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16-17 November 2009
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Immunization, Vaccines and Biologicals

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Executive Summary

A meeting on HPV Vaccine Coverage and Impact Monitoring was held at the World Health Organization (WHO) in Geneva, Switzerland on 16-17 November 2009 to discuss methods for HPV vaccine coverage monitoring and to further delineate objectives and strategies for HPV vaccine impact monitoring. Participants included experts in epidemiology, surveillance, programme, and laboratory in the areas of immunization, cancer, sexually transmitted infections, and adolescent health from WHO, five WHO regions, IARC, CDC, PATH, and national and academic institutions. This meeting took place following prior meetings to address this topic in January 2009 and May 2009.

With regards to HPV vaccine coverage, it was agreed that monitoring HPV vaccine coverage by dose and by age was important for meeting the goals of programme monitoring and of vaccine impact monitoring. In addition, a summary indicator of proportion of girls vaccinated with 3 doses by age 15 years will be useful to compare HPV vaccine coverage trends over time and across geographic areas.

As noted in the 2009 WHO position paper on HPV vaccines, HPV disease monitoring is not a prerequisite or an essential requirement for an HPV vaccination programme. Monitoring HPV vaccine impact is complex and should be done with good technical support and clear understanding of caveats in order to avoid arriving at erroneous conclusions. Complete and accurate vaccine coverage information is necessary for interpretation of data on vaccine impact measures.

The potential monitoring endpoints which were reviewed included HPV infection among young women shortly after sexual debut, positive cervical cancer screening tests, cervical intraepithelial neoplasia (CIN) 2-3 and adenocarcinoma in situ (AIS), cervical cancer, non-cervical HPV cancers, and genital warts. The two endpoints that were identified as important to consider for assessing HPV vaccine impact were monitoring of HPV prevalence and of cervical cancer. Monitoring HPV prevalence among sexually active young women in one or two select settings was felt to provide an important early indication of HPV vaccine impact but requires considerable resource commitment for at least 5-10 years. Cervical cancer is the primary disease of interest for cervical cancer prevention and control programs and thus, all countries should consider establishing or improving reporting to cervical cancer registries in order to measure impact of HPV vaccine and impact of cervical cancer screening programmes.

Where resources are available for implementing HPV vaccine impact monitoring, developing such monitoring is a capacity building opportunity which may be used to strengthen cervical cancer screening and cancer registries, and which may result in linkages and synergies between adolescent health, reproductive health, immunization, cancer, and education programmes.

Meeting Objectives

In 2009, the WHO position paper on the use of HPV vaccine was published and both the bivalent and the quadrivalent vaccines were pre-qualified. The quadrivalent and bivalent vaccines have each been licensed in >100 countries. As of the end of 2009, 27 countries had introduced HPV vaccine in their national immunization schedules.

Since HPV vaccine needs to be administered to a population that has not previously been routinely served by EPI and the impact from the vaccine can not be measured in short timeframes, it is generally recognized that compared to infant EPI vaccines, new approaches to monitoring vaccine coverage and impact are needed for HPV vaccine.

The primary objectives for this November meeting were to:

1) agree on the architecture of guidance on monitoring HPV biologic endpoints (i.e., endpoints that measure HPV or subsequent changes caused by HPV)
2) outline an approach to HPV vaccine coverage monitoring.
3) identify any special studies which might be needed to provide more complete country guidance on monitoring.
4) identify partners and resources for HPV surveillance and monitoring.

I. Background presentations

A. HPV and HPV vaccines, Eileen Dunne

Dr. Dunne provided a brief epidemiologic review highlighting that cervical cancer is primarily a disease of poor women, with 85% of cervical cancer deaths occurring in the developing world where cervical cancer is the leading cause of cancer deaths of women. Seventy percent of these cancers are associated with HPV 16 (54.4%) and 18 (15.9%). Both the quadrivalent and the bivalent vaccines have high efficacy against HPV 16/18 and related cervical intraepithelial neoplasia (CIN) 2+. The quadrivalent vaccine also has demonstrated high efficacy against HPV 16/18 related vulvar intraepithelial neoplasia (VIN) 2+, vaginal intraepithelial neoplasia (VaIN) 2+, and HPV 6/11 related genital lesions. Both vaccines have demonstrated some cross protection against CIN2+ due to high risk types other than HPV 16/18; the bivalent vaccine may have broader cross protection. Geometric mean antibody titers and local site reactions are greater for the bivalent vaccine. It is unclear if any differences in duration of protection are present between the vaccines; currently available data demonstrate protection for 5-8 years.

Discussion highlighted the challenges of planning vaccination programs without knowledge of long-term duration of protection or correlate of protection. Antibody levels due to vaccination decline but titers remain well above naturally acquired antibody levels. Mathematical modelling suggests that vaccine may provide 15-18 years of protection, but the need for a future booster vaccine dose remains an important research question. Antibody levels may not be the best measure of how well HPV vaccine provides protection.

B. Goals for vaccine impact monitoring and brief background on work to date on HPV vaccine impact monitoring, Susan Wang

Dr. Wang reviewed the rationale for measuring vaccine impact: to demonstrate impact on morbidity and mortality; to demonstrate vaccine effectiveness in real world settings, and to understand epidemiologic changes in disease patterns after vaccine implementation (e.g., identify changes in age distribution of disease or changes in strains causing disease, assess long-term immunity, assess herd immunity). She reviewed strategies for assessing vaccination programs: 1) program performance can be measured through program review and vaccine coverage; 2) program and vaccine impact may be measured through surveillance of disease, through mortality data, and through economic evaluations; 3) vaccine performance and quality may be monitored through vaccine effectiveness case-control studies, assessment of immune response, and surveillance for adverse events following immunization (AEFI). The possible biologic endpoints for HPV vaccine impact monitoring were reviewed (i.e., HPV prevalence, CIN II-III prevalence and HPV type distribution, invasive cancer and associated HPV

types, positive screening tests and referrals for treatment) and qualitatively compared in terms of resources needed, whether they were a direct measure of the desired outcome, and timeliness of information (Appendix 3). She used the example of hepatitis B virus, another cancer-causing virus with a long time interval between infection and disease manifestation. In Taiwan, hepatitis B vaccine impact assessments were done using 1) serosurveys to evaluate reduction in chronic HBV infection in 5 year olds who had been vaccinated as newborns and 2) cancer registries to assess reduction in liver cancer in 6-14 year olds approximately 6-12 years after vaccine introduction.

Discussion focused on the mechanisms of monitoring hepatitis B vaccine impact. National EPI programs have conducted HBsAg serosurveys of 5 year olds as an early measurement of impact, while cancer registry data were examined as a more final measure of impact in those countries with cancer registries in place. Generally, there was not an effort to improve or develop cancer registries where they were not already in place. For cervical cancer, high resource settings commonly have cancer registries but in sub-Saharan Africa, there are currently only four African countries with quality cervical cancer registries. Existing population-based registries will be important for impact monitoring.

C. Overview of HPV and cervical cancer screening tests, Beth Unger

Dr. Unger reviewed the challenges with the current state of cervical cancer screening, including cytology which requires histology for confirmation, "see and treat" which is sensitive but not specific and requires training of personnel, and HPV testing either alone or in combination. HPV DNA tests only detect current presence of virus and HPV presence is NOT equivalent to disease. HPV tests can guide management of women with abnormal cytology results and in some settings are useful for primary cervical cancer screening. A summary of HPV DNA tests was shared (see Appendix 4), although the list was acknowledged to be incomplete as new tests are rapidly being added. The cutoff values for clinical tests are established to give best correlation with disease, so analytic sensitivity for HPV using clinical tests is less than that achieved with research tests. Research tests for HPV DNA are type-specific with high specificity and analytical sensitivity. Many are available commercially, but research labs may produce their own tests.

The cost of testing, level of training required for performing tests, and extent of standardization varies with each assay. HPV tests have the potential to be more standardized than cytology. Molecular testing requires highly specialized laboratory space and equipment and skilled technologists. HPV LabNet participants report the following costs: clinical test $15-$39 per sample (median $27), research test $10-$200 per sample (median $72).

There was discussion about which cervical cancer screening method was best post-vaccination. Cytology will be less efficient as the vaccine is expected to significantly reduce true disease (signal), but will have less effect on cervical inflammatory changes and low grade changes that mimic disease (noise). As disease prevalence falls, the positive predictive value of a positive cytology test will necessarily fall. This will occur despite the absence of change in screening test specificity as the ratio of false positives to true positives rises. Additionally it is expected that the reduction in prevalence of high grade lesions will adversely impact the technical performance of cytologists because a larger number of slides will have to be read in order to detect any significant abnormality.

Laboratory quality assurance will be very important in HPV testing. Self-sampling for HPV DNA testing is possible and may be a good way to reach more women for screening.

D. Overview of monitoring and evaluation of cervical cancer screening programs and overview of cancer registries, R Sankaranarayanan

Dr. Sankar reviewed information systems for monitoring and evaluation of screening programs such as population-based, program-based, and supplementary active data collection. The progress and success of cancer screening programs are monitored and evaluated with a set of process indicators (e.g., monitoring target population participation level) and outcome measures. Outcome measures are essential to evaluate the impact of the program on the disease burden. Intermediate outcome measures (e.g., stage distribution, 2- and 5-year survival rates, and case fatality rates), do not measure final outcome and are prone to lead time, length, volunteer and over-diagnosis biases. Final outcome measures, such as incidence and mortality, are not prone to biases. Additional factors to consider in cervical cancer screening programs include feasibility, acceptability, safety, and quality of life. Monitoring and evaluation of screening programs requires adequate program databases and information systems, and ability to capture and link data.

Discussion regarding outcome measures ensued. In the example of monitoring hepatitis B vaccine impact in Taiwan, it was possible to link hepatitis B vaccine coverage data with reduction in hepatocellular cancer incidence. Hepatitis B vaccine impact in reduction of pediatric liver cancer was demonstrated 10-15 years after vaccine introduction. In developed countries, screening for other outcomes should help with detecting earlier measures of vaccine impact than cervical cancer. For example, in Australia, a 35% reduction in genital warts has already been demonstrated. Ultimately, a few outcome indicators derived from quality data sources are likely to provide indications of HPV vaccine impact within 10-15 years.

It will be necessary to continue to monitor immunogenicity data from clinical trial cohorts over the next 15-20 years to identify any changes in immunity over time and any correlation with loss of vaccine efficacy. When monitoring immunogenicity, it is important to keep in mind that HPV infection occurs in the epithelium rather than systemically.

II. Workgroups and plenary discussion of workgroup outputs

During the May 2009 HPV Surveillance and Monitoring Meeting, workgroups were formed to address each of the proposed biologic endpoints for HPV vaccine impact monitoring. Using output from the May meeting, interim work was done by May meeting participants, particularly by those serving as workgroup facilitators for the current meeting, and further discussions about the endpoints were held via conference calls. This interim work resulted in detailed outlines for each of the four proposed biologic endpoints. The four outlines were the basis for the workgroups at this November meeting. The workgroup objectives were as follows:

1) To review the workgroup outline and incorporate input from the group regarding characteristics of the outcomes to be monitored and method of monitoring (target population, sites, assays, methods, etc.).

