high-grade cervical intra-epithelial neoplasias, and thus an intermediary step on the causal pathway to cancer.

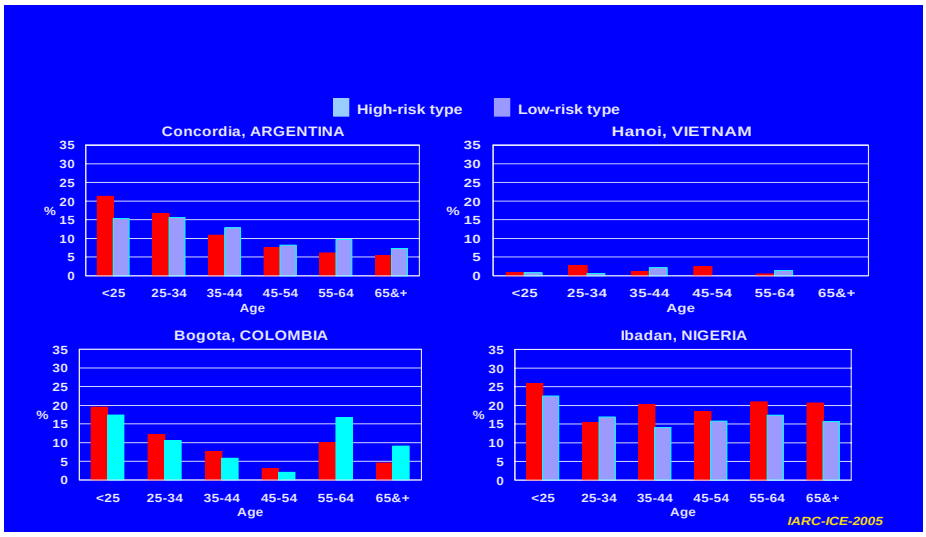
Figure 2: Age-specific incidence per 100 women-years of high-risk (upper curve) and low-risk HPV types among cytologically normal women in Bogotá, Colombia, 1993–2001



Source: Reproduced with permission from the University of Chicago Press from: Muñoz N et al. (2004b). © 2004 by the Infectious Disease Society of America

Age-specific trends in the prevalence of HPV infection vary between countries. In Bogotá, Colombia, as well as in Costa Rica and Mexico, there is a bimodal distribution with a first peak in young women and a second peak in women over 50 years of age, similar to the findings from the prospective study of HPV incidence in Colombia shown in Figure 2. In Concordia, Argentina, however, prevalence of both low-risk and high-risk HPV types is highest in women aged <35 years, then falls progressively with age. A third pattern of age-specific prevalence is seen in Ibadan, Nigeria, where the prevalence of low-risk and high-risk types is high across all age groups (Figure 3). Similar flat curves for HPV prevalence have been found in a few areas, particularly rural areas, where cervical cancer incidence is high (e.g. southern India and Peru) suggesting that the variations of HPV prevalence by age do not only reflect the natural history of HPV infection but also cohort effects (e.g. differences in the probability of being infected across different generations of women in different countries).

Figure 3: Prevalence of cervical HPV DNA by age and HPV type among women with normal cervical cytology



Source: IARC Multi-centre HPV Prevalence Survey. Figure kindly provided by Dr Silvia Franceschi

The age-standardized prevalence of HPV 16 infection is fairly similar across all regions, and ranges from 1.5% in Europe to 3.2% in Africa. The prevalence of other high-risk types, however, is much higher in Africa (14.6%) than Europe (2.3%), with other regions being intermediate, and similar differences are seen for the prevalence of low-risk types.

In summary, data so far indicate that overall the prevalence of HPV infection is highest in Africa. Among women with HPV infection, compared to HPV-positive women in Europe, HPV-positive women in Africa are relatively less likely to be infected with HPV 16 and relatively more likely to be infected with low-risk HPV types and high-risk types other than HPV 16 (notably HPV 35). HPV-positive women in South America and Asia have intermediate patterns of HPV infection (Clifford et al., 2005). Data from the Middle East are lacking. Dr Silvia Franceschi described IARC's plans to expand population-based HPV survey to areas of the globe where no current information is available in order to compare HPV prevalence in young and old women, and the frequency of high-risk HPV types other than 16 and 18. Priority areas for study are those at high risk for cervical cancer (e.g. sub-Saharan Africa, Eastern Europe), and those where social changes and/or urbanization may increase HPV infection among young generations (e.g. China, Mongolia, Turkey).

Constraints on interpreting the data on HPV prevalence among women with normal cervical cytology were discussed. The Middle East and sub-Saharan Africa have been underrepresented in these surveys and more data are needed to represent the wide range of settings in these regions. To date, there are relatively few data from girls aged 10–15 years. The data are from cross-sectional surveys, and hence differences in age-specific rates of cancer and of HPV may reflect either true age-specific differences in risk, or cohort effects (changes over time in risk), or both. In addition to between-country variation, there are interesting differences within countries. In Viet Nam, for example, HPV prevalence and cervical cancer incidence in Ho Chi Minh are about six times higher than in Hanoi city, clearly for historical rather than genetic reasons. Such differences should be further explored to understand their

causes. HPV prevalence can change rapidly with changes in lifestyle, thus even countries such as China, where HPV prevalence is currently very low, need to monitor the situation closely.

Dr Franceschi also presented IARC's suggested approach to the future post-licensing evaluation of the impact of HPV vaccines. The prevalence of HPV is expected to decline in a vaccinated population, but the vaccine effect can be confounded by changes in sexual behaviour. HPV types **not** included in vaccine can act as "controls" to account for any background changes in HPV prevalence that are not related to vaccine. Thus, one way to evaluate vaccine impact would be to monitor the ratio of HPV 16/18 to other high-risk types, which should be lower in follow-up studies after vaccine introduction than in baseline studies before vaccine introduction.

Update on HPV vaccine trials *(Dr Elaine Esber and Dr Gary Dubin)*

Two pharmaceutical companies, GlaxoSmithKline (GSK) and Merck & Co., Inc., have developed candidate prophylactic HPV vaccines and presented updates on their vaccine evaluation programmes. The US National Institutes of Health developed a candidate HPV 16 vaccine but subsequently concentrated its resources on testing the commercially viable GSK vaccine candidate in independent trials in Central America. At the time this decision was made, Merck's trials were already well underway. The vaccines are developed from DNA-free virus-like particles (VLPs), synthesized by self-assembly of fusion proteins of the major capsid antigen L1. Merck's vaccine is a quadrivalent vaccine containing L1 VLPs of types 6, 11, 16 and 18 expressed in *S. cerevisiae* yeast. Inclusion of types 6 and 11 in a prophylactic vaccine is expected to prevent more than 90% of cases of genital warts and to protect against the early cervical dysplasia seen with types 6 and 11. GSK's vaccine contains VLPs of types 16 and 18 and is based on recombinant baculovirus technology.

These candidate vaccines are expected to be able to prevent about 70% of cervical cancer cases worldwide, among women who have not yet been infected with HPV of high-risk types (to date, there are no predictions regarding prevention of cancer among women who have already experienced an infection). The prevalence of types 16 and 18 varies between countries, however, and the coverage would be slightly lower (around 65%) in Latin America and sub-Saharan Africa. A vaccine that included the seven most common HPV types worldwide (16, 18, 45, 31, 33, 52, 58) is predicted to be able to prevent 87% of all cases, with little regional variation. It was noted, however, that addition of multiple new VLP types in a single vaccine might present technical hurdles for manufacturers.

