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Executive Summary

This report summarizes a meeting on HPV surveillance and monitoring that was held at the World Health Organization in Geneva, Switzerland, with participants from CDC, PATH, IARC, and the National HPV Vaccination Register, Australia. Implementation of Human Papillomavirus vaccines provides a unique opportunity for primary cervical cancer prevention as part of a coordinated strategy to decrease cervical cancer. Multiple industrialized countries and a few middle income countries have introduced HPV vaccine in their national immunization schedules and HPV vaccine is in use in the private sector in all regions. On 26 January 2009, a meeting was held at WHO with participants from multiple WHO divisions, CDC (by teleconference), IARC, and PATH to start discussions regarding surveillance and impact monitoring for this new vaccine. A follow-up conference call occurred on 23 March 2009. From these discussions, the key monitoring areas of biologic endpoints (HPV infection, precancerous cervical lesions, and invasive cervical cancer), HPV vaccine coverage and HPV vaccine safety were chosen for development in a 2 day meeting held on 6-7 May 2009 in Geneva, Switzerland.

Experts in HPV laboratory tests, HPV disease manifestations, epidemiology, cancer prevention, reproductive health, vaccine coverage and vaccine safety discussed the issues in work group and plenary sessions. At the conclusion of this meeting, participants agreed that HPV vaccine safety monitoring and HPV vaccine coverage monitoring are important components for implementation of HPV vaccine. For coverage monitoring, the HPV vaccine coverage reported by countries for the annual WHO-UNICEF Joint Reporting Form should be calculated based on the population recommended for vaccination, rather than based on vaccine delivery strategy. However, monitoring vaccine coverage by vaccine delivery strategy is useful for programs to identify best delivery strategies or areas needing improvement. Administrative data will be needed for routine monitoring (i.e., a vaccine coverage monitoring system should not be based on survey alone). Additionally, periodic coverage surveys may be needed to validate estimates.

In the discussions on biologic endpoints to monitor HPV vaccine impact, participants agreed that such monitoring may need to be opportunistic, may occur at sentinel sites covered by cancer registries or precancerous lesion registries, may vary according to country capacity, and would require sampling populations at different ages depending on whether measurement of proximal or distal vaccine impact was desired (e.g., reduction in HPV infection prevalence versus reduction in precancerous lesion incidence or invasive cervical cancer incidence). As noted in the WHO position paper on HPV vaccines, HPV disease monitoring (e.g., population-based cancer registries) is not a pre-requisite or essential requirement for an HPV vaccination program. However, such activities should be encouraged as part of a comprehensive national cancer control plan. Meeting participants were in agreement that further reflection and discussion are needed before more specific technical advice for HPV vaccine biologic endpoint monitoring can be shared. It was agreed that another meeting to discuss HPV surveillance and monitoring should be scheduled in the fall of 2009.
Meeting Objectives

1. To delineate objectives and strategies for
   a. HPV vaccine impact monitoring
      i. HPV prevalence studies
      ii. Precancerous lesions surveillance
      iii. Cancer registries
   b. HPV vaccine coverage monitoring
   c. HPV vaccine safety monitoring
2. To identify partners and resources for HPV surveillance and monitoring

Desired Meeting Outcomes

1. Agreement on short- and long-term objectives for HPV vaccine impact, coverage, and safety monitoring
2. Agreement on who is taking the lead for the various areas of work
3. Agreement on a layered approach to HPV vaccine impact monitoring so that countries can select components of monitoring according to their resources and expertise
4. Agreement on priorities for short-term studies to inform development of guidelines for HPV vaccine impact monitoring
Participants

IARC
Infections and Cancer Epidemiology Group - Gary Clifford
Descriptive Epidemiology Production Group - Maria-Paula Curado (joined by video)
Screening Group - Eric Lucas (joined by video), Catherine Sauvaget (joined by video)

WHO
FCH/IVB/Expanded Programme on Immunization: Carsten Mantel, Susan Wang, Tracey Goodman, Jos Vandelaer, Cristiana Toscano
FCH/IVB/Initiative for Vaccine Research: Joachim Hombach, Linda Eckert
FCH/IVB/Quality Safety Standards: Aleksandra Caric, Tiequn Zhou
FCH/RHR/Sexually Transmitted Infections: Nathalie Broutet, Francis Ndowa
FCH/Child and Adolescent Health: Vicky Camacho
NMH/CHP/Chronic Diseases Prevention and Management: Andreas Ullrich, Jördis Ott
IER/Measurement and Health Information Systems: Robert Jakob
PAHO: Silvana Luciani (joined by video)

PATH
Aisha Jumaan

CDC
Division of STD Prevention – Lauri Markowitz (joined by telephone), Eileen Dunne (joined by telephone), Susan Hariri
Division of Cancer Prevention and Control – Mona Saraiya
Division of Viral and Rickettsial Diseases – Beth Unger (WHO Global Reference Lab/HPV LabNet)

National HPV Vaccination Register, Victorian Cytology Service, Australia
National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases
Julia Brotherton

Meeting
This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.
Final Agenda for the Meeting:

Wednesday, 6 May 2009

9:00 am - 9:30 am  Welcome, introduction, and meeting objectives
Susan Wang, WHO
Room C102

9:30 am - 11:30 am  1st work group session
Work Group 1: HPV prevalence studies, Room C102
Work Group 2: Precancerous lesion surveillance and cancer registries, Room E232