2) To answer the following questions regarding the proposed outcomes to be monitored:

    a) Is this an important outcome to measure for country or regional decision-making with regards to a) the HPV vaccine programme, b) the cervical cancer screening programme, c) both programmes?

    b) How important is it for developing countries to measure these particular outcomes? Are there any concerns or cautions associated with measuring these particular outcomes? Can one distinguish changes in these outcomes that are due to HPV vaccine introduction versus changes due to increased cervical cancer screening?

3) To review and assess feasibility of implementation of the monitored outcomes:

    a) Infrastructure requirements: identify material and human resources needed.

    b) Process requirements; identify policies or actions necessary to create this monitoring system.

4) To identify the primary stakeholders for the outcomes being monitored:

    a) What programme or sector in a country has primary, secondary, tertiary responsibilities in this area (i.e., who will accomplish this)?

    b) Who are the interested partners?

5) To identify any gaps or questions that need to be addressed before country guidance on this outcome could be provided.

Below are the key messages from each workgroup as reported in plenary. Additional specific work group discussions are reflected in the revised outlines for the four biologic endpoints (see Appendices 5, 6, 7, 8).

A. Workgroup 1: HPV DNA prevalence *(Revised outline in Appendix 5)*

Impact monitoring is most readily accomplished where accurate vaccine coverage data are available. Testing 15-20 year old women soon after sexual debut for genital HPV DNA prevalence by HPV type could offer a short-term biologic endpoint that demonstrates HPV vaccine impact. The shorter the time period between vaccination and sexual debut, the sooner impact may be assessed.

HPV DNA prevalence monitoring requires an affordable test with standardized specimen collection and handling and consistent standardized test methodology. The setting for this monitoring could be in various clinical venues and would most likely be opportunistic. More ideal study designs, such as following a cohort to determine transient versus persistent infection or a population-based method, were felt to have limited feasibility.

Discussion affirmed that monitoring HPV prevalence as an early measure of vaccine impact is feasible for only a few settings as it will require intensive financial and human resources and a commitment of 5-10 years to demonstrate results. The group stressed the important distinction between HPV genotyping tests using the highly sensitive nucleic acid amplification methods that are assays used for epidemiologic monitoring of HPV vaccine impact versus clinical HPV genotyping tests used for cervical cancer screening which are less sensitive but have clinical predictive value. Cervical cancer screening is not generally indicated in the young target age group in which assessment of HPV prevalence would give the earliest measure of vaccine impact so HPV prevalence monitoring likely could not readily be incorporated into routine clinical care for this population.

The clinical significance, if any, of a positive test needs to be carefully considered when designing the study. The long-term significance of a positive HPV DNA test in women under 30 years old is often not clear because of the high prevalence of transient HPV infection in this age group. Anonymous HPV testing may be an option in some settings, however, most meeting participants felt that women would want their HPV test results. Careful counselling and education should be offered when providing HPV test results back to young women but this is challenging to provide since it is unclear what the young women should be told. There is a need to explore frameworks for education regarding the meaning of test results. This type of HPV prevalence monitoring activity could pose ethical challenges if it were done in a country without existing cervical screening services. However, introduction and increased use of clinical HPV genotyping tests for cervical cancer screening could build laboratory infrastructure and capacity and thereby facilitate monitoring of vaccine impact on HPV types.

B. Workgroup 2: CIN 2/3 and AIS prevalence and associated HPV types *(Revised outline in Appendix 6)*

Cervical cancer precursors are the endpoints used for vaccine clinical trials and are an acceptable surrogate for measuring vaccine efficacy in preventing cervical cancer. However, monitoring CIN2/3 in the absence of a robust clinical, laboratory, and surveillance infrastructure is challenging and resource intensive. Importantly, these cancer precursor endpoints are only detected as a result of screening. Therefore, any changes in screening and diagnostic practices will impact prevalence of observed CIN and AIS. Despite the utility of these endpoints in evaluating screening programs, they are fraught with the potential to give misleading information about vaccine impact. Additionally, the cost of establishing new programs (including testing, histologic review, and quality control of the screening program) would be high and could detract from resources needed for vaccine administration. Therefore, in settings with no existing routine screening, or when screening is being established alongside vaccine introduction, routine monitoring of cancer precursor endpoints is not recommended apart from research settings where defining study population and appropriate histologic verification and typing of the lesions are possible. In settings with established routine screening, it may be possible to use cancer precursor endpoints, but caution is required. It may be challenging to correctly ascribe any change in lesion prevalence to vaccination rather than to other changes in the screening pathway (e.g., changes in lesion detection and interpretation that are due to changes in screening practices or changes in recruitment strategies or media reports resulting in recruitment of previously unscreened women). Analysis of these lesions for HPV DNA would generally need to be performed by a reference laboratory. As is the case for the other endpoints, information on HPV vaccine coverage for the screened population will be needed.

C. Workgroup 3: Invasive cervical cancer and associated HPV types *(Revised outline in Appendix 7)*

Invasive cervical cancer is the key biologic outcome to monitor for HPV vaccine impact. To assess earliest impact at the earliest timepoint, cervical cancer incidence and mortality in women under 30 or 40 years old would be important to measure.

Cancer registries can be population-based or hospital-based registries. Comprehensive cancer registries which include diverse cancers are ideal. Where comprehensive cancer registries don't exist, consideration should be given to specifically establishing cervical cancer registries in areas where HPV vaccine is being implemented. For population-based registries, the minimum standard requirements defined by IARC include age, anatomic site, histology, behaviour, and stage. Countries collect different data in their cancer registries and some may include linkage to vaccine coverage data. For monitoring invasive cervical cancer, the denominator is the female population.

When designing new registries, feasibility is a crucial consideration. Establishing a cancer registry requires training cancer registrars. Countries that wish to establish new cancer registries or fortify existing ones may be able to obtain technical assistance from IARC or CDC.

Hospital-based registries can not be used to determine vaccine impact on cervical cancer incidence since they lack the ability to ascertain a denominator, but they can provide some numerator-based information. Minimal requirements for hospital-based registries are the same as for population-based registries. In the absence of population-based cancer registries, hospital-based registries can monitor number of cervical cancer cases by age, histology, and possibly genotype. To assess cancer mortality, a valid vital registration is sufficient, and it is not necessary to have a cancer registry in place. If a cervical cancer registry is not in existence and can not be established, at a minimum, it would be useful to monitor number of cervical cancer cases and deaths by age.

HPV typing of cervical cancers, especially those diagnosed in young women, is desirable, but feasible only in countries with resources and technical ability, or as a special project. It may be possible to develop regional projects to perform HPV typing of cervical lesions with the technical support and assistance of the regional WHO HPV LabNet reference laboratories. Countries with resources and technical ability to perform HPV typing should consider incorporating HPV typing of cervical cancers as a routine practice and including data on HPV type in their cancer registries.

Linkage of individual patient cervical cancer diagnosis with HPV vaccine status would be helpful in assessing vaccine impact, but this is also limited to areas with resources and capacity. More commonly, it will be possible to make a community-level ecological correlation between cervical cancer incidence and HPV vaccine coverage.

D. Work Group 4: Positive cervical cancer screening tests and referrals for treatment *(Revised outline in Appendix 8)*

For countries with established cervical cancer prevention programmes, the proportion of cervical cancer screening tests that are positive is an important programme measure. In such countries, the same measure has been proposed as a potential approach for assessing HPV vaccine impact. However, a number of cautions are necessary. Changes in type of screening tests used, test sensitivity and specificity, populations screened or other programme practices could lead to changes in the proportion of positive screening tests.

National standards determine the definition of a positive screening test as well as the population tested. The numerator is the number with a positive test and the denominator is number of women tested. It is not clear how eliminating HPV vaccine types will change sensitivity, specificity, or positive predictive value of current methods of cervical cancer screening. Special studies are needed to determine how HPV vaccine may impact each screening method. For example, visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) are known to have false positive results due to non-specific inflammation. Reduction of true positive VIA or VILI test results due to elimination of lesions from HPV vaccine types may thus result in higher proportion of false positives for VIA and VILI. Currently there are no data assessing how HPV vaccine will impact cervical cancer screening test positivity rates.

III. Plenary discussion: monitoring HPV vaccine impact on other HPV disease outcomes

A. Genital Warts

Ninety percent of genital warts are caused by HPV 6 and 11. Compared to monitoring cervical HPV DNA prevalence or cervical dysplasia, genital wart surveillance does not require special tests or equipment so it may permit an assessment of vaccine impact on genital warts which costs less and which can generate results sooner than an assessment of vaccine impact on cervical cancer. In Australia, reduction of genital warts following quadrivalent vaccine introduction has been demonstrated. Sentinel clinic-based surveillance may be the most feasible method for monitoring genital warts. Baseline rates of presentation with warts prior to and during vaccine introduction and periodic estimates of HPV vaccine coverage in the population attending the clinic would be needed. Analysis of warts presentations over time in the population attending the clinic should consider age, sex, and, where routinely available, gender of sexual partners. Recurrent warts episodes should be distinguished, where possible, from incident presentations. Monitoring rates of presentation with other STIs can provide reassurance that the source population for the clinic and their sexual behaviour patterns have not changed substantially over time as changes in source population could otherwise explain changes in rates of genital warts presentations. Reductions in genital warts that are measured over time in a stable population sample in which significant changes in sexual behaviour are excluded could provide indication of effective vaccine coverage with biologically active vaccine.

However, there are a number of important factors to consider before selecting genital warts as a primary endpoint to monitor HPV vaccine impact. A significant issue is that monitoring genital warts does not demonstrate impact on cervical cancer burden, the disease of primary interest for HPV vaccine. For countries with limited resources to measure HPV vaccine impact, demonstrating vaccine impact on cervical cancer burden would be a higher priority. Another factor is that in many settings, standardized diagnosis and a surveillance system for genital warts are lacking. True population-based surveillance with estimation of population-based genital warts incidence is not generally feasible due to reporting biases such as incorrect diagnoses in primary care settings, under-reporting from providers, and under identification because many patients with warts do not present for medical care to avoid stigma (e.g., in China).

A further caution to monitoring genital warts as a measure of vaccine impact is that this biologic endpoint is only appropriate for monitoring impact of the quadrivalent vaccine on genital wart disease burden. In countries using both bivalent and quadrivalent vaccines, only monitoring reductions in genital warts may underestimate the total impact of the vaccines on other HPV-related diseases.

B. Other HPV-associated cancers

Monitoring incidence and HPV genotyping of other HPV 16/18 associated genital cancers (vulvar, vaginal, anal, penile) is possible if a comprehensive cancer registry is in place that collects these diagnoses. These are rare outcomes and the power to detect significant reductions in incidence may require pooling of registry data across a region or regions.

IV. Presentation of HPV vaccine coverage monitoring, Tony Burton, and plenary discussion

Mr. Tony Burton reviewed strategies for monitoring of HPV vaccine coverage (see Appendix 9 for Draft approach to monitoring HPV vaccine coverage). The challenges of monitoring HPV vaccine coverage are unlike those for current infant EPI vaccines. HPV vaccine is not recommended for a specific age as are most infant vaccines, but for an age range. In addition, multiple and mixed delivery strategies may be used to vaccinate the target age group of 9 to 13 year old girls.