Proof of principle studies by both companies have given highly promising results. Vaccine efficacy was 100% in preventing persistent HPV infection by the genotypes included in the vaccine, in both studies (Koutsky et al., 2002; Harper et al., 2004; Villa et al., 2005). Persistent HPV infection is a key biological intermediate in cervical carcinogenesis. There are also encouraging results concerning prevention of cervical intra-epithelial neoplasia.

Pivotal trials of efficacy against CIN 2/3+ (high-grade precancerous dysplasia associated with a vaccine type) are ongoing in young women aged 15–25 years. Merck expects to submit a licence application to the United States Food and Drug Administration (FDA) in the fourth quarter of 2005, and GSK expects to file in EU/International in 2006. Merck's phase III trials of its candidate vaccine (Gardasil™) have enrolled over 25 000 women in 34 countries, at about 150 sites. The programme will have up to 3.5 years of post-vaccination follow-up, and will define efficacy against vaccine type-related CIN 2 or worse, all grades of CIN, and genital warts. In the participating sites in the Nordic region, which has mass-screening programmes and legislation that allows registries to use data for research, long-term follow-up will be conducted to evaluate the duration of efficacy and long-term safety.

GSK's vaccine is being evaluated in two phase III trials covering over 90 sites in 15 countries. A global multi-centre trial is enrolling 18 000 women aged 15–25 years in Asia Pacific, Europe, Latin America and North America. The National Cancer Institute (NCI) efficacy study is a population-based trial in Guanacaste, Costa Rica, that is enrolling about 12 000 women aged 18–25 years. Both trials are assessing CIN 2 and worse endpoints.

Both companies are including in trials women who already have evidence of prior or ongoing HPV infection, but the primary endpoint will be evaluated among women who were HPV-naive at recruitment. Data may eventually be available, therefore, on efficacy against CIN 2 or more severe conditions among women who had HPV infection prior to vaccination. This would greatly help to define the upper age limit to initiate vaccination. Bridging immunogenicity and safety studies are being

conducted in younger age groups, down to 9 years of age (boys are included in Merck's studies) and in women >23 years old. Efficacy (infection and CIN) in women aged 24 to 45 years will be demonstrated through large trials by both companies. Merck has recently begun a trial among HIV-infected persons in the USA.

Men have high rates of genital warts, and transmit HPV to women, while homosexual men are at increased risk of anal cancer. Merck has, therefore, a vaccine evaluation programme in boys and young men, in studies to evaluate efficacy against genital warts, HPV infection and anal precancer.

Immune correlates for protection and the ability to bridge between populations were discussed. It was pointed out that if the vaccine had a high efficacy as predicted, the breakthroughs required to determine correlates of protection would not be available. If bridging studies showed immune profiles similar to those found in the efficacy trials, it would be fair to assume a likely similar efficacy. The situation would be more difficult, however, if immune markers (e.g. serum antibody levels) were lower in the subjects included in the bridging studies than in the efficacy studies, because the protective level of antibody required is not known and thus the clinical significance of any difference in antibody levels would be difficult to interpret.

There is also a lack of an identified marker for predicting the duration of protection. This will have to come from longer-term follow-up of vaccine recipients. As is the case with other vaccines, a decline in antibody levels over time is being seen, despite continued efficacy in phase II trials, and the implications of this decline in antibody levels are not known. The meaning of persistence of antibody is also not known or whether priming the immune system will be sufficient for long-term immune memory. The presence of local antibodies was queried. These were found in phase IIa studies and are being studied in the phase III trials, though the significance is unknown.

The potential administration of HPV vaccines concurrently with other vaccines was discussed, and although data on simultaneous administration are not currently available, co-administration studies are underway and further studies are planned.

The possibility of replacement of one viral type in a niche created by vaccination was discussed, with the view expressed that while this was a theoretical concern, it was unlikely to be an issue, and will be explored in large population-level phase IV trials. Conversely, the possibility of cross-protection against other HPV high-risk genotypes is being evaluated in ongoing trials and, if shown, would lead to a greater reduction in cervical cancer.

In a related presentation, Dr Matti Lehtinen outlined data that will be obtained in Finland from follow-up of ongoing phase III vaccine trials, and from a planned phase IV (post-licensure) vaccine trial. The objectives of Finnish phase III/IV high-risk HPV vaccination trials are to define vaccine efficacy against high-risk HPV infection and its long-term sequelae; evaluate the means for significant reduction of common high-risk HPV infections and establish new public health policy against the common STIs and their sequelae. Altogether 7000 girls aged 16–17 years participating in the phase III HPV vaccination trials, and 22 000 non-vaccinated girls aged 18–19 years who would have been willing to participate in the phase III trials, will be passively followed up to detect new cases of cervical carcinoma precursors through the population-based Finnish Cancer Registry. General cross-over vaccination may not be organized because the girls will be invited to participate in organized screening for cervical cancer starting at the age of 25 years. The first intention-to-treat analyses on vaccine efficacy against cervical cancer are anticipated in 2012 and 2014.

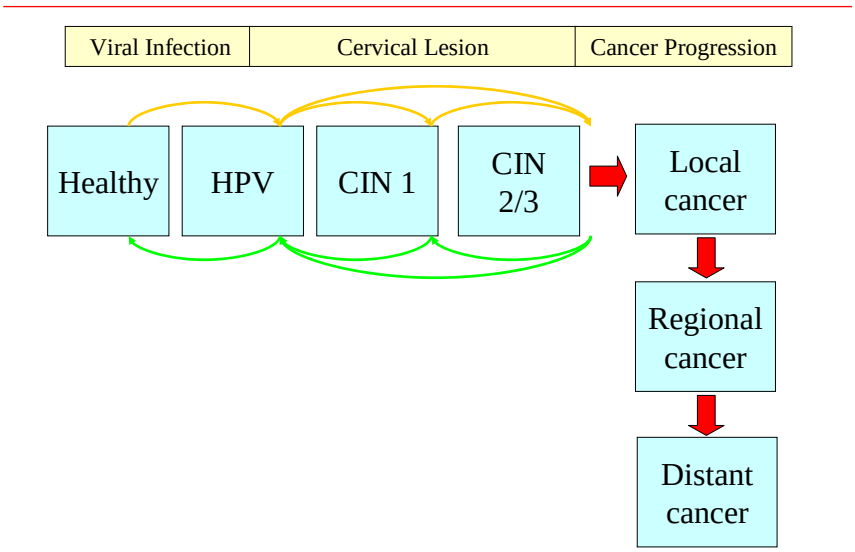
A community (HPV or hepatitis B vaccine) randomized phase IV trial is planned to start in 2006 in Finland and has been submitted for funding and to appropriate ethical review committees for approval.

The protocol aims to stratify communities by STI and cancer history; randomize communities to HPV vaccine or hepatitis B vaccine, and vaccinate up to 70 000 adolescents before sexual debut in four birth cohorts of 13–14 year old girls, within two school years. Cross-over vaccination will be conducted after 3–5 years. Assumptions underlying the trial design are that prevalence of high-risk HPVs is 20% by the age of 18–19 years among girls in non-vaccinated communities, and prevalence is reduced by 65–95% by the age of 18–19 years in communities where 30% to 70% of the preadolescents received HPV vaccine. This community randomized phase IV trial is considered feasible in Finland provided cross-over vaccination is organized.