11:30 am - 1:30 pm  Lunch

1:30 pm - 4:00 pm  Continuation of 1st work group session

4:00 pm - 6:00 pm  Plenary: Feedback and discussion of output from 1st work group session
Chair: Gary Clifford, IARC
Rapporteur: Linda Eckert, WHO
Room C102

Thursday, 7 May 2009

9:00 am - 12:00 am  2nd work group session
Work Group 3: HPV vaccine coverage, Room C102
Work Group 4: HPV vaccine safety monitoring, Room M421

12:00 am - 1:00 pm  Lunch

1:00 pm - 3:00 pm  Plenary: Feedback and discussion of output from 2nd work group session
Chair: Joachim Hombach, WHO
Rapporteur: Tracey Goodman, WHO
Room C102

3:00 pm - 5:00 pm  Plenary
1. Identify persons/groups leading the areas of work, partners, resources, timelines, and next steps
2. Discuss strengthening of cervical cancer prevention programs as a program activity integrated with HPV vaccine implementation
Chair: Carsten Mantel, WHO
Rapporteur: Susan Wang, WHO
Room C102
Work Group Reports
Combined Reports: Work Group 1 (HPV prevalence monitoring) and Work Group 2 (pre-cancerous cervical lesion and invasive cervical cancer monitoring)
For copy of each Work Group's specific questions and topics discussed, see appendices.

Work Group 1
HPV prevalence studies
Facilitator: Francis Ndowa
Rapporteur: Beth Unger
Participants: Julia Brotherton, Gary Clifford, Linda Eckert, Susan Hariri, Carsten Mantel, Tiequn Zhou

Work Group 2
Pre-cancerous cervical lesion surveillance and invasive cervical cancer registries
Facilitators: Nathalie Broutet (pre-cancerous lesion surveillance) and Andreas Ullrich (cancer registries)
Rapporteur: Mona Saraiya
Participants: Aleksandra Caric, Maria-Paula Curado (by video), Robert Jakob, Aisha Jumaan, Eric Lucas (by video), Silvani Luciani (by video), Jördis Ott, Catherine Sauvaget (by video), Susan Wang

Objectives
1) To delineate objectives and strategies for biological endpoint monitoring of HPV Vaccine Impact
   a. Identify endpoints
   b. Identify population/site required for this monitoring
   c. Identify tests to be used
      i. Type of test
      ii. Support needed to allow testing
2) Identify the next steps.

Background Discussions: Both groups met separately for discussions and separately reported out during the first plenary on 6 May. During the plenary, it was recognized that there was considerable overlap in the issues between the work groups and it was decided that for this meeting report, the conclusions and plan for the 2 work groups would be combined.

Common Conclusions:
As per the WHO Position Paper, disease monitoring is not a pre-requisite or essential requirement for an HPV vaccination program. However, it is acknowledged that many countries will want or require their own surveillance data to demonstrate vaccine impact, and therefore guidance on appropriate vaccine impact monitoring approaches are needed.
1) Biologic endpoints for monitoring HPV vaccine impact in the short-, medium-, and long-term were identified and their characteristics were reviewed and summarized (see Table).
2) Monitoring vaccine impact on HPV infection prevalence is not possible at a population level in most low-resource settings. HPV vaccine impact on precancerous lesion incidence and invasive cervical cancer incidence will be known for those populations where good quality population-based cancer registries with accurate cervical cancer coding exist prior to HPV vaccine introduction and where sustainable infrastructure provides follow-up cervical cancer incidence data for ≥20 years following HPV vaccine introduction. Where precancerous cervical lesion registries are available, impact of HPV vaccines may be measurable much earlier.

3) Sentinel site surveillance for HPV biologic endpoints may be feasible in a number of settings.

4) To measure HPV vaccine impact soon after vaccine introduction, it would be desirable to test vaccinated girls soon after initiation of sexual activity (typically, girls who are teenagers or in their early 20s) to demonstrate reduction in prevalence of HPV infections due to the vaccine related HPV types. However, this target population for measuring vaccine impact is not the same as the population of women routinely targeted for cervical cancer screening (typically, women who are ≥ 30 years old).
   a. Initiating vaccine impact monitoring may be used as an opportunity to strengthen cervical cancer prevention strategies.
   b. Vaccine impact monitoring of cervical HPV DNA infections is ONLY possible where follow-up is in place (e.g., cervical cancer screening and treatment or referral is available).
   c. Cervical HPV DNA prevalence in vaccinated girls may be compared to either historical controls if pre-vaccination HPV DNA type specific cervical DNA prevalence data are available, or to prevalence among non-vaccinated girls in the same setting, if vaccine coverage is not complete.

5) The use of opportunistic settings for HPV vaccine impact monitoring will be crucial and these settings are appropriate as long as the methods and sampling frame are consistent over time.

6) Where cervical HPV infection is the biological endpoint being monitored, both point of care clinically relevant HPV testing may be desirable as well as more sensitive testing methods conducted by the local or regional WHO HPV LabNet Laboratory.

7) The WHO HPV LabNet should be continued and could serve a valuable role in HPV vaccine impact monitoring.

8) Changes in detection rates of cervical abnormalities detected by screening are subject to a wide range of possible factors outside of vaccination. These include changes in populations screened, targeting of cervical screening programs to new groups, changes in screening policies, changes in laboratory or specimen quality, and changes in technology. Therefore, monitoring of cervical abnormality rates per se is problematic as a routine measure of vaccine impact and may be best interpreted in settings with population-based cervical cancer registries and stable cervical cancer screening programs.