Country-specific data on immunization including administrative immunization coverage data are primarily monitored through an annual questionnaire, the WHO/UNICEF Joint Reporting Form (JRF) on immunization. The current JRF requests information on country schedules for HPV vaccine, but not coverage data. Since the JRF is revised every two years, it will be possible to add collection of HPV vaccine coverage to a future version.

For the purpose of measuring HPV vaccine impact, it will be necessary to monitor HPV vaccine coverage by age and by dose. Therefore, date of birth, date of vaccine administration, and dose number should be recorded for every dose administered. It was agreed that a useful summary indicator to compare vaccine coverage trends over time and across geographical regions would be the proportion of girls vaccinated with 3 doses of HPV vaccine by age 15 years.

Determining vaccine coverage can be challenging, given the range of ages at which the vaccine is given. Research is needed on how to accurately monitor the proportion of the target population receiving the vaccine and how to best quantify the target population. HPV vaccine administered in special settings such as factories or hospitals or in the private sector may not be captured in national immunization coverage data. For school-based vaccine delivery, coordination between schools and immunization programs for recording immunizations is necessary. In EURO, a number of countries have experience with vaccinating adolescents for diphtheria, tetanus, and hepatitis B but it was necessary to encourage establishment of immunization registries. It was felt that in low and middle income countries, introduction of HPV vaccine might be used to support improved adolescent health services and immunization registration.

Delivering HPV vaccine through a campaign approach has been suggested for low-resource settings. In measles or polio campaigns, all children of the target ages are typically immunized and individual information on vaccines received is not routinely recorded. However, these particular campaigns are done to address an acute and urgent public health need. It was generally agreed that since HPV infection does not have the same acuity or disease control urgency, HPV vaccine delivery should not be in the style of polio and measles campaigns and instead, time should be taken to record individual HPV vaccine doses administered.

An HPV vaccine demonstration project in Uganda utilized "Child Days, Plus," successfully delivering HPV vaccine with an outreach approach. Challenges did include determining the age of the girls eligible for vaccination in a culture where birth dates are not recorded. In countries where a high proportion of the target age group leave primary school, a mixed strategy of school-based vaccination and campaign approach may be needed to achieve high coverage. More research on best approaches to vaccine delivery and vaccine coverage monitoring is needed in these settings.

In addition to administrative data, vaccine coverage data can come from national vaccine coverage surveys or from Demographic and Health Surveys (DHS) or Multiple Indicator Cluster Surveys (MICS). It was noted that the 2010 DHS in Colombia will collect information on knowledge of HPV and on whether 13-49 year old women have received HPV vaccine.

Maximizing adolescent retention of immunization cards was discussed. In general, it was noted that girls may not keep their immunization cards into adulthood, or remember being vaccinated. In the Uganda PATH project, card retention was about 60% and it was observed that parents who had the HPV immunization cards were the same parents who also had their children's infant immunization cards. Providing an adolescent health service package (e.g., treatment for helminths, folate, iron, vitamin A, vision screening, and bed nets along with immunizations that might include typhoid, tetanus, hepatitis B, diphtheria) and creating a combined adolescent health record may be more useful and more memorable. However, providing such a package would need to be done in a resourced way that does not overwhelm the EPI program.

A participant from EMRO noted that selected countries in that region have individual electronic medical records, even in the private sector, but for other countries, it would require significant effort and investment to link HPV vaccination coverage with HPV disease. In Australia, there is no adult immunization registry, but a specific HPV vaccine registry was created to permit future linkage to cytology data from Pap test registers and to cancer registries. This HPV vaccine registry also sends reminders to girls when they are due for dose 2 and dose 3.

V. Presentation of HPV vaccine safety monitoring, Patrick Zuber, and plenary discussion

The Global Advisory Committee on Vaccine Safety (GACVS) advises WHO on vaccine safety issues, and has thus far examined HPV vaccine safety issues on three separate occasions (http://www.who.int/vaccine_safety/topics/hpv/en/index.html). Assessments have thus far been reassuring. As of March 2009, >60 million HPV vaccine doses had been administered in 21 countries; additional safety data are available from demonstration projects in 4 countries. Studies have been initiated in Africa to include HIV-infected patients.

The most common adverse reactions to HPV vaccination have been injection site and muscle pain. Some allergic reactions have been observed, along with syncope. Limited data on the inadvertent administration of HPV vaccines shortly before pregnancy or during pregnancy are reassuring. Use of the ASO4 adjuvant in the bivalent vaccine has has been studied by GSK in close to 20,000 vaccinees who were followed-up for a median of 2 years; no significant safety issues have been identified.

In the United States, the Vaccine Adverse Events Reporting System (US, VAERS) data found a possible increase in thromboembolic events, (JAMA. 2009;302(7): 750-757). Researchers are following this issue with ongoing studies to determine how the background increased number of venous thromboembolic events occurring in girls taking oral contraceptives is related to thromboembolic events in vaccinees as both exposures affect similar populations.

Addressing HPV vaccine safety should include ensuring surveillance of adverse events following immunization (AEFI) and establishing a good risk communication strategy to cope with spurious media reports. Examples were shared of media reports following adverse events, and the harm done to HPV immunization programmes. Having a communication message and strategy in place prior to HPV vaccine implementation is critical. Since the vaccine is targeted at an age group not routinely served by EPI and is targeted at girls only, and since there may be social or cultural sensitivities about HPV as a sexually transmitted infection, adequate attention and time are needed to assess acceptability of the vaccine among girls, parents, and health workers, and to develop and implement communication messages in advance of introducing HPV vaccine.

Improving AEFI monitoring so that there is more geographic diversity in the source of safety data is currently underway but it will take time to build capacity globally to collect these data. For some AEFIs, such as ones which do not occur immediately, it may not be necessary to have a country by country system and regional monitoring may be sufficient. Efforts are currently focused on ensuring quality vaccine safety data from two countries in each WHO Region. Training to understand AEFI issues is needed for persons administering vaccines. Meeting participants suggested that it may be useful for WHO to develop AEFI messages which can be shared with Ministries of Health. It was noted that additional funding is needed to support MoHs in developing communication plans to address vaccine safety and risk communication..

VI. Plenary discussion of laboratory needs for HPV vaccine impact monitoring, Joakim Dillner

The WHO HPV LabNet was launched in 2006 and includes two global and seven regional reference laboratories. The participating laboratories were selected on the basis of their research experience and expertise in performing quality assurance. The mission of LabNet is to support HPV vaccine introduction and the monitoring of HPV infection and associated disease. LabNet has played a key role in international standardization of HPV testing, with actual epidemiologic testing and screening as a secondary aim.

A major LabNet achievement has been the development of international standards and reference reagents for a variety of HPV DNA and serology tests. These have included defining units for HPV DNA (16 and 18 and seven other oncogenic types) and HPV 16 antibodies. Additionally, a laboratory manual with standard operating procedures (SOP) for HPV testing and quality assurance has been completed. The HPV LabNet has also performed proficiency testing for DNA and serology assays. Eighty one labs world-wide enrolled in the HPV DNA proficiency test. The 73 that provided data were evaluated for their ability to detect 50 IU of HPV type 16 DNA; less than one third were proficient (20/73). A clear need for proficiency testing exists as the eight most common tests for DNA typing have high inter-lab variability and no clear patterns of proficiency, suggesting laboratory experience may be more important that the specific test used.

Another role of HPV LabNet has been training of laboratory personnel. Training has only recently been initiated as standardized assays were needed before conducting training workshops. Regional networks affiliated with regional reference laboratories have been established.

Upcoming priority areas for HPV LabNet include developing quality assurance for the collection and handling of biologic samples; developing a standard format for recording, interpreting, and communicating data; and establishing direct interactions with National HPV Reference laboratories for surveillance and monitoring. These activities are intended to enhance the ability to have internationally comparable laboratory test results and to support HPV vaccine introduction and surveillance of HPV infection and disease.

HPV LabNet could also have a central role in evaluating new HPV tests for cervical cancer screening or vaccine impact monitoring and in recommending best methods and tests for vaccine-related uses besides impact monitoring. For example, LabNet could provide guidance on use of HPV assays for phase IV vaccine trials and for 2nd generation vaccines.. HPV LabNet could also be used to assist with defining correlates of immunity.

It was agreed that the HPV LabNet's work to develop HPV test standards is useful. The HPV test types and test sensitivities needed for evaluating HPV vaccine impact are likely different from what is needed for routine cervical cancer screening, and it would be important to have ongoing work to establish international standards and quality assurance for both types of tests. HPV LabNet could also play a useful role in providing laboratory training in lower resource settings. National reference laboratories would like to be part of a global network, such as HPV LabNet, to problem-solve technical issues around HPV testing. Regional laboratories could help ensure the quality of national laboratories and conduct training for personnel. It was suggested that it may be desirable for a future network to include more partners and be less centralized.

HPV LabNet could have an important role in facilitating the HPV genotyping of cervical cancer histology specimens and in offering guidance to pathologists on best methods for testing of archival specimens. In Latin America, multiple local laboratories are conducting HPV DNA typing. Regional reference laboratories can assure standardization and quality of test results. HPV LabNet could also perform confirmatory (inter-laboratory) testing of random subsamples of cervical cancer specimens for disease burden and cervical cancer HPV type distribution studies.

VII. Meeting conclusions

Overall key concepts concerning HPV vaccine impact monitoring were identified:

1) Monitoring HPV vaccine impact is not necessary for HPV vaccine introduction.

2) Monitoring vaccine impact on HPV infection outcomes is complex and should be done with good technical support and clear understanding of caveats (regarding tests to be used, interpretation of test results, screening methods, population sampling, etc.) to avoid arriving at erroneous conclusions.

3) The primary objective of any impact evaluation for HPV vaccine programs is to demonstrate a reduction in incidence and mortality of cervical cancer.

4) Long term linkages between the array of programmes (reproductive health, sexually transmitted infections, adolescent health, school health, cancer control, and immunization) which are involved in cervical cancer prevention and control are needed in order to monitor HPV vaccine outcomes.

5) HPV vaccine coverage data are needed to interpret biologic endpoints and assess HPV vaccine impact.

Specific conclusions were reached for various topics that had been discussed, as follows.

A. Monitoring HPV DNA Prevalence

1) It would be useful to monitor HPV prevalence among young sexually active women in a few select settings globally to provide an early measure of HPV vaccine impact. It is not necessary for all countries to perform this type of monitoring.

2) Challenges for monitoring this biological endpoint is that it requires commitment of substantial resources for a sustained period (5-10 years).

3) Appropriate methods for conducting this type of monitoring still need to be developed (e.g., sample size calculations, methods for collection of genital samples for HPV testing, appropriate tests to use, as well as when and how these HPV test results should be reported back to the participants).

B. Monitoring CIN 2/3 and AIS

1) Monitoring CIN 2/3 and AIS is important for monitoring cervical cancer screening programmes but it is not useful for routine monitoring of HPV vaccine impact. Countries should not use their CIN 2/3 cervical cancer screening data without very careful scrutiny as the risks of arriving at erroneous conclusions regarding HPV vaccine impact are quite high.

C. Monitoring Cervical Cancer

1) All countries should consider establishing or improving reporting to cervical cancer registries as they are important for measuring impact of both HPV vaccination programs and cervical cancer screening programs.