Cost effectiveness of HPV vaccines *(Dr Sue Goldie and Dr Evan Myers)*

Research groups led by Dr Sue Goldie and Dr Evan Myers have developed comprehensive state-transition Markov models of the natural history of HPV and cervical cancer that are used to project cancer incidence and mortality, life expectancy, lifetime costs and incremental cost–effectiveness ratios (i.e. the net increase in health care cost divided by its net additional health benefit, compared with the base-case strategy) associated with different cancer prevention policies. The approach taken is to develop a computer-based model of the natural history of disease (Figure 4). The models simulate a cohort of women beginning at e.g. age 12 and follow them through to e.g. age 85 years. Movement through the health states of the model (i.e. HPV infection, CIN 1, CIN 2–3, cancer) over time is based on transition probabilities derived from a combination of clinical and economic data from multiple published and unpublished sources (clinical trials, cohort studies, national surveys, databases). The models are *calibrated* to achieve the best possible fit to population-based data in a given setting (that may be global or country-specific) and *validated* by predicting outcomes that are compared for consistency with observations from independent data. Different interventions are then "simulated" to estimate their consequences (e.g. life expectancy, quality of life, costs).

Figure 4: Disease simulation model



Source: S. Goldie, April 1995

These models have been validated and published for the United States (see e.g. Goldie et al., 2003; Kulasingam & Myers, 2003). In collaboration with WHO, the models are being applied to other settings, exemplified by the United Republic of Tanzania and India (Chennai and New Delhi). Strategies assessed have included vaccination (initiated at age 12 years or at a later age), cytological screening (varying numbers of screening visits using different screening methods, e.g. direct visual inspection, Pap smear, or HPV testing, at different ages), and combined vaccination and screening strategies. Sensitivity analyses assess the effects of variation in assumptions regarding quality and coverage of cervical cancer screening, vaccine efficacy and coverage, waning immunity and competing risks associated with prior infection with non-16/18 HPV types in vaccinated women. The assumed cost for vaccine was US$ 2 per dose, but sensitivity analysis was done for varying costs of up to $6 per dose (the anticipated prices of the vaccine for private or public markets are not yet known). Vaccine costs in the model also included costs of the programme based on a WHO micro-costing of hepatitis B vaccination. The "no intervention" scenario included the costs of minimum treatment and palliative care.

Although cost components differed between countries, strategies were identified that would be considered very cost effective. The degree of predicted cancer reduction was most sensitive to the ability to enhance linkages between screening and treatment (i.e. if lesions are detected, adequate treatment must be available to make a difference to cancer incidence and survival). Cost–effectiveness results were most sensitive to the screening target age and costs associated with cancer (treatment or productivity loss). The choice between different screening methods was most sensitive to test performance and cost.

Preliminary findings of the Indian case study using base-case estimates suggest that a combination of a one-time screen with HPV and vaccination may be a cost–effective strategy. Duration of protection and age that vaccine is given are key considerations. These preliminary results also suggest that regional differences in cancer incidence will be an important determinant of the effectiveness and cost effectiveness of a vaccine to prevent infection with HPV. Compared to New Delhi, for example, data from Madras show a higher risk of cervical cancer. In this setting of high cancer incidence, a combined strategy of two screening tests or screening and vaccination may be preferable to a strategy that uses a single screening test or vaccination alone. In the exploratory Tanzanian case study, in the most optimistic vaccine scenario evaluated (100% coverage, 90% vaccine efficacy with no waning of protection over time), the lifetime risk of cervical cancer was reduced by nearly 60% with HPV 16/18 vaccination in early adolescence; 12–43% by screening depending on modality and frequency; and 66–80% by combined vaccination and screening. HPV vaccination in the United Republic of Tanzania may be promising and a combined approach of vaccination of young girls and single-lifetime screening in older women is likely to be cost effective. Results were most sensitive to vaccination coverage, cost of administering the vaccine, and the duration of protection provided by vaccination.

The findings from these and other case studies were reported to be limited by the lack of adequate data for the following:

- population-based data for HPV prevalence of all high-risk types;
- the natural history of HPV in older women (in places where a second peak in HPV infection occurs, does this represent new infection or re-activation of latent infection?);
- stage-specific cancer data;
- regional differences in factors not included in the model that may affect when cancer is clinically detected – access to health care, degree to which symptoms of early cancer are considered abnormal, etc.;
- data on the costs associated with screening, diagnosis and treatment, including costs of training and monitoring;
- unidentified heterogeneities in HPV incidence and vaccine effectiveness;
- duration of vaccine effectiveness;
- effect of HIV on vaccine effectiveness and cervical cancer incidence; and
- data on vaccine effectiveness in women who have already been infected.

The lack of inclusion of herd immunity in the vaccination modelling was noted. Potential effects of cross-protection or of replacement infection, should either of these occur, have not been incorporated. Dr Goldie briefly described the future plans for use of a transmission dynamics model, which generates similar results to those of the models published by Dr Geoffrey Garnett. Future work will build on partnerships with IARC, the University of Barcelona and other groups to obtain empirical data to answer the key uncertainties around the parameters in the model.

Programmatic issues regarding HPV vaccine introduction *(Dr Ciro de Quadros*)

Currently, in developing countries, the main vaccines administered to persons in the age group 9–25 years are: tetanus toxoid (up to five doses are administered through routine programmes, usually at antenatal clinics, and many countries also conduct mass campaigns to deliver two or three doses to women of childbearing age); and measles and rubella vaccines (through mass campaigns of boys and girls, usually conducted once in this age group – follow-up campaigns typically target only children under 5 years of age). In the lowest income countries, there are currently no routine health service programmes that reach a high proportion of children of this age group on a continuous basis. School enrolment rates have increased over the last decade or so, but attendance falls rapidly especially in girls. By age 9, a minority of girls are still in school in many countries, although there is considerable between-country and within-country variation in school attendance rates by age and sex.

Elimination programmes for measles, rubella and neonatal tetanus have had great success in the Americas. These programmes have included mass campaigns of women and men and attained very high coverage. Some campaigns have been conducted among women only, while others included men. In all instances, acceptance of vaccination has been high in the target age groups, which have extended up to age 30–40 years. This experience could be built upon to develop annual campaigns for HPV and other interventions.

There may be several programmatic challenges in introducing HPV vaccines in many countries. On the one hand, it may seem attractive to link HPV vaccine to tetanus toxoid administration, because both are targeted to young adult women, have a schedule requiring three or more doses, and have similar intervals between doses. On closer analysis, however, the following problems with linking these two vaccines can be anticipated (Jos Vandelaer, UNICEF/WHO, personal communication). TT vaccine coverage through routine services is only around 50% globally, and much of the vaccine is given to women who have already had one or more pregnancies (though ideally, immunity to both infections would be assured before the first pregnancy). TT campaigns ("supplementary immunization activities", or SIAs) are usually a one-time activity in a given country and target only the districts considered high risk for neonatal tetanus. Funding for SIAs may not be continued after 2008 as it is expected that most countries will have completed these activities in the high-risk areas by then, and the emphasis will shift to ongoing routine immunization. TT is also given to school-aged children, but can be given at school entry since the duration of immunity is known, and early vaccination offers direct protection to schoolchildren. In contrast, for HPV vaccine it will be difficult to recommend school-entry vaccination initially, because data on effectiveness in this age group are not available, data on duration of protection are not available, and children of this age group are not at risk of HPV infection hence do not gain immediate direct benefit from vaccination at this age.