9) HPV typing from a sample of CIN2, CIN3 lesions or cancers will be an important long-term measure of HPV vaccine impact. Sentinel surveillance models are also appropriate methods for such surveillance activities but will require consistent sampling and HPV detection methods over time.
10) Reduction in cervical cancer incidence is the most important, although long term, desired outcome of HPV vaccination. Thus, efforts to establish or improve reporting to cervical cancer registries are an important part of ensuring adequate long term monitoring of HPV vaccination programs.
<table>
<thead>
<tr>
<th>BIOLOGICAL MEASURE</th>
<th>INTERVAL FROM VACCINATION TO WHEN BIOLOGICAL ENDPOINT NEEDS TO BE MONITORED (YRS)</th>
<th>PREREQUISITES</th>
<th>SOURCE OF SURVEILLANCE</th>
<th>DENOMINATOR*</th>
<th>FEASIBILITY SCORE (1-5) 1-very feasible</th>
<th>CONSIDERATIONS FOR INTERPRETATION OF DATA</th>
</tr>
</thead>
</table>
| PREVALENCE OF HPV INFECTION (HPV DNA type prevalence and distribution) | 1-4                                                                             | 1. Diagnostic HPV test approved for clinical use  
2. Standardized HPV DNA typing tests (used for surveillance only)  
Rapid type-specific HPV DNA preferable, ideally one that distinguishes the vaccine-targeted HPV types (e.g. Qiagen HPV 16/18/45 test) | Sentinel sites – Targeting young sexually active women  
Antenatal care clinic, family planning clinic, with other STI testing | Number of women tested | 1 - With secure funding. Need to know vaccine status of tested women. | Requires consistent sampling framework/source population |
| CERVICAL SCREEN TEST POSITIVITY (VIA, PAP, HPV) | 2-5                                                                             | Secondary cervical cancer prevention program | All of sample health facilities | Number of women screened | 1- Assuming cervical cancer screening services available.  
Need to know vaccine status of screened women. | This is highly dependent on screening test type, screening strategy, cohort effect  
Low specificity may give false impression of lack of vaccine impact  
Limited to previously

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
<th>Method</th>
<th>Eligibility</th>
<th>Decision</th>
<th>Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2-3</td>
<td>3-5</td>
<td>Cytology-Histology available</td>
<td>All or sample health facilities</td>
<td>To be determined</td>
<td>Highly dependent on screening and diagnostic practices. Recommended for high resource settings with stable screening programs and population based registries</td>
</tr>
<tr>
<td>HPV type distribution in histologically confirmed cervical biopsies</td>
<td>3-6</td>
<td>Standardized HPV typing tests</td>
<td>Opportunistic screening activities</td>
<td>To be determined</td>
<td>Reference laboratory likely the appropriate location for reproducible HPV typing tests</td>
</tr>
<tr>
<td>Treatement referral</td>
<td>3-6</td>
<td>Secondary-tertiary centers</td>
<td>All or sample of referral hospitals</td>
<td>To be determined</td>
<td>Highly dependent on availability of treatment centers in country, changes in treatment and referral guidelines</td>
</tr>
<tr>
<td>Invasive Cancer</td>
<td>15-20</td>
<td>Histology</td>
<td>National or regional population-based cancer registry</td>
<td>To be determined</td>
<td>Registry may not be in location where population is at highest risk</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>1-3</td>
<td>Use of quadrivalent HPV vaccine</td>
<td>Sentinel clinics</td>
<td>To be determined</td>
<td>Will not give absolute population incidence of warts. Only useful for monitoring trends over time, but an early and visible vaccine impact may be simple and require fewer resources than other surveillance methods</td>
</tr>
</tbody>
</table>

*Denominator measure proposed is tentative and may change pending further discussion*
Specific challenges and opportunities
1) HPV prevalence monitoring requires introducing a new test in an opportunistic setting (such as prenatal clinic, or STI clinic, or other clinic that serves the target population - i.e., adolescent girls or young women who are newly sexually active), appropriate interpretation of the test, and appropriate response to test results.
   a. Opportunity: for capacity building
   b. Challenge: will require protocol and resources to address positive clinical test results in adolescent girls since HPV screening is not routinely recommended for this population
2) Most desirable types of rapid HPV DNA tests are not yet available (need tests that are type specific for vaccine related HPV types cross-protected types, e.g., HPV 16/18/45 Qiagen test in trials).
   a. Opportunity: for technology development
3) Genital wart monitoring may allow relatively rapid monitoring of impact of quadrivalent vaccine. Currently, no good system in place in low- and middle-income countries for monitoring warts.
   a. Opportunity: to characterize current and future genital wart disease burden
4) For precancerous lesions, genotyping in reference laboratories is needed to produce quality results.
   a. Opportunity: for HPV LabNet
   b. Opportunity: to train local and regional laboratories in standard PCR methods for HPV DNA testing
5) Collection of cervical specimens for baseline HPV infection prevalence or of cervical biopsy specimens for genotyping should be encouraged before vaccinated cohorts reach age of opportunistic screening settings so that baseline data on unvaccinated populations are obtained.
6) Where cervical specimens are not readily collected, non-cervical samples (e.g., urine specimens, vaginal swabs) may be useful alternatives for monitoring trends in genital HPV infection with vaccine targeted HPV types.
   a. Opportunity: continued development and validation of non-cervical HPV DNA tests
   b. Challenge: possible limitation when using non-cervical samples to reflect cervical infection.
7) Ensure all HPV vaccinated individuals have immunization records. Interpretation of HPV vaccine impact evaluations will be considerably enhanced by having accurate HPV vaccine status of monitored women. Unfortunately, HPV vaccination status may be unknown in all but a few well-organized countries.