2) It is not a prerequisite for HPV vaccine introduction to have a cervical cancer registry. However, initiating vaccine impact monitoring may be used as an opportunity to strengthen cervical cancer registries.

3) If a cervical cancer registry is not in existence, at a minimum, it would be useful to monitor number of cervical cancer cases and deaths by age.

4) Where resources exist, genotyping of cervical cancers is useful, particularly for cervical cancer lesions identified in women younger than 40 years old.

5) If non-cervical HPV cancers are recorded in cancer registries, analyzing changes in incidence of these non-cervical HPV cancers (vaginal, vulvar, penile, anal) may demonstrate impact of HPV vaccine on these other cancers. Because non-cervical HPV cancers have low incidence, these analyses may best be done by pooling data from several countries.

D. Monitoring Positive Cervical Cancer Screening Tests

1) Monitoring the rate of positive cervical cancer screening tests is useful for assessing cervical cancer screening programs but is insufficiently specific for monitoring HPV vaccine programs. Many non-vaccine factors impact the number of positive test results (e.g., changes in screening tests, access to screening, screening practices) making it difficult to assess vaccine impact from data on changes in positive test results.

E. Monitoring Genital Warts

1) Monitoring genital warts has drawbacks which do not make it ideal for HPV vaccine impact monitoring in resource-poor settings. Most importantly, genital wart monitoring does not measure vaccine impact on cervical cancer or cancer precursors and can be a measure for genital wart impact only for quadrivalent vaccine.

F. HPV vaccine coverage monitoring

1) For HPV vaccine impact monitoring, it is necessary to monitor HPV vaccine coverage by age and by dose. Therefore, date of birth, date of vaccine administration, and dose number should be recorded for every dose administered.

2) A useful summary indicator to compare vaccine coverage trends over time and across geographical regions will be the proportion of girls vaccinated with 3 doses of HPV vaccine by age 15 years.

3) Approaches need to be developed and piloted for a) registering HPV vaccine doses for program coverage monitoring, b) recording HPV vaccine doses in an adolescent health record which will be retained by a girl over her lifetime.

4) A number of challenges will need to be addressed as approaches for HPV vaccine coverage monitoring are piloted. These include how to ascertain denominator (i.e., size of target population), how to record age in societies where birth dates are not recorded, and how to monitor coverage where multiple vaccine delivery strategies are used (e.g., delivery through private sector, schools, campaign or child health days, clinics).

G. HPV vaccine safety monitoring

1) Addressing HPV vaccine safety should include ensuring AEFI surveillance and establishing a good risk communication strategy to cope with spurious media reports. Having a communication message and strategy in place prior to HPV vaccine implementation is critical. Since the vaccine is targeted at an age group not routinely served by EPI and is targeted at girls only, and since there may be social or cultural sensitivities about HPV as a sexually transmitted infection, adequate attention and time are needed to assess acceptability of the vaccine among girls, parents, and health workers, and to develop and implement communication messages in advance of introducing HPV vaccine.

2) Compiling references and data on background rates for illnesses in adolescents will be useful for interpreting adverse events attributed to HPV vaccine.

Appendix 1: Meeting Agenda

HPV Surveillance and Monitoring Meeting,
16-17 November 2009
World Health Organization
20, Ave Appia
1211 Geneva
Switzerland

Main Building, Salle B

Monday 16 November 2009

08:30–10:00	**Welcome, Introductions, and Meeting Objectives**	Carsten Mantel
	Plenary: Background	
	Facilitator: Mike Chirenje *Rapporteur: Terri Hyde*	
	a) HPV and HPV vaccines	Eileen Dunne
	b) Overview of goals for surveillance and vaccine impact monitoring; brief background on work to date on HPV vaccine impact monitoring	Susan Wang
	c) Overview of HPV and cervical cancer screening tests	Beth Unger
	d) Overview of monitoring and evaluation of cervical cancer screening programs and overview of cancer registries	R Sankaranarayanan
	Discussion: What outcomes are needed for country and regional policy deliberations? What data are needed for vaccine introduction? Why do impact monitoring? What are the objectives, what data are needed?	
	Charge to Workgroups	
10:00–10:30	*Break*	

10:30–12:30 **Workgroups**

1) HPV prevalence, Room C102

Facilitator: Gary Clifford
Rapporteur: Eileen Dunne

2) CIN II-III prevalence and HPV type distribution, Salle B

Facilitator: Susan Hariri
Rapporteur: Beth Unger

3) Invasive cervical cancer and associated HPV types, Room C202

Facilitator: Mona Saraiya
Rapporteur: Jördis Ott

4) Positive screening tests and referrals for treatment, Salle B

Facilitator: Aisha Jumaan
Rapporteur: Nathalie Broutet

12:30–13:30 *Lunch*

13:30–15:30 **Plenary: Report of output from workgroups**

Facilitator: Quek Swee Chong
Rapporteur: Linda Eckert

Discussion: How do monitoring the different endpoints compare with regards to feasibility, target population, cost, infrastructure needs, etc.? What are the research needs or demonstration projects that need to be done in order to provide more complete guidance on best approaches to monitoring HPV vaccine impact?

15:30–16:00 *Break*

16:00–17:30 **Plenary: Other outcomes to consider monitoring for HPV vaccine impact**

Facilitator: Kimberley Fox
Rapporteur: Linda Eckert

— Genital warts
— Non-cervical HPV-associated cancers in registries

Tuesday 17 November 2009

08:30–10:30	**Presentation:** *HPV vaccine coverage monitoring*	*Tony Burton*
	Discussion *Facilitator: Marta Gacic-Dobo* *Rapporteur: Deblina Datta*	
10:30–11:00	**Break**	
11:00 –12:00	**Presentation:** ***HPV vaccine safety monitoring***	*Patrick Zuber*
	Discussion *Facilitator: Julia Brotherton* *Rapporteur: Mary Agocs*	
12:00–*13*:00	**Lunch**	
13:00–14:30	**Discussion** of laboratory needs of HPV vaccine impact monitoring *Facilitator: Joakim Dillner* *Rapporteur: Susan Hariri* What are the needs of HPV impact monitoring which might be provided by a laboratory network such as HPV LabNet? What are the costs and how might it be supported?	
14:30–15:00	**Break**	
15:00–16:30	**Brainstorming session on program synergies and how to accomplish impact monitoring** *Facilitator: Julietta Patnick* *Rapporteur: Silvana Luciani* What are the synergies to link surveillance and monitoring with existing screening activities? How can the pragmatic issues be addressed? Who are the partners and the resources? Who funds, who collects data, who will monitor? EPI? STI? Cancer? What are the next steps? Other issues — For example, the ethical/logistical issue of what should be done about HPV+ women who are identified by screening programs? How should the findings be explained? What kind of follow-up can be offered and how will it be supported? — What is the role for strengthening cervical cancer screening activities in a coordinated manner with HPV vaccine introduction? How can this be done?	
16:30–17:00	**Review** of outputs from meeting and next steps *Facilitator: Carsten Mantel* *Rapporteur: Susan Wang*	

Appendix 2: Meeting Participants

List of participants

Julia Brotherton National HPV Vaccination Program Register Victorian Cervical Cytology Registry PO Box 310 East Melbourne 8002 Australia	Laia Bruni-Loccos Cancer Epidemiology Research Program (CERP) Unit of Infections and Cancer (UNIC) Catalan Institute of Oncology Avda. Gran Via, s/n Km. 2,7 08907 L'Hospitalet de Llobregat, Barcelona Spain
Mike Chirenje Department of Obstetrics and Gynaecology College Health Sciences University of Zimbabwe P O Box A178 Avondale Harare Zimbabwe	Quek Swee Chong Preinvasive & Screening Unit Senior Dept of Gynaecological Oncology KK Women's & Children's Hospital Singapore 229899 Singapore
Gary Clifford Consultant & Head Infections and Cancer Epidemiology International Agency for Research on Cancer 150 Cours Albert Thomas 69372 Lyon Cedex 08 France	Heather Cubie Director Scottish National HPV Reference Laboratory Specialist Virology Centre Royal Infirmary of Edinburgh Edinburgh United Kingdom
Kate Cuschieri Deputy Director Scottish National HPV Reference Laboratory Specialist Virology Centre Royal Infirmary of Edinburgh 51 Little France Cres Edinburgh, United Kingdom	Deblina Datta Division of STD Prevention, NCHHSTP Centers for Disease Control and Prevention Atlanta, GA USA
Joakim Dillner WHO Global Reference Laboratory/HPV LabNet Lund University Sweden	Eileen Dunne Division of STD Prevention, NCHHSTP Centers for Disease Control and Prevention USA

Linda Eckert Consultant 6613 Woodlawn Avenue Seattle, Washington USA	Susan Hariri Division of STD Prevention, NCHHSTP Centers for Disease Control and Prevention Atlanta, GA USA
Isabelle Heard Joint - Director French National HPV Laboratory Institut Pasteur Paris France	Becky Howell-Jones International Agency for Research on Cancer 150 Cours Albert Thomas 69372 Lyon Cedex 08 France
Terri Hyde Global Immunization Division, NCIRD Centers for Disease Control and Prevention Atlanta, GA USA	Aisha Jumaan PATH 1457 NW Leary Way Seattle WA 01210 USA
Katy Irwin Consultant 2006 23rd Ave East Seattle, WA 98112 USA	You-Lin Qiao Department of Cancer Epidemiology Cancer Institute Hospital Chinese Academy of Medical Sciences Beijing Peoples' Republic of China
Emmanuel Mugisha Country Manager PATH HPV Vaccine Project WHO Building 4, Hannington Rd PO Box 24578 Kampala Uganda	Julietta Patnick Director NHS Cancer Screening Programmes Sheffield United Kingdom
Marion Piñeros Instituto Nacional de Cancerología Ministerio de Protección Social - Colombia Calle 1 No. 9-85 Bogotá Colombia	R. Sankaranarayanan, M.D. Head, Screening Group International Agency for Research on Cancer 150 cours Albert Thomas 69372 Lyon Cedex 08 France
Mona Saraiya Division of Cancer Prevention and Control, NCCDPHP Centers for Disease Control and Prevention Atlanta, GA USA	Sepehr Tabrizi Molecular Microbiology Laboratory Faculty of Medicine Dentistry and Health Department of Obstetrics and Gynaecology University of Melbourne Melbourne Australia
Beth Unger Division of Viral and Rickettsial Diseases, NCZVED Centers for Disease Control and Prevention Atlanta, GA USA	

Via Telephone

Xavier Bosch Catalan Institute of Oncology Avda. Gran Via, s/n Km. 2,7 08907 L'Hospitalet de Llobregat, Barcelona Spain	Lauri Markowitz Division of STD Prevention, NCHHSTP Centers for Disease Control and Prevention Atlanta, GA USA
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WHO RO's

AFRO Regional Office Barthelomew Akanmori	WHO Country Office UGANDA Andrew Bakainaga
WPRO Regional Office Kimberly Fox	PAHO Regional Office Silvana Luciani
AFRO Regional Office Khadi Mbaye	EURO Regional Office Liudmila Mosina
EMRO Regional Office Nadia Teleb	