For countries with low school attendance among girls aged 9 years and upwards, the most practicable delivery method may be the conduct of annual immunization campaigns, for example by holding an "annual young persons immunization month" or an "annual young persons' health month". HPV vaccination could be combined with other interventions depending on local circumstances. Such interventions could include any or all of: rubella and/or measles-containing vaccines, tetanus toxoid vaccine, anthelminthics, bednets, anti-tobacco education, etc.

In the long term, there is considerable interest in studies to determine the potential to integrate HPV vaccine into routine infant or childhood immunization schedules. Vaccination at school entry would be more feasible through routine programmes than vaccination of girls after 9 years of age. It will take many years to generate information that would allow this to be recommended, and hence such studies should begin as soon as possible. There are theoretical reasons to expect that the response to

vaccination would be even better in infants than in adults, and hence data that will be obtained on the kinetics of the response in adults cannot necessarily be extrapolated to infants. Inclusion of one or two doses of HPV vaccine in infant immunization schedules might mean that only one dose is needed in the pre-teen or early teen years, which would be much simpler to deliver programmatically. There was considerable support for the early initiation of the long-term studies that will be needed to answer this question.

3. Discussions

Attitudes to HPV vaccines

The discussions on programmatic issues highlighted the need to understand community and governmental attitudes to HPV vaccines. In many countries, awareness of the role of HPV in cervical cancer is low. There is also great potential for misperceptions about HPV and HPV vaccines. Examples of potential misperceptions noted with concern by participants included the following:

- because HPV vaccine is a vaccine against a sexually transmitted infection: "If I'm vaccinated, I'm protected against all STIs";
- because HPV is sexually transmitted: “Giving a vaccine to prevent it, means health authorities are encouraging promiscuity”; and
- because HPV vaccine prevents cervical cancer: "I'm protected and I don't need to get screened".

In addition:

- there may be confusion between HPV and HIV due to the similarities of the acronyms; and
- there are false expectations among some health professionals that HPV vaccine could reduce transmission of HIV, because of knowledge that other STIs influence HIV transmission.

Some participants commented that men could be very motivated to receive a vaccine that would prevent male anogenital cancers. Current trials, however, do not have male cancers as endpoints. In the absence of data on protection against cancers, HPV vaccines cannot be promoted as vaccines against cancer in men. It was also noted that one company will request approval for vaccination of both sexes to prevent both genital warts and cervical cancer, while the other will only label the vaccine for females, for prevention of cervical cancer. This could create confusion in many countries.

Several participants expressed concern that promoting HPV vaccine as an intervention against sexually transmitted infection might reduce the acceptability of vaccine in some parts of the world. Although HPV infection is very common, many women may not perceive themselves or their children to be at risk for a sexually transmitted infection (often linked with promiscuity and core groups), which may undermine the cervical cancer primary prevention efforts. On the other hand, in some countries such as South Africa, awareness of the problems of STIs is high and stigma has been greatly reduced. There is substantial interest in vaccines that can prevent STIs, especially HIV. A vaccine against an STI could therefore be welcomed. There was agreement that local research will be needed to develop appropriate materials for information and education activities.

Despite these concerns, the experience from vaccine trials gave cause for optimism, since there have been very high participation rates in both industrialized and developing country settings. In the USA, research suggests that acceptability will be high once the vaccine and nature of the disease have been

explained. Market research often finds people are surprised not to have been better informed, and there is a low level of knowledge of HPV and cervical cancer amongst physicians and other health care professionals. In Finland, acceptability among 13 year old girls in a vaccine trial was good with 90% giving consent. In Costa Rica acceptance for entry into the trial has been 95%. There was consensus that much needs to be done to educate health professionals and communities about the importance of cervical cancer, its causes, and the means of prevention through screening and vaccination.

Information gaps regarding HPV and HPV vaccines

Following the updates on HPV epidemiology and vaccine trials, the outstanding information gaps relating to the potential future introduction of HPV vaccine into national immunization programmes were reviewed in small group sessions. Topics highlighted by the groups are summarized in Table 2.

Table 2: Information gaps for development of guidelines

Topic / Area	Information needed
Vaccine production and prices	Current capacity Ability to scale-up Possibility for future technology transfer to emerging manufacturers Price and tiered pricing prospects
Vaccine schedules	Number of doses needed for adequate protection Flexibility in the primary immunization schedule, e.g. 2 or 3 doses given 1 year apart instead of a 0, 2, 6 month schedule Duration of immunity after primary immunization in adolescence/ adulthood Whether booster doses will be needed Immunogenicity in children <9 years old, including infants Duration of immunity after primary immunization of preschool-aged children or of children at school entry Safety and efficacy in Africa Safety and immunogenicity in pregnant women Safety and immunogenicity in populations with a high prevalence of HIV
Epidemiology of HPV and cancer	Data on HPV genotype distribution among women with normal cytology, in the areas of the world where there is currently very little information, such as Africa, China, central Asia and the Middle East Age at onset of sexual activity in different countries and regions and its relation to the regional differences seen in HPV prevalence and type distribution Investigate whether concurrent causes of immune impairment (parasites, HIV, etc.) contribute to the high prevalence of HPV types other than 16 in some populations Conduct surveys to obtain data needed for models of disease transmission, in women aged around 45 years (for current burden of disease) and women aged around 20–30 years (to predict future burden of disease). Surveys should include cervical cytology with HPV DNA testing on cervical cells, HPV serology, and questionnaires on sexual behaviour and other epidemiological risk factors Understand the temporal variations in HPV prevalence, e.g. the reported decline in HPV prevalence in Mumbai, India, in the absence of any intervention Data on other HPV-related cancers including penile, anal, vulvar, vaginal and oro-pharyngeal cancers
Natural history of HPV	Investigate factors important for clearing HPV e.g. host immune response; susceptibility markers Investigate reasons for the 2nd peak in HPV infection – latency versus new infection? Could data come from vaccine trials? What is the shape of the curve of HPV infection in different countries and regions?
Surveillance methods	Develop methods for monitoring trends in HPV prevalence, which can be used to monitor the effectiveness of vaccination post-licensure: e.g. sentinel surveillance to monitor HPV DNA prevalence among women at the time of first delivery; inclusion of cervical cancer in studies using "verbal autopsies"
Development of appropriate and relevant information, education and communications activities	Determine knowledge and attitudes towards cervical cancer prevention, HPV and other HPV-related diseases, in order to develop messages through consultation with: Health care providers at all levels Community leaders including school teachers and religious leaders Politicians Parents Adolescents