Outcomes and consensus: The road forward
1) Sentinel site monitoring will be dependent on country capacity, resources, and opportunities. Low resource settings may need to rely on data obtained from other sites.
2) HPV vaccine impact monitoring will require coordination, and will need buy-in by regions and countries considering vaccine implementation.
3) Another meeting to further discuss specific approaches to monitoring is planned for 4th quarter, 2009. Issues that will require further discussion include:
a. Defining optimal sentinel sites
b. Ways to monitor vaccine status
c. Target age groups for specific biologic endpoints
d. Techniques for HPV DNA or precancerous lesion monitoring

Other topics discussed in work groups included:
1) Extensive discussion led by Beth Unger on the types of HPV tests available including clinical HPV tests, HPV detection and typing assays for epidemiologic studies, and HPV serology tests
2) Presentation by Gary Clifford on the IARC multicentre prevalence surveys - 26 sites to date. Challenges of obtaining a population sample and of transporting specimens were reviewed. HPV prevalence varies greatly in different countries, or in different regions of different countries. HPV 16 is consistently most common of the high risk HPV DNA type.
3) Not recommended that each country collect its own type-specific HPV prevalence data. However, for countries which do cervical cancer screening, could link HPV DNA typing with current screening to get baseline type-specific HPV prevalence of cervical cancer specimens.
4) If HPV DNA vaccine impact monitoring were done in an STI clinic, the type of specimen for HPV DNA test (i.e., cervical sample) and the type or sample needed for STI screening (i.e., urine sample) may differ. Adding cervical specimen collection may be problematic.
5) Developing a mechanism for central typing of cervical cancers for each country would be a good long term goal for vaccine impact monitoring.
6) 25% of the global population of women is covered by cervical cancer registries.
7) Capacity building for recording and information systems needed to assist in accurate monitoring. Data collection should be centralized.
8) VIA may be difficult to use for monitoring vaccine impact because so many non-vaccine HPV types contribute to low grade lesions seen on VIA.
Most discussion has already been captured in the Table and above summary. Additional points:

1) Testing for HPV DNA to monitor vaccine impact creates ethical concerns with regards to ability to provide immediate clinical feedback for timely screening and treatment vs. specimens being processed in a central laboratory with delays in clinical feedback and potential loss to follow-up.

2) Monitoring needs to be in controlled, small, well-tracked groups to get better reproducibility.

3) Strengthening reproductive health and secondary cancer prevention infrastructure with HPV vaccine introduction would be desirable.

4) It may not be possible to separate out the impact of vaccination and the impact of a screening program. One would expect that monitoring vaccine impact will result in reduction of HPV disease since screening would result in treatment of lesions.

5) A challenge to monitoring is that HPV tests and testing strategies are still evolving so it is hard to know how to monitor biologic endpoints over time if methods (technology and protocols) of measuring those endpoints are changing over time.

6) It is estimated that it will require sustained high HPV vaccine coverage of at least 70% over time to measure impact of HPV vaccination.
Work Group 3
HPV Vaccine Coverage Monitoring Workgroup
Facilitator: Aisha Jumaan
Rapporteur: Susan Hariri
Participants: Gary Clifford, Carsten Mantel, Susan Wang, Jos Vandelaer, Cristiana Toscano, Nathalie Broutet, Francis Ndowa, Mona Saraiya, Beth Unger

Objectives
(1) To identify short- and long-term objectives for HPV vaccine coverage monitoring
(2) To identify strategies to accomplish these objectives

Background
Current vaccine coverage monitoring approaches were reviewed.

Routine infant immunization
WHO and UNICEF annually request coverage data from countries via the WHO-UNICEF Joint Reporting Form (JRF). Guidance is provided on methods to estimate numerator and denominator and immunization programs report administrative data. The JRF currently does not request HPV vaccine coverage data and does not currently provide guidance for HPV coverage monitoring. EPI Cluster Surveys to assess vaccination coverage are not required, but some countries choose to occasionally conduct such surveys to gather coverage data. Using data reported by countries on the JRF, together with any data from DHS, MICS, and EPI cluster surveys, WHO and UNICEF jointly estimate vaccine coverage and time trends using standardized estimation methods.

TT for women of child-bearing age
Tetanus toxoid (TT) is administered on a pregnancy-based schedule. WHO recommendations are to administer to 2 doses during the 1st pregnancy, 1 dose each during the 2nd, 3rd, and 4th pregnancies for a maximum of 5 total doses. Protection requires at least 2 doses so vaccine coverage monitoring is based on "TT2+" coverage. Denominator is the number of pregnant women, which can for example be calculated by estimating a certain fertility rate (e.g., 4% of all childbearing age women), or by using the number of live births (sometimes increased by a certain percentage). Monitoring of TT2+ administration is calculated by adding all pregnant women who received TT2, plus those who received TT3, plus those with TT4, and those with TT5, divided by # pregnant women. In practice, usually TT is given to pregnant women during antenatal care (ANC) visits. During such ANC visits, women are asked how many TT doses they have received previously, and the dose given is recorded accordingly. In many settings, only previous doses that are recorded on immunization cards are considered, resulting in TT2+ being an underestimate of real coverage, given the low card retention rates.