WHO HQ

Mary Agocs FCH/IVB/EPI	Nathalie Broutet FCH/RHR/STI
Anthony Burton FCH/IVB/EPI	Vicky Camacho de Barrios FCH/CAH/ADH
Bruce Dick FCH/CAH/ADH	Martha Gacic-Dobo FCH/IVB/EPI
Tracey Goodman FCH/IVB/EPI	Joachim Hombach FCH/IVB/IVR
Carsten Mantel FCH/IVB/EPI	Gill Mayers FCH/IVB/EPI
Jördis Ott NMH/CHP/CPM	Andreas Ullrich NMH/CHP/CPM
Susan Wang FCH/IVB/EPI	Patrick Zuber FCH/IVB/QSS

Workgroup Participants

1) HPV prevalence
Facilitator: Gary Clifford, Rapporteur: Eileen Dunne

Becky Howell-Jones, IARC
Heather Cubie, Scottish National HPV Reference Laboratory
Joakim Dillner, WHO Global Reference Laboratory
Emmanuel Mugisha, PATH Uganda
You-Lin Qiao, China Academy of Medical Sciences
Bartholomew Akanmori, WHO AFRO
Silvana Luciani, WHO PAHO
Linda Eckert, University of Washington
Katy Irwin, Consultant to IARC
Nadia Teleb, WHO EMRO
Isabelle Heard, French National HPV Laboratory
Laia Bruni Coccos, ICO

2) CIN II-III prevalence and HPV type distribution
Facilitator: Susan Hariri, Rapporteur: Beth Unger

Julia Brotherton, National HPV Vaccination Registry
Deblina Datta, CDC
Andreas Ullrich, WHO
Carsten Mantel, WHO
Kate Cushieri, Scottish National HPV Reference Laboratory

3) Invasive cervical cancer and associated HPV types
Facilitator: Mona Saraiya, Rapporteur: Jördis Ott

Julietta Patnick, NHS Cancer Screening Programmes
Liudmila Mosina, WHO EURO
Andrew Bakainaga, WHO Uganda
Marion Piñeros, Colombia
Mary Agocs, WHO
Sepehr Tabrizi, The Royal Women's Hospital and The Royal Children's Hospital

4) Positive screening tests and referrals for treatment
Facilitator: ***Aisha Jumaan,*** **Rapporteur:** ***Nathalie Broutet***

Mike Chirenje, University of Zimbabwe
Terri Hyde, CDC
R. Sankaranarayanan, IARC
Kimberley Fox, WHO WPRO
Khadi Mbaye, WHO AFRO
Quek Swee Chong, KK Women and Children's Hospital

Appendix 3: Table showing Comparison of Methods to Evaluate HPV Immunization

Table 1: Comparison of Methods to Evaluate HPV Immunization Programs

	Coverage		HPV prevalence monitoring	Positive screening tests	Precancerous lesion surveillance	Cervical cancer registry
	Administrative	Survey				
Accuracy of information	+/-	+	+	+/-	+/-	+
Requires ongoing commitment	+	-	++	+	+	+
Expense	-	+	+++	+	+++	++
Direct measure of desired outcome	-	-	+/-	+/-	++	+++
Technical input (e.g., laboratory)	-	+/-	+++	+	+++	+
Timeliness of information	+++	++	+	-	-	-

Appendix 4: Tables of HPV tests

Table 1: HPV DNA tests for Clinical Use

Test	Manufacturer	Method/Sample Prep	Types Detected (Molecular Target)
*Hybrid Capture 2§	Qiagen (Valencia, CA)	Signal amplification/Lysis	13 HR types (Genomic)
*Cervista	Third Wave Technologies, Hologic (Madison, WI)	Probe Amplification Invader technology/DNA extraction	14 HR types (Proprietary)
*Cervista 16/18			HPV 16 and 18 (Proprietary)
AMPLICOR HPV	Roche Diagnostics (Indianapolis, IN)	PCR/DNA extraction	13 HR types (L1 consensus region)
PreTect HPV-Proofer	NorChip (Klokkarstua, Norway)	Nucleic Acid-based sequence Amplification/RNA extraction	5 HR types (E6/E7 mRNA)
APTIMA HPV Assay	Gen-Probe (San Diego, CA)	Transcription mediated amplification/RNA extraction	14 HR types (E6/E7 mRNA)

* US FDA approved
§ Anticipated release of CareHPV, low cost version HC2

Table 2 - HPV Detection and Typing Assays for Epidemiologic Studies

Test	Manufacturer	Method/Sample Prep	Types Detected (Molecular Target)
Linear Array (RUO)	Roche Diagnostics (Indianapolis, IN)	L1 consensus PCR- PGMY/DNA extraction	37 types (type specific oligos, strip hybridization)
INNO-LiPA (RUO)	Innogenetics (Gent, Belgium)	L1 consensus PCR- SPF10/DNA extraction	28 types (type specific oligos, strip hybridization)
MyHPV Chip	MyGene Co (Seoul, Korea)	L1 consensus PCR – GP5+/6+/DNA extraction	24 types (type specific oligos microarray)
CLART	Genomica (Spain)	L1 consensus PCR – PGMY/DNA extraction	? types (type specific oligos, array)
PGMY-CHUV	"Home brew", CHUV Evaluated by WHO LabNet	L1 consensus PCR- PGMY/DNA extraction	32 types (type specific oligos, chemilum. Filter hyb)
PCR Luminex	"Home-brew"	L1 consensus PCR – GP5+/6+/DNA extraction	24 types (type specific oligos, Luminex)
PCR-APEX	"Home-brew", IARC	E6/E7 primer extension/DNA extract	Luminex detection
RFLP	"Home-brew"	L1 consensus PCR/DNA extraction	Varies

Many other published assays, increasingly commercially available.

Table 3: HPV Serology Tests – No commercial reagents

Test	
L1 VLP	ELISA
cLIA	Competitive Luminex immunoassay, VLP antigen (Merck)
Pseudovirion Neutralization (PsVN)	NCI (John Schiller)

Anticipated commercial serology test [VLP], also potential WHO reagents

Appendix 5: Work Group 1 Outline - HPV DNA Prevalence

Monitoring impact of HPV vaccination on HPV DNA prevalence

Work Group Facilitator: Gary Clifford
Rapporteur: Eileen Dunne

I. Purpose

To monitor the impact of HPV vaccines on the prevalence of HPV infection in low- and medium-resource countries.

II. Main indicators being monitored

Prevalence of HPV infection (based upon detection of HPV DNA) in genital samples.

III. List of possible approaches to monitor the desired indicators

A. HPV DNA prevalence in females soon after sexual debut (aged <25yrs mostly): impact expected 5-10 years after vaccine program initiation.

B. HPV DNA prevalence in females undergoing cervical cancer screening (aged ≥25yrs mostly): impact would be seen 10+ years after vaccine program initiation.

IV. Minimal requirements:

A. HPV DNA prevalence in females soon after sexual debut

1. Opportunistic setting for access to young (15-20 yrs old) sexually active women

   These may include a) STI clinics; b) family planning clinics; c) ante-natal clinics; d) pre-marital health check-ups (e.g., in some Asian countries); e) university clinics. These young women and girls would be offered a cervical/vaginal collection of cells for the detection of HPV DNA, or self sampling. This procedure might require consent, especially in settings where such a sampling would not otherwise have been done.

   Population-based recruitment of young women to sentinel sites is expected to be much more challenging as young sexually active women are hard to identify in the community, however this could be one alternative to clinic based assessments.

2. Good coverage of HPV vaccination

To allow statistically meaningful age-specific comparisons of HPV prevalence in vaccinated versus non-vaccinated women at the same point in time, sample size calculations that would allow sufficient power to determine reduction in vaccine type HPV infection given different scenarios of HPV vaccine coverage, baseline HPV prevalence, and time frame for assessment would be needed.

Note: Women coming through the opportunistic setting may not represent the coverage of HPV vaccination in the wider population

3. Knowledge of HPV vaccination status

Vaccination status of girls, presumably vaccinated between ages 11-14, will need to be known 5-10 years later when they are teenagers or in their early 20's.

This information will need to come from a) individual vaccination registers; b) vaccination cards; c) personal recall; or d) surveys/other evaluations.

The ability to confirm vaccination status in an individual might be improved by linking information given by the women with historical data on school- and/or village-specific vaccination campaigns (**NOTE:** possible link with recommendations for vaccine coverage monitoring).

Theoretically, under conditions of fast roll-out and high coverage levels, the impact of the vaccination program on HPV prevalence might be evaluated even in the absence of the knowledge of HPV vaccine status. This approach would compare age-stratified HPV DNA prevalence over time in cohorts of women with unknown individual-level vaccination status. However, even under reasonable models of vaccine roll-out and coverage, the sample sizes required may be very large and would require the assumption that the population sampling framework, patterns of sexual behavior, and HPV testing protocols remain consistent over a long period of time, perhaps >10 years.

B. HPV DNA prevalence in females undergoing cervical cancer screening

1. Good quality cervical cancer screening program

Routine data is most likely to arise predominantly from cervical cancer screening clinics.. One method used for screening could be an HPV test. In low-resource settings, there may be future programs using point of care HPV tests, tests that determine infection with 13-14 high risk HPV types with the primary purpose of cervical cancer screening, so threshold of detection is matched to optimize correlation with disease. Therefore these tests are not optimal for the purposes of measuring HPV vaccine impact as the tests generally do not provide HPV type specific information and have a lower analytic sensitivity than assays used in vaccine clinical trials and epidemiologic studies of HPV. However, the collection of a specimen for purposes

of cervical cancer screening may facilitate HPV monitoring of vaccine impact by providing a specimen for HPV type specific evaluations, possibly in centralized laboratories with a high level of technical expertise.

There may be an opportunity to collect specimens for HPV testing using other cervical cancer screening methods including cytology and VIA. However, limitations include lack of efficiency (HPV tests need to be done on all women only for the sake of monitoring) and potential ethical challenges about providing test results to HPV-positive women.

2. Good coverage of HPV vaccination

   These issues are much the same as for females soon after sexual debut, with the additional challenge that vaccination status needs to be assessed >10 years after vaccination.

3. Knowledge of HPV vaccination status.

   These issues are much the same as for females soon after sexual debut, with the additional challenge that vaccination status needs to be assessed >10 years after vaccination.

V. Recommended sites and target population

A. For the younger population of women, the above pre-requisites can be expected to be met only by relatively few low- and medium-resource settings, i.e. settings where there will be fast and widespread roll-out of HPV vaccine, good recording of vaccination status, and commitment of funds and infrastructure to monitoring for at least 10 years.

B. The monitoring of HPV prevalence in older women is additionally challenged by the much longer time frame to appreciate impact and the fact that a cervical cancer screening program, needs to be in place.

C. Thus, monitoring the impact of HPV vaccines on HPV infection in low-resource settings might remain the domain of special studies only, requiring substantial investment in infrastructure and expertise.

VI. Outcomes being monitored through this approach and their case definitions

A. Evaluation of type-specific HPV prevalence (including HPV 16, 18) in vaccinated women compared to non-vaccinated women at the same time point, or a baseline reference. Cohort or cross-sectional assessments could be performed.

   Advantages: Gives specific results of impact on HPV16 and HPV18 infection, as well as that on other HPV types (e.g., to test for cross-protection).

   Disadvantages: Requires genotyping, which is presently time-consuming, expensive, and needs to be done using a standardized protocol in a good-quality laboratory.