	Attitudes of men and women to the potential targeting of HPV vaccine only to women Attitudes to genital warts and their possible prevention by vaccine
Evaluation of vaccination effectiveness post-licensure	Pre- and post-vaccination surveillance of cervical cancer and HPV-type distribution may be difficult to achieve worldwide (and variation in the sensitivity of surveillance may lead to false conclusions), therefore will need to conduct demonstration projects in certain countries (criteria for country selection to be defined). Potential methods to evaluate impact in demonstration projects include the following: • In phased vaccine introduction, use sites introducing vaccine late as "controls" for sites introducing early (but will the time difference between sites be long enough for lesion endpoints?) • Use age groups just older than the designated target age groups as controls • Consider community-randomized introduction, with non-placebo control and endpoint of CIN 2/3 (requires screening to be in place) or cancer (requires registry and diagnostic services to be in place) • Monitor the prevalence of HPV types, and the ratio of types 16&18 to other types, to control for possible temporal variation in HPV infection due to factors other than vaccination (e.g. changes in sexual behaviour)
System questions for design of delivery strategies	Human resource and other capacity Infant first dose of diphtheria–tetanus–pertussis (DTP1) coverage through routine services (as indicator of access to health services) and coverage and cost of previous immunization campaigns (as indicator of ability to implement supplementary immunization activities) School attendance rates by age and sex (note, actual attendance may be very different from official enrolment rates) School health services in place, and their coverage Adolescent health services in place, and their coverage Acceptability of different potential strategies among different groups Financing options and potential sources of funding – experience in financing immunization, reproductive health, cancer control; local fund-raising capacity Cervical cancer-screening programmes in place; their coverage, quality, cost and impact Ability to establish screening as part of comprehensive cervical cancer control How will programmes be monitored – vaccine coverage; HPV prevalence and serotype distribution; cervical cancer mortality?

4. Update on work by PATH and WHO in the field of HPV and HPV vaccines

PATH ***(Dr Jacqueline Sherris)***

Many of the data outlined in Table 2 will be generated from ongoing trials and acceptability studies that companies are conducting, and from projects planned at Harvard (modelling of costing issues), IARC (epidemiology of HPV and cervical cancer), in Finland (evaluation of vaccine effectiveness), and at PATH and WHO, with support from the Bill and Melinda Gates Foundation and other sources. PATH and WHO presented overviews of their work relating to HPV vaccines and their future plans.

Dr Jacqueline Sherris summarized past work at the Program for Appropriate Technology in Health (PATH) relating to cervical cancer prevention, funded by the Bill and Melinda Gates Foundation. The Alliance for Cervical Cancer Prevention (www.alliance-cxca.org) has assessed the safety and effectiveness of new screening and treatment approaches; developed service-delivery guidelines for using new technologies and protocols; involved communities in programme planning, implementation and evaluation; and advocated for appropriate and effective cervical cancer prevention programmes. Through their work, they have found that demand for cervical cancer prevention services is strong among women and communities, and that organized prevention programmes are feasible and can be integrated with existing services. The START (Screening Technologies to Advance Rapid Testing) project aims to develop rapid biochemical tests appropriate for low resource settings that detect precancerous cervical lesions. These tests (for HPV DNA and HPV protein biomarkers) may enhance acceptability and coverage, reproducibility of results and equity of service delivery, as well as accuracy and cost effectiveness of testing. PATH's work related to HPV vaccine aims to advance HPV vaccines and promote evidence-based cervical cancer prevention approaches. In the planning phase from April 2005–March 2006, PATH aims to build partnerships with industry; complete an investment case for HPV vaccine using the Global Alliance for Vaccines and Immunization (GAVI) framework; clarify GAVI, UNICEF, and Pan American Health Organization (PAHO) Revolving Fund positions on HPV vaccine and develop a strategy for working with international/regional procurers in 2006–2009. They aim to complete four country assessments of preparedness for HPV vaccine introduction: two in Asia, one in Latin America, and one in Africa. Findings related to programme capacity, policy readiness, sociocultural issues, service-delivery options, clinical study needs and so on, will be synthesized and used to inform all other planning components. PATH will integrate HPV vaccine information into the Alliance for Cervical Cancer Prevention (ACCP) information/advocacy mechanisms, update the report *HPV Vaccines: Promise and Challenges*, and survey stakeholders to understand information needs, in order to develop an advocacy/communication plan for 2006–2009, in collaboration with WHO. By March 2006, they expect to have a detailed road map for 4–5 years of work to provide evidence and establish systems for introducing HPV vaccine in several developing countries in different geographic regions.

WHO ***(Dr Teresa Aguado, Dr Nathalie Broutet)***

Dr Teresa Aguado summarized the work of the WHO Initiative for Vaccine Research (IVR) in the field of HPV vaccines. In the last six years, WHO has hosted technical meetings on the status of development of prophylactic vaccines against HPV infection; the assessment and harmonization of

laboratory diagnostic procedures related to HPV vaccine research and development; the development of international HPV reference reagents; and key issues for HPV vaccine trials. The report of the 2003 meeting on HPV vaccine efficacy outcomes (Pagliusi & Aguado, 2004) summarized the expert advice for decisions regarding endpoints for clinical trials, with recommendations on endpoints for evaluating HPV vaccine efficacy and additional research for evaluating HPV vaccines in developing countries, including long-term studies to evaluate duration of vaccine protection, and ethical considerations for HPV vaccine efficacy trials.

WHO launched international collaborative studies to harmonize HPV reagents for diagnostic reagents, and reviewed the data at a technical workshop in 2003; generated data on manufacturing costs of HPV vaccine candidates based on current technologies; updated data on HPV type-specific prevalence in cancer and lesions worldwide, in collaboration with IARC (Clifford et al., 2003a; 2003b); assessed manufacturing capacity for recombinant vaccines in developing countries, and assessed intellectual property issues related to HPV vaccines. WHO has created a basis for public–private partnerships, e.g. by obtaining a commitment from major industrial groups to collaborate with the public sector; provided expert advice for regulatory pathway decisions at FDA and European Medicines Evaluation Agency (EMEA) regarding endpoints for clinical trials, raised interest in HPV vaccine at different levels: internal, with the reproductive health and cancer programmes, and external, disseminating information and "advocating" for a coordinated public sector effort.

Future work of WHO IVR aims to facilitate the evaluation and review of clinical data, by harmonizing and standardizing laboratory procedures and creating a global HPV laboratory network to facilitate vaccine licensure and monitoring in developing countries. International Standard Reagents, with standard operating procedures for their use in HPV DNA and antibody detection assays, will be developed to facilitate the evaluation of virological and immunogenicity data. National regulatory authorities in developing countries will be supported through the Global Training Network to oversee HPV vaccine studies and vaccine use.

An international multi-disciplinary policy platform will be created to set a global agenda for future HPV vaccine introduction in consultation with regions and countries, and guidelines for HPV vaccine introduction will be developed. Information will be disseminated partly through a WHO Information Centre on HPV and Cervical Cancer, to facilitate global, regional and country-specific decisions on current and novel options for cervical cancer prevention.

Dr Nathalie Broutet and colleagues summarized the work of WHO's Reproductive Health and Research (RHR) group in the field of HPV and cervical cancer, which is conducted in close collaboration with IVR and the Programme on Cancer Control. A manual on *Comprehensive Cervical Cancer Control: A Guide to Essential Practice,* will be ready by the end of 2005. This has been developed in collaboration with IARC, the International Atomic Energy Agency, and the ACCP, from the perspective of providers at different levels of the health care system. It covers the continuum of care, including understanding anatomy, physiology, prevention, counselling, health education, screening, treatment of pre-invasive and invasive disease, and palliative care. The manual has been reviewed in depth in China, Egypt, India, Lithuania, Trinidad and Zimbabwe.