Approaches for monitoring HPV vaccine coverage in countries which are currently administering the vaccine
United States: Uses the National Immunization Survey (telephone) which is validated with medical record reviews (13-17 yrs).
Australia: Uses HPV vaccine registry; healthcare providers remunerated for reporting.
Switzerland: Canton-based vaccine coverage monitoring. Geneva Canton pays providers for reporting.

Uganda and Peru: PATH HPV vaccine demonstration project:
1. School-based (grade-based in Ibanda-Uganda and Peru): Clearly defined numerator and denominator; did not include girls not enrolled in school. Used administrative data to estimate coverage, which was then validated using the WHO multi stage cluster coverage survey.
2. Age-based in Nakasongola; girls 10 year of age through Child Days Plus: Difficult to assess age and therefore may have vaccinated girls outside the eligible age. Denominator from census; may be outdated and may have under-estimated the number of 10 year old girls in the population. Issues with both numerator and denominator resulted in over-estimation of coverage using administrative data.

Specific challenges for HPV vaccine coverage monitoring – issues discussed

Administrative data
- Numerator sources and issues
  - Tally number of vaccinated girls; each dose is tallied separately.
  - Use of vaccination/adolescent card may improve numerator data, but retention of cards may not be high, especially in low-resource settings.
  - Missing information on DOB may lead to vaccinating girls outside the eligible age and therefore leads to overestimation of coverage.

- Denominator sources and issues
  - Census data
    - May be outdated leading to over/under estimation of coverage.
    - Defining cohorts by age may be challenging in areas where age is not recorded or where families and girls don’t know exact age of individuals.
  - Countries have school enrolment data. Sometimes, data on school attendance is also available. School enrolment data can be stratified by grade and by sex. But school attendance or enrolment data do not account for children out of school.
  - UNICEF and UNESCO provide estimates of school attendance and completion by grade and sex at the regional level.

- Regional data indicate that the majority of boys and girls (over 70%) complete primary school in most regions.
  - Regional data demonstrate a significant drop in attendance between primary and secondary school (6th grade)
  - School attendance varies across and within countries

Coverage surveys
- Provide estimates of coverage and assess vaccination in both public and private systems. Can be used to cross-check administrative data. Will be useful if conducted at intervals every few years or until coverage estimate approximates those reporting from administrative data.

Vaccine delivery strategies include
• Routine administration, e.g., school or clinic or health center-based
  – Example: pregnancy-based TT vaccination, measles, other childhood vaccines
• Campaign-based
  – Routine vaccine delivery to target age groups such as TT to school aged girls in Child Health Days in Africa.
  – Targeted to control outbreak such as polio vaccination (includes outbreaks)
  – Campaigns at regular intervals can also be used instead of routine immunization, but they tend to be more labour-intensive and more expensive.

Possible method to estimate HPV vaccine coverage in a target population using an approach along the lines of what is used for TT2 vaccine coverage monitoring.

• Denominator: single target age cohort (youngest year of the range of ages for whom HPV vaccine is recommended, e.g., if vaccine is recommended for 10-15 year olds, denominator would be all 10 year olds).
• Numerator: all vaccinated girls in given age bracket (several age cohorts)
  o Initially overestimates coverage but will become more accurate as fewer age cohorts are included in the numerator
  o Initial overestimation will give false sense of adequate coverage to health care workers. In earlier years, absolute numbers of girls immunized will also be important.

Will need surveys to validate results in first few years.

**Outcomes and Consensus**

1. HPV vaccine coverage reporting by countries for the WHO-UNICEF JRF should be calculated based on the whole target population (i.e., denominator = all girls in the age range recommended for HPV vaccine in a given country), rather than based on vaccine delivery strategy. However, monitoring vaccine coverage by vaccine delivery strategy is useful for programs to identify best delivery strategies or areas needing improvement.

2. Administrative data will be needed for routine monitoring; i.e., a monitoring system should not be based on surveys alone.

3. Periodic surveys may be needed to validate estimates.

**Next steps**

1. Explore details of PAHO methods for estimating adolescent HepB and HPV vaccine coverage as possible models for global guidance on estimating HPV vaccine coverage (e.g., Panama, Mexico)
2. Explore creation of an adolescent immunization card (would need to make it valuable or important enough so that it would reliably be retained over time)
3. Explore how the EPI cluster survey could be modified to capture HPV vaccine coverage
4. Explore inclusion of HPV vaccine coverage data in existing periodic surveys (DHS and MICS)
5. Field test the above-mentioned method of monitoring.
6. Eventual goal is to develop guidance for HPV vaccine coverage monitoring and to add collection of these data to the WHO-UNICEF JRF.
Objectives:
(1) Identify existing mechanisms (systems) and challenges for safety monitoring of HPV vaccines.
(2) Identify next steps for the improvement of HPV vaccine safety monitoring.

Overview of existing mechanisms for monitoring vaccine safety – points discussed (regulatory and programmatic issues)

At the 61st World Health Assembly in May 2008 it was agreed as part of Resolution 61.15 (Global Immunization Strategy) that vaccine safety monitoring is a priority requiring attention by urging:
- member states ‘to develop, strengthen and/or maintain surveillance systems for vaccine-related adverse events, linked with systems for monitoring compliance with safe injection practices’; and
- the Director General ‘to provide guidelines and technical support to Member States in order to establish integrated surveillance of adverse events following immunization and to minimize unnecessary vaccine-related adverse events.’

Therefore, safety surveillance of vaccines used in countries is not a choice, it is the responsibility for the public health measure introduced.