B. Cervical or cervicovaginal samples are the optimal material for the detection of HPV DNA. Alternatives to cervical samples, especially if they improve participation and help obviate the need for reporting of HPV test results back to women could include urine samples, although this approach has been found to be less sensitive, and not easily performed even in resource rich settings.

VII. Recommended laboratory assays

A. The optimal HPV test to use for the purpose of monitoring HPV vaccine impact is unclear and may depend on the setting. An optimal test would be sensitive and allow consistent determinations over time of type specific HPV infection, HPV 16, 18 (and possibly 6, 11 in settings in which the quadrivalent HPV vaccine is used). Due to the inevitable evolution in tests for HPV detection and genotyping over time, it is recommended that, whenever possible, a fraction of genital samples for all evaluations be frozen in a central location for long-term storage, allowing for possible historical comparisons in the future.

B. Routine monitoring of HPV prevalence in screening programs based upon an HPV test that includes 13-14 high-risk HPV types could facilitate HPV monitoring for vaccine impact. There would likely need to be an HPV type specific assessment in most scenarios to delineate HPV vaccine impact on HPV 16, 18 infection (these assessments could be performed following a clinical HPV test using the same specimen). Genotyping should only be done using a well-validated protocol in a well-validated laboratory.

C. More desirable types of point of care HPV 16, 18 DNA tests may yet become available that would avoid the need for expensive genotyping and could provide information both for cervical cancer screening purposes, as well as monitoring HPV vaccine impact. However clinical tests will not detect low copy numbers of HPV vaccine types and the reliability of these tests for vaccine monitoring has not been verified.

VIII. Definition of denominator

A. HPV DNA prevalence in females soon after sexual debut.

Denominator = All women from opportunistic setting accepting HPV test and with a valid HPV test result.

This denominator is assumed not to be representative of the general population, but only to allow a very early evaluation of the impact on vaccination in an exposed group of young women. It is also likely that this denominator is very sensitive to changes in sexual behaviour and the "catchment" of the clinic. Hence, the interest to compare non-vaccinated and vaccinated women at the same time-point, rather than overall trends in HPV prevalence over time.

B. B. HPV DNA prevalence in females undergoing cervical cancer screening

Denominator = All women undergoing cervical cancer screening accepting HPV test and with a valid HPV test result

This denominator is assumed to be reasonably representative of the population. Nevertheless, the access to cervical cancer screening may well be differential for vaccinated and non-vaccinated women.

IX. Challenges

A. This monitoring approach requires extensive resources (financial and personnel) and commitment for a long period of time to ensure the obtaining of meaningful, rather than misleading, outcome data. This has important implications for funding sources.

B. There is a very important time-factor to be considered. Assuming that vaccination is offered to 11-14 year olds in low-resource settings, a substantial cohort of vaccinated women will not arrive, even in the opportunistic setting of STI clinics, for at least 5 five post-vaccination. For the cervical cancer screening population, this time point is at least 10 years.

C. Furthermore, when a reasonable time for the piloting and rolling-out of a vaccination program to high coverage levels is factored in, these time points might be delayed by another 5 to 10 years.

D. Arguably, the above pre-requisites, that would make the monitoring of HPV vaccine on HPV prevalence both logistically feasible and statistically meaningful, can be expected to be met only by relatively few low- and medium-resource settings.

E. Ethical issues

HPV infections in young women, especially under the age of 25 years, are likely to clear and are not a useful indicator of future cervical cancer risk. It would be optimal in the setting of evaluation of HPV in young women to not provide test results back to participating young women for this reason. Anonymyzing test results, if acceptable, could facilitate this objective. However, given that many settings may require these results be given back to women for a number of reasons, more information is needed on the best methods to give this information and the impact that this information has for the woman and her partner. In settings in which there are cervical cancer screening programs, women participating in an HPV vaccine monitoring evaluation would be recommended to follow-up later through the screening programs. However, in settings in which there are no cervical cancer programs, an HPV prevalence monitoring activity may need to closely align with future provision of cervical cancer screening in older females.

X. Gaps/Outstanding Needs

Arguably, given the above issues, monitoring of the impact of HPV infection in low-resource settings is almost entirely the domain of research, requiring well-standardised centre-specific protocols and significant investment in infrastructure and training.

Outstanding needs for HPV monitoring includes the temporal framework for these evaluations, the best HPV test to use for monitoring, and the information needs of women receiving HPV test results (if required).

XI. Any existing experience in this monitoring approach

No experience exists for the monitoring of HPV prevalence in low- and medium- resource settings.

However, the above types of studies have been designed in various high-income countries that are presently rolling out HPV vaccine (Australia, UK, USA). There is no current standard approach to evaluating the impact on HPV types, but most assessments will at minimum evaluate for reductions in HPV 16 or 18 (or HPV 6, 11, depending on the vaccine used).

Experience with HBV vaccination in low- and medium-resource settings is perhaps the most similar precedent, but has been somewhat facilitated by a meaningful serological marker for chronic infection (HBsAg) that does not exist for HPV.

XII. Feasibility

Given the logistical, temporal and ethical considerations, monitoring of the impact of HPV vaccination on HPV prevalence will not be done in a routine manner in low- and medium-resource settings. Select sentinel sites in different regions may be used to provide information that may be relevant to other settings.

Appendix 6: Work Group 2 Outline - CIN 2/3 and AIS

Monitoring HPV vaccine impact on pre-invasive cervical lesions (cervical intraepithelial neoplasia grades 2+ (CIN 2/3) and adenocarcinoma in situ (AIS)) and associated HPV types

Work Group Facilitator: Susan Hariri
Rapporteur: Beth Unger

Purpose

High-grade cervical lesions (CIN 2/3 and AIS) may develop within 5-10 years of initial HPV infection, and if left untreated, have a high likelihood of progressing to cervical cancer. CIN 2/3 were used as surrogate endpoints for cervical cancer in clinical vaccine efficacy trials and are the most robust proxy for measuring the desired impact of vaccine (i.e., reducing the burden of cervical cancer) at the population level.

Main indicator being monitored

- Distribution of HPV types associated with diagnosed CIN 2/3 and AIS lesions
  - Incidence of CIN2/3 and AIS lesions could be used, but with more potential for errors in interpretation

Possible approaches

Add HPV type-specific CIN2/3 and AIS monitoring to existing colposcopy program

- Methods
  - Establish systematic CIN2/3 and AIS case reporting and specimen collection in one or more clinics providing colposcopy/histology services
- Minimal requirements
  - Infrastructure
    - Stable cervical cancer screening program
    - Existing clinic(s) performing colposcopy and biopsy
    - Existing laboratories and experienced pathologists for histology preparations and HPV DNA testing

- Capacity
  - Ability to interpret histologic results (or send for interpretation)
  - Availability of appropriate follow-up and treatment services
  - Ability to collect diagnostic histology specimens and transport to reference lab for DNA typing
  - Optional: Ability to identify clinics that screen and refer women to colposcopy clinic
  - Optional: Ability to collect data on total number of women screened and referred by each referral clinic
- Types of patient data collected
  - Age
  - Cervical histology results (verified by consensus review)
  - Optional: Vaccine status; other demographic information

- Recommended site/population
  - Target population- young, sexually active women at or above the lowest age limit recommended for cervical cancer screening up to age 40 years
  - Setting- Any health care facility performing colposcopy and biopsy along with histology laboratory processing biopsy. Examples include tertiary care hospitals and colposcopy referral clinics

- Endpoints (case definitions)
  - HPV type distribution (proportion of vaccine types) in histologically diagnosed CIN2, CIN3, CIN2/3, AIS, or any combination of these (e.g., CIN2 + AIS, etc) in age eligible female

- Recommended laboratory assays
  - Type-specific HPV DNA assay
  - Optional: virtual slide for histology review

- Denominator (definitions)
  - Age-eligible women screened for cervical cancer during same time period (i.e., includes women screened at the main facility and at other clinics that refer to the main facility)
  - Age-eligible women with abnormal screening results who were referred to main clinic for colposcopy

- Challenges
  - CIN2/3 and AIS can only be detected through screening and are directly affected by changes in cervical screening practices. Changes in screening practices may result in increased CIN diagnosis, leading to potential misinterpretation of vaccine impact on burden of cervical precancers
  - Changes in screening, laboratory assays, and unstable populations could result in poor reproducibility and inability to monitor trends over time
  - Laboratory capacity to collect and test specimens using standard methods may not exist and/or difficult to establish and sustain
  - Interpretation of histology results can be subjective and imprecise, thus requiring verification and standardization of diagnoses
  - May be difficult to adjust estimates (denominators) to account for changes in lesion detection (i.e., enumerate all referral clinics, and number of women screened/referred for colposcopy within each clinic)
  - Collecting baseline data prior to vaccination is resource intensive and may impede vaccine introduction efforts
  - Number of diagnosed cases may be small if screening and/or referral is low (lack of power to detect expected percent reductions, especially if vaccine uptake is low)
  - Existing screening and referral may not exist, and new programs may be difficult to establish and sustain
  - May be difficult to determine vaccine status at individual level in absence of vaccine registries (poor recall given long interval between vaccination and CIN2/3, adolescents less likely to maintain immunization cards)
  - May be difficult to monitor vaccine coverage at the population level

- Examples of existing experience with this approach
  - Pilot projects underway in the U.S. and other developed countries with routine and widespread screening programs

- Feasibility
  - May be feasible as a well-designed research (sentinel) project in settings with routine screening. HPV testing of the lesions will be needed to evaluate impact of vaccine independently of screening practices. Histologic verification of lesions would be optimal for monitoring trends.
  - Not recommended in settings with no routine screening

Opportunities

- Strengthen and expand existing cervical cancer screening activities and link to vaccine monitoring activities
- Strengthen existing laboratory and anatomic pathology capacity
- Build and strengthen capacity for clinical services provided (including cervical cancer screening, referral and follow-up, treatment) and linkage to vaccine monitoring
- Strengthen existing or establish new data reporting, collection, management, and linkage systems
- Establish new systems and programs

Outstanding issues

- Determine sample sizes required to measure impact for various vaccine uptake scenarios for guidance in decision making

Appendix 7: Work Group 3 Outline - Cervical Cancer

Monitoring HPV vaccine impact on incidence and mortality of invasive cervical cancer cases and associated HPV types

Work Group Facilitator: Mona Saraiya
Rapporteur: Jördis Ott

Purpose

- Invasive cervical cancer is an important biological endpoint in monitoring the impact of the HPV vaccine, but such an impact may take anywhere from 15 to 20 years, and is highly dependent on vaccine coverage and screening and treatment infrastructure.