RHR is piloting the implementation of screening services by visual inspection (VIA) at health centre level, as well as the treatment of VIA-positive lesions by cryotherapy at the district hospital, in a total of seven sites in Madagascar, Malawi, Nigeria, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe. The aim of this project is to assess the adherence to and the feasibility of implementing a cervical cancer prevention programme based on a VIA and cryotherapy approach in Africa. It is hoped that this will provide information on methods to enhance access to cervical cancer screening and

increase utilization of screening services. This information will be important for scaling up the programme to reduce the incidence of invasive cervical cancer.

RHR is also sponsoring research on HPV in HIV-positive pregnant women. The overall study objective is to increase knowledge on the natural history of HPV infections in HIV-seropositive women during late pregnancy and early postpartum and on the prevalence of cervical lesions postpartum. Specific study objectives are to assess HPV prevalence during late pregnancy and HPV incidence from the last months in pregnancy to early postpartum; to determine the prevalence of precancerous lesions of the cervix at three months postpartum and to assess the feasibility of integrating HPV testing during pregnancy as well as HPV and cytology-based screening in the postpartum visit.

RHR's approach to product introduction, and in particular for new contraceptives to increase reproductive choices, has involved the use of a strategic planning tool to identify and prioritize policies and programmatic interventions; undertaking action research to assess the agreed interventions, and scaling up the tested interventions.

HPV vaccine is a critical public health need for all women but particularly for poorer women in less developed countries. The large socioeconomic differences in risk of cervical dysplasia and cancer (Parikh et al., 2003) raise several questions regarding methods to provide equitable access to an affordable quality vaccine, and the role of WHO, industry, other partners and private–public partnerships in facilitating access in less developed countries. For HPV vaccine introduction, strategic questions identified by RHR include the following:

- How accessible are, and what is the quality of, national immunization and cancer screening services, and reproductive health information provided by national health and education programmes?

- What are the target populations?

- How can services incorporate the delivery of an HPV vaccine and address the educational and informational needs?

- How can communities, and particularly women, be empowered to ensure access to and use of an HPV vaccine?

4. Recommendations from the HPV meeting

By 2006, data on efficacy of HPV vaccines against CIN 2 or more severe conditions caused by HPV 16 and 18 will be available for women aged 15–25 years, from at least one company. Vaccines may be licensed with a label for this age group, or, if bridging immunogenicity data are accepted, for females aged 9 years and upwards. One of the vaccines may also be approved for vaccination of males.

Globally, the primary aim of HPV vaccination will be to prevent cervical cancer. At least in the short term, vaccination will be targeted to women and young girls, either from age 15 years or age 9 years. The upper age limit may depend on the epidemiology of HPV infection in the country or region, and on data that will accrue on the effectiveness of HPV vaccines in women who have prior HPV infection of the types included in the vaccine.

There was consensus that countries will expect guidance from WHO as to the place of HPV vaccine in their disease control programmes, once HPV vaccines are licensed. Since it is likely that at least one vaccine will be licensed in 2006, WHO was urged to begin writing guidelines now. HPV vaccine will be an additional tool in the strategies to reduce morbidity and mortality from cervical cancer but will not replace screening and early treatment. Guidelines on HPV vaccine use should, therefore, be developed through an integrated approach with adolescent health, reproductive health and cancer control programmes at national and international levels.

The priority information needs for the development of guidelines on HPV vaccine use can be summarized from a public health viewpoint as follows:

What would a Minister of Health want to know before introducing HPV vaccine?

1. What is the burden of disease related to HPV in their country, or in a country of similar demographic circumstances in the same region?
2. What are population attitudes towards cervical cancer and HPV?
3. What is the peak age of infection with HPV, and what are the implications for the choice of target age group?
4. What is the number of doses needed to generate adequate immunity through the high-risk period, and, in particular, is it possible to use a two-dose vaccination schedule instead of a three-dose schedule?
5. Might HPV vaccination be integrated in the infant immunization schedule, or at school entry, at any time in the future, with or without a booster dose just before the high-risk period?
6. Can the vaccine be administered simultaneously with other vaccines, such as those containing measles and rubella vaccines and tetanus toxoid?
7. What are the cold chain requirements for the vaccine?
8. What is the cost of the vaccine, and what are potential mechanisms to finance this?

Additional research should be promoted to answer the information needs detailed in Table 2 and prioritized above. Much of this research is already planned by vaccine manufacturers, IARC, Harvard

and others. The main gaps for which research is needed but for which definite plans and sources of funds have not yet been identified include:

- evaluation of vaccine safety and efficacy (immunogenicity and prevention of persistent HPV infection) in Africa, particularly populations with high HIV prevalence;
- evaluation of the immune response to vaccine at school entry (when contact with girls would be much easier than in later years) and in infancy (e.g. at age 9–12 months, together with measles or MMR vaccine);
- evaluation of simultaneous administration of HPV vaccine with tetanus toxoid, measles, mumps and rubella vaccines;
- development of toolkits with applied research and surveillance methodologies, to enable countries to conduct local assessments of:
  - knowledge and attitudes of health professionals, teachers, community leaders, parents and adolescents regarding HPV, cervical cancer and HPV vaccines;
  - coverage and quality of adolescent health services; and
  - methods for monitoring and evaluating HPV vaccination programmes.

WHO should work with partners to identify the means to enable this research to be conducted as soon as possible. WHO and partners should help countries create awareness and conduct education and information activities, taking care to avoid potential misperceptions such as those noted during this consultation. The vaccine should be promoted as a vaccine to prevent cervical cancer, but the fact that HPV is sexually transmitted needs to be acknowledged. Infection is widespread and virtually all women are at risk. It should be made clear that it is not only promiscuous people who acquire HPV infection. One suggestion was that the vaccine be called a vaccine against a "sexually transmitted cancer virus". Public health messages with respect to HPV vaccine should be clear, and consistently promoted by all partners. The development of toolkits for local assessments will enable countries to develop messages that are appropriate for the local situation.

WHO will take forward this work through the relevant programmes, regional and country offices, in consultation with partners and expert advisors.

5. References

Clifford GM et al. (2003a). Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *British Journal of Cancer*, 89(1):101–105.

Clifford GM et al. (2003b). Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *British Journal of Cancer*, 88(1):63–73.

Clifford GM et al (2005). Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet*, 366:991–998

Goldie SJ et al. (2003). A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cance*r, 2003;106(6):896–904.

Goldie SJ et al. (2004). Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *Journal of the National Cancer Institute*, 96(8):604–615.

Harper DM et al. (2004). Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*, 364(9447):1757–1765.

Koutsky LA et al. (2002). A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine*, 347(21):1645–1651.

Kulasingam SL, Myers ER (2003). Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *Journal of the American Medical Association*, 290(6):781–789.

Manhart LE, Koutsky LA (2002). Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sexually Transmitted Diseases*, 29(11):725–735.

Muñoz N et al. (2004a). Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *International Journal of Cancer*, 111(2):278–285.

Muñoz N et al. (2004b). Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *Journal of Infectious Diseases*, 190(12):2077–2087.

Pagliusi SR, Aguado MT (2004). Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine*, 23(5):569–578.

Parikh S, Brennan P, Boffetta P (2003). Meta-analysis of social inequality and the risk of cervical cancer. *International Journal of Cancer*, 105(5):687–691.

Smith JS et al. (2003). Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet*, 361(9364):1159–1167.

Villa LL et al. (2005). Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncology*, 6(5):271–278.

World Health Report 2004 (2004). Geneva, World Health Organization.

Zur Hausen H (1999). Papillomaviruses in human cancers. *Proceedings of the Association of American Physicians*,1999, 111(6):581–587.