Traditionally, vaccines are developed and used first in the developed, industrialized world in which regulatory decisions for these products are taken. Regulatory authorities in developing countries frequently have been considered weak and their functionality varies. WHO has defined the functions to assess national regulatory authorities (NRA), one of which is surveillance of vaccine field performance- safety and efficacy. In order to strengthen NRAs in developing countries, WHO is providing training to vaccine regulatory staff also in the area of vaccine regulation, to avoid reflex political decision making without a scientifically rigorous assessment. Vaccine vigilance practice can be improved through training of immunization programme staff in surveillance for adverse events following immunization (AEFI), and epidemiological methods. It is also very important to have communication materials available and ensure exchange of information between program managers and regulatory authorities.

International monitoring of vaccine safety can potentially be achieved through countries providing AEFI surveillance data to the global database at the Uppsala Monitoring Centre (a WHO collaborating centre for international drug monitoring). The database currently contains about 4.5 million reports, most of which (90%) are for drugs. There are about 100 members and 20 associated members (countries). To report to the database, a country is assessed for ability to report and, if successful, becomes a member. The reports are made anonymous. However, the reporting forms and software used were primarily designed for drugs and there is more vaccine specific work to be done. Data mining is
done by the Uppsala centre on a regular basis with the purpose to facilitate identification of safety signals (potential safety issues). Doses distributed or administered are not available, making rate calculations potentially problematic.

A relatively recent initiative created to monitor newly pre-qualified vaccines is the Global network for post-marketing surveillance of pre-qualified vaccines. This Network was created because there is a large number of vaccines recently prequalified that are either not used in the country of original license/manufacture, or the vaccine will be used in the country of manufacture but where there is limited capacity for post marketing surveillance (needs further strengthening). These products will be targeted at the highest level of priority, however, reports for all vaccine products are expected. Currently, there are 2 countries per WHO region included in the Network, with the exception of WPRO (total of 11 countries in the Network). The Network will ensure collection of reliable safety data from the countries, and these will be submitted to the common network database in Uppsala. The technical oversight committee is established within the Network structure to provide technical support in terms of data reporting and analysis, causality assessment, and design and conduct of special studies if and when needed. Manufacturers of the targeted vaccines will be requested to share relevant safety information (e.g. PSURs) on a regular basis. Of note, both currently available HPV vaccines are in the final phase of WHO prequalification process.* Vaccine focal point has been recently appointed and initiated work on vaccine specific issues. These were outlined at the recent technical meeting of the Network (April 2009): mapping Brighton collaboration definitions with MedDRA and WHOART, use of free text fields in the existing reporting form, data to report: unique ID, dob, age, gender, gestational age, pregnancy details, birth weight, health status at time of vaccination (optional free text), vaccine name, manufacturer, lot no, (expiry date, diluent), date of vaccination, dose no, mode admin, event: type of AEFI, date and time onset, clinical description, local reaction site size, fever, treatment and management e.g., hospitalization details, outcome (recovered or not recovered, death). Also, there is ongoing work to determine how best to collect data on deaths in settings where autopsies are not performed.

Specific challenges for HPV vaccine safety monitoring – issues discussed:
1. Pre-qualification status for HPV vaccine proceeding - manufacturers filed end 2007, is entering final phase, expected in second quarter 2009.* In contrast to impact monitoring for disease endpoints, safety monitoring needs to be established for HPV vaccines immediately.
2. Not usual target age group so the vaccine providers different (traditionally not involved with vaccination), and may not be aware of, or used to, reporting AEFIs.
3. Denominator population difficult to determine – high mobility of adolescents/young women.
4. Expected rates of incident medical conditions (background) in this age group unknown in many places.
5. Developed world data suggests incidence of autoimmune and immune mediated conditions starts to rise in this age group – high likelihood of chance temporal association with vaccination.
6. Very high profile and expensive vaccine – high risk if adverse events not managed appropriately.

Outcomes and Consensus

Where HPV vaccine is in use, there should be a safety monitoring system in place.

1. The system should be able to systematically document AEFIs notified by vaccine providers, analyse the data and report findings quarterly.
2. Serious events should be immediately reported to the National Regulatory Authority. Where expert advice is needed, WHO should be notified of suspected vaccine safety signals (role of Global Advisory Committee on Vaccine Safety- GACVS).

Countries developing vaccine safety monitoring systems for HPV vaccines should:

1. Strengthen capacity for investigation and causality assessment at a local and/or national level (e.g., through WHO training).
2. Where feasible, classify AEFI reports using Brighton collaboration definitions to ensure comparability with cases internationally as well as internal validity.
3. Review data collection fields for vaccine safety reports and, where possible, ensure that these include the minimum fields recommended for vaccine reporting to the Uppsala Monitoring Centre. Countries are strongly encouraged to apply for membership of the Uppsala Monitoring Centre, or if already members to timely submit AEFI reports, to support a wide reaching and comprehensive global vaccine safety monitoring network.
4. Ensure that vaccine recipients have a documented record of vaccination (at one or all of individual/clinic/program levels) that can be accessed in the case of an adverse event following immunisation occurring or a program level vaccine safety problem arising. WHO recommends that coverage records of HPV vaccination are retained long term (see WHO HPV vaccine position paper).
5. Encourage vaccine providers to report all vaccinations inadvertently given during pregnancy to the local country pregnancy register or, where there is no local register, to the manufacturer for compilation on their global registers.
6. Raise awareness of AEFI reporting requirements amongst vaccine providers and health providers who may treat AEFIs.
7. Provide information to all immunisation providers for managing possible acute reactions following immunisation and for reporting these if they do occur. e.g. syncope, anaphylaxis, mass reactions.
8. Consider the possibility of mass psychogenic reactions occurring given the setting (e.g. schools) and age group of vaccinees and ensure procedures are in place to reduce the likelihood of these occurring.
9. Develop communication strategies as part of program planning, to respond to publicised AEFI events. Plans should include identification of spokespersons, and methods for rapid communication to vaccine providers, the NRA, government, manufacturer, and the public.
10. Develop risk management strategies to respond to vaccine rumours and scares (e.g., infertility, coincidental events).
**WHO and vaccine safety partners should:**