Main indicators that burden of cervical cancer has been reduced

- Decrease in incidence (earliest indicator would be decreased incidence in youngest age)
- Age-specific incidence
- Change in histology distribution of cancers, increasing of proportion of adenocarcinomas
- Decrease in mortality (all countries have this information available for cause of death, not regional)
- Decreases in vaccine type-specific cancers (especially with a focus on cancers diagnosed in younger women)

Possible Approaches

- Population-based
- Clinic-based (with availability of denominator data)
- Numerator-Based

Population-based

Minimal requirement

- Existent population based cancer registry in collaboration with hospital-based registry.
- Minimal data covered on incident cancer case
  - Age
  - Primary Site (cervix)
  - Histology (squamous cell carcinoma vs. adenocarcinoma)-use standardized morphology codes ICD-3
  - Behavior: in situ vs. invasive
  - Stage of diagnosis Stage 0 to IV (this is often collected as treatment is based on this piece of data but would not be essential)
  - Most valid basis of diagnosis –histology , cytology
- Recommended Sites and Target Populations
  - Consistency across where vaccine is targeted and where registries exist in the same areas
  - Consider targeting capturing cancers among young women (under 30, 40)
- Outcomes being monitored through this approach
  - In situ cervical cancers (if these are collected)-CIN III, 8077/2, severe dysplasia, HSIL
  - Invasive cervical cancer (C53 site code, any histology)
    - Make sure all possible sources of cancer diagnosis are captured.
- Recommended laboratory assays
  - HPV genotyping via PCR (many assays)
- Definition of denominator
  - Catchment area through official census data
  - Urban vs. rural breakdown
  - Use of Census for area
  - Population at risk of getting cervical cancer (women)
    Women with intact cervix (i.e. no hysterectomy)-ideal
    Fertility rates in the area covered in young ages.
- Challenges
  - Resource intensive
  - Expensive
  - Active vs. passive surveillance
  - Continue or periodic surveillance
  - Unclear if vaccination status will be available

- Areas requiring Research
  - Feasibility/capability of genotyping
- Any existing experience in this monitoring approach-important to asses any research study in the area as case control studies.
- Feasiblility-de novo cancer registry might be difficult but if focus is only on cervical cancer, this might be really doable mainly in low income areas.
- Minimal quality assurance of cancer registry based on (IARC 1991, Principles of Cancer Registration)
  - Percentage of cases with microscopic confirmation
  - Ratio of mortality to incidence
  - % Death certificate
  - % Clinical Diagnosis
  - Stability of the rates over time
- Definition of Population coverage of the area covered by the cancer registry for the period of data collection minimal period required to evaluate the incidence trends 20 years

Hospital-based (convenience sample, not population-based approach)

Minimal requirement.

- Hospital-based clinic (tertiary, referral center)
- Minimal data covered on incident cancer case
  - Age
  - Primary Site (cervix)
  - Histology (squamous cell carcinoma vs. adenocarcinoma)-use standardized morphology codes
  - Behavior:in situ vs. invasive
  - Stage of diagnosis (this is often collected as treatment is based on this piece of data)
  - Most valid basis of diagnosis same as for population based cancer registries
- Recommended Sites and Target Populations
  - Consistency across where vaccine is targeted and where registries exist
  - Consider targeting capturing data on cancers among young women (if limited resources)
- Outcomes being monitored through this approach
  - In situ cervical cancers (if these are collected)-CIN III, 8077/2, severe dysplasia, HSIL
  - Invasive cervical cancer (C53 site code, any histology)
  - HPV vaccine status (optional)

- Recommended laboratory assays
  - HPV genotyping via PCR (many assays)
- Definition of denominator
  - Catchement area through census data
  - Urban vs. rural breakdown
  - Use of Census for area
- Challenges
  - Resource intensive
  - Expensive
  - May be problematic as population changes or tertiary hospitals are added
- Areas requiring Research
  - Feasibility/capability of genotyping
- Any existing experience in this monitoring approach-important to asses

Numerator-Based Only approach (where hospitals are not able to get denominators)

- Minimal data covered on incident cancer case
  - Age
  - Primary Site (cervix)
  - Histology (squamous cell carcinoma vs. adenocarcinoma)-use standardized morphology codes
  - Behavior:in situ vs. invasive
  - Stage of diagnosis (this is often collected as treatment is based on this piece of data)
  - Most valid basis of diagnosis same as for population based cancer registries
- Recommended Sites and Target Populations
  - Consistency across where vaccine is targeted and where registries exist
  - Consider targeting capturing data on cancers among young women (if limited resources)
- Outcomes being monitored through this approach
  - Insitu cervical cancers (if these are collected)-CIN III, 8077/2, severe dysplasia, HSIL
  - Invasive cervical cancer (C53 site code, any histology)
  - HPV vaccine status (optional)
  - HPV genotyping in cancers

- Challenges
  - May be problematic as population changes or tertiary hospitals are added
- Areas requiring Research
  - Feasibility/capability of genotyping

Additional (non-essential) criteria for all approaches

- Ability to monitor trends in cervical cancer screening utilization and treatment in the general population by age over time (cannot tease out effect of screening vs. treatment vs. vaccine)
- Capacity for specimen collection and transport to reference lab (for DNA genotyping), could refer outside of country
- Data Quality in Population based Cancer registry information (that meets criteria established by IARC) vs. local hospital-based cancer registry
- Ability to link vaccine coverage data with cancer registry incidence cases.

Challenges

- Existing cancer registry may not be in place where vaccination program or highest risk population live
- Africa and Latin America/South America have limited population coverage and low # of quality cancer registries,
- Mortality data for cervical cancer might not be differentiated from rest of uterus (c55, uterus not specified)
- Tertiary hospital may see many referral patients from other areas
- Few Pathology Lab and may not be in country.
- May be difficult to monitor vaccine coverage and changes in screening recommendations and practices at the population level
- With limited screening infrastructure, changes may be more likely to be attributed to vaccine vs. screening

Opportunities

- Strengthen and giving sustainability for the existing population based cancer registries or cancer control.
- Strengthen existing laboratory capacity for HPV typing
- Strengthen Screening capacity in genotyping HPV.
- Making HPV typing of cervical cancer routine, especially in young women
- Where cervical cancer mortality/incidence is already being collected, a similar strategy of monitoring incidence /mortality /HPV genotyping of cancers may be considered for other HPV-associated cancers with a clear cut etiology to HPV (vulvar, vaginal, anal, penile)

Outstanding issues

- Many technical issues may be needed to assess how cancer registration would optimally take place (include determination of software, how to determine completeness, validity and timeliness). This can be strength in collaboration with IARC and CDC to assist the target countries with special attention to the countries with high incidence of cervical cancer.

Appendix 8: Work Group 4 Outline - Positive Cervical Cancer Screening Tests

Monitoring positive cervical cancer screening tests

Work Group Facilitator: Aisha Jumaan
Rapporteur: Nathalie Broutet

Introduction

HPV types 16, 18, 45, 31 and 33 account for about 83% of cervical cancer cases globally. HPV types 16 and 18 that are in the vaccines account for about 70% of the cases (Muñoz, 2004).

Purpose

Evaluate the medium term impact of HPV vaccination on the rate of positive screening tests (on average, 15 years post HPV vaccination).

Method

Measure trends of positive screening tests starting before vaccination (baseline) and regularly till cohorts of vaccinated women are captured. The rates will be assessed regularly (pre-defined intervals: yearly, etc).

Tests to be used:

The current tests that are used for screening include VIA/VILI, PAP and HPV tests. However, the performance of these tests in terms of sensitivity and specificity vary.

1) VIA/VILI

   This involves a naked-eye visual inspection of the cervix, after application of 5% acetic acid (VIA) or of Lugol's iodine (VILI) to detect precancerous lesions or early invasive cancer. The determination of the results depends on the color changes observed on the cervix.

   The appearance of whitish areas (VIA) or yellowish (VILI) in the transformation zone is indicative of a positive test. The final diagnosis is established by pathological examination of specimens from the cervix.

   These methods require trained personnel to distinguish benign inflammation from CIN or invasive cancer; these may include doctors, midwives, and nurses. Good lighting and examination equipment are needed.

2) PAP

An abnormal Pap smear test indicates damaged cervical cells. The Bethesda System results include:

Squamous intraepithelial lesion (SIL) describes precancerous changes in cervical cells.

a) Atypical squamous cells of undetermined significance (ASCUS) – indicates the presence of equivocal cervical cell changes requiring further evaluation to determine if there is a significant histologic abnormality.

b) Squamous intraepithelial lesion (SIL) – describes precancerous abnormal cervical cell changes. SIL is either low grade (LSIL) or high grade (HSIL). LSIL indicates the presence of low grade cervical cell changes suggesting an underlying histology of Cervical Intraepithelial Neoplasia (CIN1) (HPV infection and mild dysplasia). HSIL indicates more serious cervical cell changes suggesting an underlying histology of CIN2 and CIN3 (moderate and severe dysplasia).

c) Other results such as Atypical Squamous cells (ASCH), and Atypical glandular cells (AGC) –require further evaluation to rule out presence of cancer in the glandular epithelium.

d) Cancer – describes abnormal cervical cells that may have spread beyond the basal layer of the cervix.

3) HPV

A positive HPV DNA test indicates the presence of a high-risk HPV type that have risk of progressing to cancer. These include: types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 73.

Main Indicators to monitor

- Proportion of positive tests (test dependent)
- Rate/proportion of screening coverage

The pre and post vaccination evaluation: it will be important to monitor screening service coverage as it is likely that screening services may increase leading to higher numbers of positive screens. Also, it will be important to ensure that data from the same tests are compared over time. If that is not possible, understanding tests performance (sensitivity and specificity would need to be considered when interpreting the results.

Appropriate numerators

- Number of women screened (coverage of service)
- First positive screening test (test dependent: incidence)

Appropriate denominators

- All women eligible for screening in the population (all women targeted by the prevention program: i.e., women 30-50 years of age) to calculate screening coverage rates.
- All women screened in the target age group (i.e., 30-50 years) to calculate proportion of women with positive tests
- Proportions will be stratified by 5 or 10 year age group intervals.

Target ages to monitor

This will depend on the country. Some countries have screening programs for women 30-60 years of age; others start earlier at 25 years while others may end early at 50 years of age.

Screening women between the ages of 30 and 50 may be the most appropriate option to maximize the use of limited resources and monitor impact of vaccination by screening the first vaccinated cohort to reach screening age,

Appropriate sites for monitoring; some may be sentinel

- All or a sample of screening centers that represent the country
- Family health services clinics
- Gynecology clinics
- HIV clinics that perform cervical cancer screening

Many low and middle income countries have one or more screening services or plan to establish one (IARC website). (Figure 1) http://screening.iarc.fr/activ/activity.php?lang=1

If establishing new sites, then selecting sites that have the personnel that can be trained would be the logical first step.

Link HPV vaccination status of monitored population

In most settings, it will not be practical to determine individual HPV vaccination status at the time of screening because of the long interval between vaccination and screening. Instead, the vaccination coverage in the age cohort being screened can be monitored in parallel with the outcome of screening. To determine the vaccination coverage in the age cohort being screened, we will need to know the age groups that have been targeted for vaccination in the previous years and the vaccination coverage in the country at an appropriate interval between vaccination and screening. For example in a country that vaccinates girls at age 12 years and start screen women at 25 years; then we will need to know the coverage of the 12 year olds 14 years before screening. This will change as more vaccinated cohorts enter the screening age.

Laboratory, clinical, and other requirements needed

- Requirements depend on the screening tests that are available in the country.
- VIA/VILI require clinical skills (continuous training) to improve tests' sensitivity and specificity
- PAP would require personnel with well trained cytologist
- HPV-DNA testing would also require trained staff for test performance
- Data collected: data collection should be standardized and minimal data should include the screening test used, result of the screening test, geographic site of screening, type of clinic (FP, HIV, etc), age of women screened, and parity.