Annex 1: Agenda

Time	Topic	Presenter
14 April		
9.00	Welcome; and meeting objectives	Joy Phumaphi
9.20	Overview of the link between HPV and cancers	Dr zur Hausen
9.50	Global epidemiology of cervical cancer & HPV	Dr Muñoz
10:30	*Coffee break*	
11.00	Efficacy of vaccines against infection, persistent infection, and CIN 2+; existing data and timelines for ongoing trial results	Dr Esber, Merck
11.30	Efficacy of vaccines against infection, persistent infection, and CIN 2+; existing data and timelines for ongoing trial results	Dr Dubin, GSK
12.00	Cost–effectiveness studies: Tanzania and India	Dr Goldie and Dr Myers
13.00	*Lunch*	
14.00	Proposals for further modelling of vaccination strategies	Dr Goldie
14.30	Potential immunization strategies and links with other vaccine delivery systems	Dr de Quadros
15.15	*Coffee break*	
15.30	Working groups to identify and prioritize outstanding questions on:	
	• Epidemiology of HPV/Cervical cancer	WG chairs:
	• Vaccine efficacy, duration of protection, schedules and interaction with other vaccines	Dr Mbidde Dr Herrero
	• Issues to consider at country level, in deciding whether and how to introduce HPV vaccines	Dr Muhondwa
17.30	Adjourn	
15 April		
8.45	Feedback from working groups	Working group rapporteurs
9.30	Plenary discussion of priorities for gathering additional information and types of research studies needed	
10.15	Proposals for further data on global epidemiology & genotyping	Dr Franceschi
10.45	*Coffee break*	
11.15	Proposal for phase IV evaluation of implementing HPV vaccination in national vaccination programme in Finland	Dr Lehtinen
11.30	PATH activities in HPV	Dr Sherris
12.20	WHO activities in HPV : IVR RHR	Dr Aguado Dr Broutet
13.00	*Lunch*	
14.00	**Closed session of the HEAG**	

Annex 2: List of participants

Dr Ian Frazer, Department of Medicine, University of Queensland, Center for Immunology and Cancer Research, Princes Alexandra Hospital, Woolloongabba, Queensland 4102, Australia
tel: + 61 7 3240 5315 ***fax: + 61 7 3240 5310*** ***email: ifrazer@cicr.uq.edu.au***

Dr Ketayun Dinshaw, Director, Tata Memorial Centre and Professor, Dept of Radiation Oncology, E. Borges Marg. Parel, Mumbai 400 012, India
tel: + 91 22 2413 9318 ***fax: + 91 22 2416 8440*** ***email: dinshaw.tmc@vsnl.com***

Dr Irena Klavs, Head, AIDS/STD/HAI Unit, Communicable Diseases centre, Institute of Public Health of the Republic of Slovinia, Trubarjeva 2, 1000 Ljubljana, Slovenia
tel: +386 1 2441 477 ***fax: + 386 1 2441*** ***email: Irena.Klavs@ivz-rs.si***

Dr Lauri Markowitz, Centers for Disease Control (CDC), DSTD MS E-02, 1600 Clifton Road, Atlanta, Georgia 30333, USA
tel: +1 404 639 8359 ***fax: +1 404 639 8610*** ***email: lem2@cdc.gov***

Dr Nubia Muñoz, Former Unit chief at the International Agency for Research on Cancer, Unit of Field Research Studies, 24 Quai Fulchiron, 69005, Lyon, France
tel: +33 478 42 90 21 (home) ***fax: +33 478 42 90 21*** ***email: nubia.munoz@free.fr***

Dr Punnee Pitisuttithum, Mahidol University, Faculty of Tropical Medicine, The Faculty of Allied Health Sciences, 420/6 Rajvithi Road, Rajthevee, Bangkok, 10400, Thailand
tel: + 66 2 643 5599 ***fax: + 66 2 643 5598*** ***email: tmppt@mahidol.ac.th***

Dr Eduardo Lazcano Ponce, Director de Epidemiologia, Centro de Investigacion de Salud Poblacional, Instituto Nacional de Salud Publica, Ave. Universidad 655, Col. Sta. Maria Ahuacatitlan, 62508 Cuernavaca, Morelos, Mexico
tel: + 52 777 320 3003 ***fax: + 52 777 329 1148*** ***email: elazcano@insp3.insp.mx***

Dr Ciro de Quadros, Director, International Programs, Sabin Vaccine Institute
1718 Connecticut Ave., N.W., Suite 700, Washington DC 20009, USA
tel: + 1 202 265 6515 ***fax: + 1 202 785 3849*** ***email: ciro.dequadros@sabin.org***

Dr David Ross, Reader in Epidemiology & International Public Health, London School of Hygiene and Tropical Medicine, Keppel Street, London EC1E 7HT, United Kingdom
tel: + 44 20 7927 2264 ***fax: + 44 71 636 8739*** ***email: david.ross@lshtm.ac.uk***

Temporary Advisers

Dr F. Xavier Bosch, Epidemiology and Cancer Registration Unit, Catalan Institute of Oncology, Hospital Duran i Reynals, Avda. Gran Via, s/n Km. 2,7, 08907 L'Hospitalet de Llobregat, Barcelona, Spain
tel: +34 93 260 7812 ***fax: +34 93 260 7787*** ***email: cris@ico.scs.es***

Dr José Eluf-Neto, Departamento de Medicina Preventiva, Faculdade de Medicina, Universidade de Sao Paulo, Av. Dr Arnaldo 455, Sao Paulo - SP 01246-903, Brazil
tel: + 5511 3062 6822 fax: + 5511 3062 6018 email: jelufnet@usp.br

Dr Silvia Franceschi, Head of the Infections and Cancer Epidemiology Group, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France
tel: + 33 472 73 8402 fax: + 33 472 73 8345 email: franceschi@iarc.fr

Dr Geoffrey Garnett, Department of Infectious Disease Epidemiology, Imperial College London, St Mary's Campus, Norfolk Place, London, W2 1PG, United Kingdom
tel: + 44 207 594 3215 fax: + email: g.garnett@imperial.ac.uk

Dr Karen L. Goldenthal, Director, DVRPA, Food and Drug Administration, 1401 Rockville Pike, HFM-475, Rockville, MD 20852-1448, USA
tel: + 1 301 827 3070 fax: + 1 301 827 3532 email: goldenthal@cber.fda.gov

Prof. Harald zur Hausen, Deutsches Krebsforschungszentrum, Im Neunheimer Feld 242, 69120 Heidelberg, Germany
tel: + 49 6221 424655 fax: + 49 6221 423851 email: zurhausen@dkfz.de

Dr Rolando Herrero, P.O. Box 125-6151, Santa Ana, 2000, Costa Rica
tel: + 1 506 220 3039 fax: + 1 506 220 3332 email: rherrero@amnet.co.cr

Dr Matti Lehtinen, School of Public Health, FI 33014 University of Tampere, Tampere, Finland
tel: + 358 40 5437862 fax:+ 358 3 2156057 email: Matti.Lehtinen@uta.fi

Prof. E. Muhondwa, School of Public Health & Social Sciences, Muhimbili University College, P.O. Box 65015 , Dar es Salaam, Tanzania
tel: + 255 22 2153371 fax: + 255 22 2151238 email: *emuhondwa@muchs.ac.tz*