1. Strengthen capacity for member states to conduct investigation and causality assessment at local level (through training provision and resource development).
2. Encourage member states to classify AEFI reports using Brighton collaboration definitions to ensure comparability with cases internationally as well as internal validity.
3. Encourage member states to meet a minimum quality of data for AEFI and preferably start reporting to Uppsala Monitoring Centre.
4. Encourage the member states where capacity exists to:
   - undertake prospective safety surveillance activities using data linkage to ascertain ongoing disease incidence in vaccinees and non vaccinees over time, with pre-determined thresholds for identification and investigation of safety signals.
   - estimate and publish background rates of diseases in the vaccine target age group, preferably before vaccine rollout (immune mediated diseases and diseases of unknown aetiology are of particular importance).
5. Encourage member states to develop vaccine coverage record systems, to provide access to denominator data for establishing safety profile of the vaccine and for safety investigations if required.
6. Provide evidence based information summaries about adverse events following immunisation to member states to assist them in informing immunisation providers and vaccine recipients about possible AEFI and the management and notification of these, and to assist member states to develop appropriate communication and risk management strategies for AEFI events.

*Note: At the time of this meeting, neither vaccine had been pre-qualified. Since the meeting, both quadrivalent and bivalent vaccines have achieved prequalification status.*
Plenary to discuss reports of Work Groups 3 and 4
Tuesday, 7 May 2009
Chair: Joachim Hombach
Rapporteur: Tracey Goodman

Work Group 3: HPV Vaccine Coverage:
1. Need to add to the WG report that all girls should be given a vaccination card to keep.
2. Some debate about proposed method of calculation according to target age, may not be easy for grade based delivery strategies. But in order to make HPV consistent with the way other vaccine coverage is calculated, preference was given to proposing a coverage estimation method based on target age. Grade based delivery would be easier because denominator and numerator are easier.
3. Question about monitoring and reporting of private sector delivery. Likely that this is outside of our responsibility.
4. Currently no adolescent card is used.

Work Group 4: HPV Safety Monitoring:
1. Difficulty of estimating background rates of diseases in the vaccine target age group. Every effort should be made to collect and compile this information, where existing, because it provides the context for potentially reported events following vaccination.
2. Need a review of expected rates of adverse events following immunization so that this general information is readily available for review of reported rates.
3. Predefined list of adverse events may be possible to develop; others cautioned against this because it may limit observation.
4. Communication strategy/plan is essential and should be updated regularly.
5. About 65% of countries do not have vaccine safety monitoring systems (according to WHO NRA assessments).
6. If vaccination is school-based, there should be a set procedure with the school for AE management/reporting, if the AE is observed after vaccinators leave.
7. Differentiate which coding system is used (ICD9/ICD10), as data mining/signal detection may result in missed signals.
8. Raise interest of peer reviewed journals to publish papers on background rates of conditions appearing typically in this age group (took more that 2 years to have the Seigrist study published).
9. Where possible, apply other methods for post-marketing surveillance besides passive surveillance (stimulated passive, active, phase IV studies).
10. Use the momentum of adding a new vaccine in the programme for starting and/or strengthening AEFI monitoring systems.
Final Plenary - Summary
Roadmap Forward
Tuesday, May 7, 2009
Chair: Carsten Mantel
Rapporteur: Susan Wang

A timeline for completion of work group reports by the rapporteurs and compilation of the overall meeting report by Linda Eckert was established. It was agreed that the meeting report should be circulated to external stakeholders for feedback and regional input.

It was noted that some aspects of HPV vaccine impact monitoring likely will be research or special studies and other aspects can be incorporated into national routine public health disease surveillance activities.

It was agreed that there remained substantial work to be done to further clarify best approaches to monitoring biologic endpoints. In particular, more discussion on how best to do HPV type monitoring for vaccine impact monitoring is needed.

It was agreed that another HPV surveillance and monitoring meeting should be scheduled by WHO in the fall of 2009 in Geneva. Stakeholders who were missing from this May meeting who should be invited to the next meeting include: representatives from other HPV LabNet sites, from the Catalan Institute of Oncology, from the United Kingdom Health Protection Agency, from countries currently implementing HPV vaccine such as Panama and Mexico, and from the field of HIV (e.g., UNAIDS).
Appendix 1 - Agenda for Work Group 1

HPV Prevalence Studies
Date: 6 May 2009
Room: C102
Facilitator: Francis Ndowa
Rapporteur: Beth Unger

Objectives of the workgroup session
1. To delineate objectives and strategies for HPV prevalence monitoring activities intended to monitor HPV vaccine impact
2. To identify current priorities for short-term studies to inform development of guidelines on HPV vaccine impact monitoring
3. To identify partners and resources
4. To identify next steps

Background information to inform discussion (brief, 1-2 slides each)
1. Methods used by IARC for prevalence study (test(s) used, sample collection types, population studied?) - Gary
2. Current tests available for HPV prevalence testing - Beth
3. HPV LabNet - Tiequn
4. Rapid test for HPV DNA - Linda