Challenges

The performance of the current screening tests (VIA and PAP) will have lower predictive value with reduced incidence of precancerous lesions following vaccinations.

Establishing sustainable surveillance systems requires resources, technical skills and political will. Many developing countries have limited capacity and lack of resources; in some of these countries data are collected in log books that make it difficult to utilize gathered data for dissemination, program evaluation or resource allocation. Therefore, it would be important identify ways to overcome the barriers such as training, automation of data collection and transmission to central level and advocacy among policy makers to allocate funding and provide evidence for the value of using surveillance data for decision making.

There is a long lag time between time of vaccination and time of expected outcome. It would be important to make sure that policy decision makers and communities understand that the impact will not be seen immediately.

Given that many HPV types can result in abnormal results; vaccine coverage would need to be high for impact to be detected. Therefore, it may take many years after the cohorts of vaccinated women become eligible for screening to see a measurable impact.

Duration of protection of the HPV Vaccines: If the vaccines offer life long protection, then we are likely to see the impact among highly vaccinated cohorts when they are eligible for screening. However, if the duration of the vaccine is less than 10-20 years; then it may be difficult to document an impact.

Areas requiring research

HPV testing: Since HPV DNA testing requires batch testing; it may not be feasible to get results to women the same day of testing. Also, data is needed to determine the next steps (triage) for women who test positive.

Any existing experience in this monitoring approach

Screening programs in developed countries have resulted in reduction of cervical cancer morbidity and mortality by identifying pre-cancerous lesions and providing treatment. Many developing countries have screening programs in place; although coverage varies widely. In addition, cost effectiveness analyses have shown that reaching 70% HPV vaccine coverage and screening vaccinated cohorts 3 times in a life time at > 30 years of age would result in life time reduction of cervical cancer mortality in many developing countries (Goldie, 2008). Therefore, it is feasible to monitor rates of positive screens over time to assess the impact of HPV vaccination.

Feasibility

Utilizing existing screening services or establishing new low cost services are feasible. Establishing a sustainable surveillance system to monitor the medium and long term impact of HPV vaccination will be challenging and would need resources, technical skills and political support.

Appendix 9: Approach to Monitoring HPV Vaccine Coverage - Draft Concepts and Methods

While information on the levels, trends, and distribution of HPV vaccine coverage is important in monitoring achievement of programmatic goals, identifying under-served populations, and determining vaccine impact, HPV vaccinations are frequently recorded without collecting and reporting sufficient information to adequately determine coverage. We describe the minimal information that should be recorded with each vaccination, suggest methods for aggregating this information, and present methods for calculating 1) coverage based on vaccine delivery strategy, and 2) coverage based on the population recommended for vaccination.

Recording HPV vaccination information

a) **Individual immunization record**. For each girl receiving HPV vaccination, a record should be provided which shows the girl's name, date of birth, location where vaccine was administered (i.e., name of clinic, school, etc.), and date of vaccination for each dose of HPV administered. For example, an immunization card that is HPV vaccine-specific might look like the following:

Name:		
Date of Birth:		
	Location where vaccine was administered (i.e., name of clinic, school, etc.)	Vaccination date
HPV1		
HPV2		
HPV3		

Additional information including lot number of the vaccine, information on adverse events suspected to be associated with the vaccine or the vaccine administration, and the vaccinator's name may be included on this record.

Where ever possible, HPV vaccination information should be included on a more general child/adolescence health card. It should be noted, however, that there may be logistic problems in retaining a card over an extended number of years (if knowledge of individual HPV vaccination status is desired at time of cervical cancer screening as an adult) and that possession of the card may need to be transferred from a parent to an adolescent, if they no longer share households.

b) **Vaccine service provider registry.** A vaccine service provider registry should record each girl's name, date of birth, location where vaccine was administered (i.e., name of clinic, school, etc.), and date of vaccination for each dose of HPV administered. An HPV vaccine-specific registry maintained in a health facility or school clinic might look something like the following:

Location					
Name	**Date of Birth**	**Date of HPV1**	**Date of HPV2**	**Date of HPV3**	**Comments**

Reporting HPV vaccination data:

In instances where it is feasible to consolidate individual vaccination information, in a national individual immunization registry for example, it is possible to calculate both coverage based on delivery strategy and coverage based on population recommended for vaccine (see below). If, because of logistical reasons (excessive number of forms, lack of copying equipment, etc.), information on individual immunizations must be aggregated, the information above may be summarized by each vaccination location and reported to the most immediate public health level, usually the district or township level. Below is a sample reporting form.

Location:		**Time period (e.g., month/year) of report:**		
Age (in years)	**Number of HPV1 vaccinations**	**Number of HPV2 vaccinations**	**Number of HPV3 vaccinations**	**Estimated size of target population**
9				
10				
11				
12				
13				
14				
≥15				

In this example, the date of birth and the date of vaccination for each HPV vaccine dose may be used to calculate the girl's age at time of vaccination. For example, a girl may be 12 years of age when she receives her first dose of HPV vaccine and 13 years old when she receives the last two. The number of HPV1, HPV2, and HPV3 vaccinations administered during the month of report are used to complete the number of HPV vaccinations for each dose. It is important to note that this table describes the number of HPV vaccinations administer during a single time period and is not a record of the vaccination status of any individual girl. For example, a girl receiving her first HPV vaccination would be represented in the second column but would not appear in any other column for that month. Her second and third dose would be reported during the months that she received those doses.

Where possible, the estimated number of girls targeted for vaccination in that month and age should be reported. In most situations where HPV vaccination is available to all girls, the estimated number of girls in each age group may be based on information from local or national statistical offices or other sources. Monthly reporting of the estimated target population may not be necessary but it is essential that, at minimum, an annual estimate of girls of each age in the target population is available.

The reporting form described above can be used as a basic template for further aggregation across administrative levels - i.e., reporting from district to province level or for summarizing information across months, or both.

National vaccination summary:

Monthly and administrative level reports should be consolidated and analysed on a routine basis (at least annually, more frequently for effective programming monitoring). The simplest summary uses the reporting template above to present an annual national level summary.

Country:		**Year of report:**		
Age (in years)	**Number of HPV1 vaccinations**	**Number of HPV2 vaccinations**	**Number of HPV3 vaccinations**	**Estimated size of target population**
9				
10				
11				
12				
13				
14				
≥15				
Total				

At the national level, the estimated target population may be calculated by summing the sub-national and periodic reports. These targets should be checked for consistency by comparing the target populations reporting with information from the national statistical office. If age-specific estimates are not available from the national statistical office, summing the target populations for ages 10-14 may be compared with sex and age-specific population numbers from national statistical offices or the UN Population Division.

The "Total" row for the number of girls receiving their 1st, 2nd and 3rd doses could be summed for an estimate of the total number of HPV vaccinations administered. The column of 3rd doses represents the total number of girls who complete their HPV vaccination schedule during the year. Drop-out can not be calculated directly because some girls will have received their first (or second) HPV vaccine doses but not be eligible for their 2nd (or 3rd) dose during the same year. Likewise some of the girls receiving their 3rd dose during the year will have received their 1st (or 2nd) dose during the previous year.

The template above can also be used to calculate age and dose specific coverage by dividing the numbers in columns 2, 3 and four by the estimated target in column five for the appropriate rows.

Additional analyses showing coverage by sub-national levels and time trends should be calculated and used to identify poorly performing areas.

The analysis above represent a summary of the programme activities and provide a framework for monitoring implementation. It is, however, difficult to use the summaries above across countries or as vaccine delivery strategies change to create a good description of the number and proportion of girls sufficiently protected when they begin to engage in sexual activity. A second analysis, based on the same recording and reporting tools above, provides essential epidemiological information, especially for estimating vaccine impact, and should also be calculated and presented.

Coverage based on population recommended for vaccination (i.e., Protection of at risk population)

We use the age and dose specific coverage information reported above to estimate the number of girls reaching 15 years of age who have received three doses of HPV vaccine. This requires maintaining records across years but is not difficult. For example, suppose that, in 2010 - the first year of the programme - we extract the number of girls 14 years of age that received their third dose of HPV vaccine - 300 in the table below. This is the number of girls reaching 15 years of age who have received three doses of HPV vaccine. The number of girls reaching 15 years of age in 2010 is 5192 in the table below, so proportion of fully vaccinated girls by age 15 years is 300 divided by 5192 or 5.8%.

Country	2010			
Age (years)	Number HPV1 vaccinations	Number HPV2 vaccinations	Number HPV3 vaccinations	Estimated target
9	10	6	2	5733
10	10	23	7	6012
11	101	98	54	5872
12	5202	4654	4001	5532
13	3021	2033	2101	5311
14	341	344	**300**	**5192**
≥15	452	320	298	5004
Total	9137	7475	6763	38656

The following year, 2011 we have the following information.

Country	2011			
Age (years)	Number HPV1 vaccinations	Number HPV2 vaccinations	Number HPV3 vaccinations	Estimated target
9	10	8	6	5733
10	12	19	9	6025
11	98	78	67	5812
12	6000	5112	4974	5621
13	3651	2657	2220	5432
14	321	311	**297**	**5375**
≥15	556	401	311	5110
Total	10648	8586	7884	39108

The number of girls reaching 15 years of age in 2011 who have received three doses of HPV vaccine is now the number of 14 year old girls in 2011 with three doses (297) PLUS the number of girls 13 years old in 2010 who received three doses (2101 for the table from 2010 above). The proportion of girls reaching 15 years of age in 2011 (5375) who have been protected with three doses is 297 (girls 14 years of age in 2011) PLUS 2101 (girls 13 years of age in 2010) which is 2398 girls divided by 5375 or 44.6%.

The process continues in 2012 when calculation of coverage by age 15 years is based on the number of girls who were 14 years of age and received their 3rd dose in 2012 PLUS the girls 13 years of age who received their 3rd dose in 2011 PLUS girls 12 years of age receiving their 3rd dose in 2010. In this way the national HPV vaccination records from previous years are used to calculate national HPV vaccination coverage for the cohort of girls reaching 15 years of age each year.

There are four important steps to ensure that this indicator can be calculated:

1) Each HPV vaccination should be recorded by the girl's age and dose number (1st dose, 2nd dose, 3rd dose).

2) Aggregated reports need to retain this information; i.e., the record of the number of HPV vaccinations administered during a specified time period needs to include both age of girl and dose number of vaccination.

3) These reports need to be retained in order to use information from previous years to calculate the vaccination history of the girls reaching 15 years of age in a given year.

4) A reasonably accurate estimate of the number of girls reaching 15 years of age must be available.

Summary:

1) HPV vaccinations should be recorded and reported by age (or year of birth) and by dose.

2) Two coverage calculations should be done and reviewed: 1) coverage by vaccine delivery strategy, in order to assess program, and 2) coverage by population recommended for vaccination, in order to assess proportion of recommended population which is protected.

3) In order to calculate coverage by population recommended for vaccination, annual reports of numbers of doses of HPV vaccine administered by age and by dose must be retained. An age-specific number of girls targeted for HPV vaccination should be estimated, validated where possible, and used as the denominator to calculate coverage.

21 April 2010
EPI/IVB/WHO

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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