Dr Evan R. Myers, Associate Professor and Chief, Division of Clinical and Epidemiological Research Department of Obstetrics and Gynecology DUMC 3279, 244 Baker House, Duke University Medical Center, Durham, NC 27710, USA
tel: +1 919-668-0296 fax: +1 919-668-0295 email: Myers008@mc.duke.edu

Dr Twalib A. Ngoma, Executive Director, Ocean Road Cancer Institute, Junction of Luthuli and Ocean Road, P.O. Box 3592, Dar es Salaam, Tanzania
tel: + 255 22 2118704 fax: + 255 22 2118704 email: ngoma@uccmail.co.tz

Dr You-Lin Qiao, Department of Cancer Epidemiology Cancer Institute/Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, P.O. Box 2258, Beijing, 100021, People's Republic of China
tel: + 86 10 8778 8489 fax: + 86 10 6771 3648 email: qiaoy@public.bta.net.cn

Professor Helen Rees, Associate Professor, Reproductive Health Research Unit
University of Witwatersrand, P.O. Berstham 2013, Johannesburg, South Africa
tel:+ 27 11 989 92 08 fax: + 27 11 989 92 71 email: h.rees@rhrujhb.co.za

Professor Peter Smith, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom
tel: + 44 207 927 2246 fax: + 44 207 927 2666 email: Peter.Smith@lshtm.ac.uk

Observers

Dr Jan Agosti, The Bill and Melinda Gates Foundation, P.O. Box 23350, Seattle, WA 98102, USA
tel: +1 206 709 3331 ***fax: +1 206 709 3170*** ***email: jana@gatesfoundation.org***

Dr Hugues Bogaerts, Director, Medical Marketing, Glaxo SmithKline Biologicals, Rue de l'Institut 89, 1330 Rixensart, Belgium
tel: + 32 2 656 83 20 ***fax: + 32 2 656 9058*** ***email: hugues.bogaerts@gskbio.com***

Ms Mahima Dalta, Vice President – SBD, Biological E. Ltd, 18/1&3 Azamabad, Hyderabad 500020, Andhra Pradesh, India
tel: +91 40 2761 7831 ***fax: + 91 40 2767 5003*** ***email: dalta@biologicale.com***

Dr Gary Dubin, 2301 Renaissance Blvd., King of Prussia, PA 19406, USA
tel: + 1 610 787 3104 ***fax: +1 610 787 7057*** ***email: gary.o.dubin@gsk.com***

Dr David Jenkins, Director, Clinical Development, Cervarix TM (HPV vaccines) GlaxoSmithKline Biologicals, Rue de l'Institut, 89 1330 Rixensart, Belgium
tel: +32 2 656 6721 ***fax: +32 2 656 80 33*** ***email: david.jenkins@gskbio.com***

Dr Elaine C. Esber, Executive Director, Medical Affairs International, Merck Vaccine Division, P.O . Box 4, WP97-A337, West Point, PA 19486, USA
tel: +1 215 652 8298 ***fax: + 1 215 652 8918*** ***email: elaine_esber@merck.com***

Dr Sue Goldie, Associate Professor, Department of Health Policy and Management, Harvard School of Public Health, 718 Huntington Avenue, Boston, MA 02115, USA
tel: + 1 617 495 4768 ***fax: + 1 617 495 8231*** ***email: sue_goldie@harvard.edu***

Dr Heiner Grosskurth, Medical Research Council Programme, P.O. Box 49, Entebbe, Uganda
tel: + 256 41 320272 ***fax: + 256 41 321137*** ***email:***
heiner.grosskurth@mrcuganda.mimcom.net

Dr Jacqueline Sherris, Program for Appropriate Technology in Health, 1455 NW Leary Way, Seattle, WA 98107-5136, USA
tel: + 1 206 285 3500 ***fax: + 1 206 285 6619*** ***email: jsherri@path.org***

Dr Vivien Tsu, Program for Appropriate Technology in Health, 1455 NW Leary Way, Seattle, WA 98107-5136, USA
tel: + 1 206 285 3500 ***fax: + 1 206 285 6619*** ***email: vtsu@path.org***

Dr Ryoko Krause, Director, Biologicals and Vaccines, IFPMA, 30 rue de St. Jean, PO Box 758, 1211 Genève 13, Switzerland
tel: + 41 22 338 3212 ***fax: + 41 22 338 3299*** ***email: r.krause@ifpma.org***

Dr Regina Rabinovich, Director, Infectious Diseases, Global Health Program, The Bill and Melinda Gates Foundation, P.O. Box 23350, Seattle, WA 98107 5136, USA
tel: + 1 206 709 3490/3579 ***fax:+ 1 206 709 3170*** ***email: regina@gatesfoundation.org***

Dr Elizabeth Unger, Centers for Disease Control and Prevention, 1600 Clifton Road, N.E, Atlanta, Georgia GA 3033, USA

tel: + 1 404 639 3533 ***fax: + 1 404 639 3540*** ***email: eunger@cdc.gov***

Dr Jimmy Whitworth, Head of International Activities, The Wellcome Trust, 215 Euston Road, London, NW1 2BE, United Kingdom
tel: +44 20 7611 7230 fax: +44 20 7611 7288 email: j.whitworth@wellcome.ac.uk

WHO Regional Offices

Dr Hinda Ahmed, WHO Regional Office for the Eastern Mediterranean **(**EMRO), WHO/EMRO, Nasr City, Cairo, Egypt
tel: +202 2765257 **fax: +202 2765445** **email: ahmedh@emro.who.int**

Dr Miraldina Manuel, WHO Regional Office for Africa (AFRO), Central Maternity in Luanda, National Coordinator of the Cervical Cancer Control Programme, Brazzaville, Congo
tel: +244 923 402213 **fax: +244 397662** **email: mlp.dc@snet.ao.co**

Dr Gunta Lazdane, WHO Regional Office for Europe (EURO), 8, Scherfigsvej, DK-2100 Copenhagen, Denmark
tel: +45 39171426 ***fax: +45 39171850*** ***email: GLA@euro.who.int***

Dr Merle Lewis, Immunization Unit, Area of Family and Community Health, Pan American Health Organization (PAHO), 525, 23rd Street, N.W. Washington, D.C. USA
tel: +202 974 3892 ***fax: +202 974 3236*** ***email: lewismer@paho.org***

WHO Secretariat

Joy Phumaphi, Assistant Director General, Family and Community Health
Dr Jean-Marie Okwo Bele, Director, Immunization, Vaccines and Biologicals (IVB)
Dr Marie-Paule Kieny, Director, Initiative for Vaccine Research (IVR)
Dr Nathalie Broutet, Reproductive Health and Research (RHR)
Dr Teresa Aguado, IVR
Dr Elizabeth Mason, Department of Child and Adolescent Health and Development (CAH)
Dr Sonia Pagliusi, IVR
Dr Tim Evans, Evidence and Information for Policy (EIP)
Dr Felicity Cutts, IVR
Dr C. Sepulveda, Programme on Cancer Control (PCC)
Dr Maureen Birmingham, Vaccine Assessment and Monitoring (VAM)
Dr Jos Vandelaer (VAM)
Dr Patrick Zuber, Expanded Programme on Immunization (EPI)
Dr David Wood, Quality Assurance and Safe Biologicals (QSB)
Dr Isabelle De Zoysa, Family and Community Health (FCH)