Proposed discussion areas
1. What are the reasons for HPV prevalence monitoring?
   a. Vaccine impact
   b. Resource planning
   c. Advocacy efforts to increase vaccine use

2. What are the outcomes of interest?
   a. Vaccine related HPV types
   b. Oncogenic types?
   c. Other?

3. How do you do prevalence monitoring?
   a. Which populations should be targeted for prevalence studies
      i. young, sexually active population?
      ii. which age?
      iii. boys and girls? vs. girls alone?
   b. Type of prevalence study
      i. academic study (done once, like IARC)
      ii. routine prevalence
         (a) Continuous or episodic
         (b) Universal vs. sentinel site
   c. Is there synergy with HPV prevalence monitoring and other programs?
i. Ct or Gc monitoring?
ii. other adolescent programs?
iii. other cervical cancer screening or monitoring programs

4. What type of technical support is needed?
   - Lab tests
   - Data tracking and recording systems

5. Is HPV prevalence monitoring necessary for HPV vaccine program monitoring?

6. What do we expect from countries?
   - e.g., Hepatitis B…very little monitoring
   - Tiered approach

7. If HPV prevalence monitoring is not necessary for HPV vaccine program monitoring, what type of HPV prevalence studies are needed and for what purpose?
Appendix 2 - Agenda for Work Group 2

Pre-cancer lesion monitoring and cervical cancer registry
Date: 7 May 2009
Room: E232
Facilitators: Nathalie Broutet (pre-cancer lesions) and Andreas Ullrich (cancer registry)
Rapporteur: Mona Saraiya

Objectives of the workgroup session
5. To delineate objectives and strategies for monitoring middle-term and long-term impact of HPV vaccine through the monitoring of cervical pre-cancer lesions and cervical cancers
6. To identify next steps for monitoring cervical pre-cancer lesions and for cervical cancer cases through cancer registries

Background and available documents
- IARC presentation on monitoring system of cervical cancer prevention programmes - Eric Lucas
- Indicators for cervix cancer screening - Rengaswamy Sankaranarayanan
- US/CDC examples and lessons learnt on monitoring pre cancer lesions - Mona Saraiya
- C4-GEP
- Presentation on cervical cancer registry: principle and availability - Maria Paula Curado

I Cervical pre-cancer lesions
8. What is a pre-cancerous lesion?
   - Positive screening test?
   - Which screening test is used? Cyto - VIA - HPV?
   - What are the outcomes of interest?
     i. VIA positive - CIN grade
     ii. Role of colposcopy - biopsy (histology)?
     iii. Source of information

9. Which indicators should be chosen for monitoring pre-cancerous lesions?
Example of indicators used for monitoring cervical cancer prevention programmes

Process measures:
- Number of eligible target women (denominator)
- Proportion of eligible women receiving the screening test
- Proportion of women with positive screening tests attending for: diagnosis / treatment / follow-up care
- Proportion of re-tested women with inadequate/inconclusive screening tests
- Time taken to deliver the screening test results / diagnosis / treatment
Intermediate outcome measures:
- Stage distribution of cervical cancer
- 2- and 5-year survival rates
- Fatality rates
- Consider also the number of women needing cryotherapy in a geographic region as a loose measure of efficacy of the vaccine and decrease in precancer lesions

Final outcome measures:
- Incidence rate of invasive cancer and non-invasive cancers
- Mortality rate from cervical cancer

10. What technical support or resources are needed for each of these measured outcomes?

11. How to adapt the system already in place?
- Which screening tests to use in a vaccinated population
- Health information according to countries?
  i. Developing countries
  ii. Middle income countries
  iii. Developed countries
- Health information according to level of care
- Sentinel surveillance or exhaustive?

12. Do we need to monitor pre-cancerous lesions to monitor HPV vaccine impact? Why?

II- Cervical cancer registry
1. Cancer data information
- Sources
- Most recent and upcoming updates
- Comparability between data bases (Globocan, etc.) and between countries
- Extent to which data is extrapolated from region to country-level

2. Monitoring the impact of HPV-vaccine on cancer burden
- Time variables (age and intended time interval)
- Consideration of HPV-prevalence

3. Possibilities for assessment and monitoring
- Routinely collect additional data (e.g. vaccine status, stage, etc.)
- Data extrapolation from study populations to overall country impact
Appendix 3 - Agenda for Work Group 3

HPV vaccine coverage monitoring
Date: 7 May 2009
Room: C102
Facilitator: Aisha Jumaan
Rapporteur: Susan Hariri

Objectives of the workgroup session:
1. To identify short- and long-term objectives for HPV vaccine coverage monitoring
2. To identify strategies to accomplish the objectives
3. To identify priorities for short-term studies to inform development of guidelines for HPV vaccine coverage monitoring
4. To identify person(s) or group(s) to lead the work, resources and partners for the work, timelines, next steps

Background:
Review current coverage monitoring approaches
- for routine infant immunization
- for TT
- for countries currently administering HPV vaccine (USA, Switzerland, Australia, etc.)
- for PATH project sites

Reference materials
1. Joint Reporting Form - A unified resource
2. 2009 JRF questions on school-based immunization
3. List of countries with HPV vaccine in their schedules per 2007 JRF
4. U.S. current HPV vaccine coverage
5. Australia HPV vaccine coverage monitoring

Proposed discussion areas:
Identify the research questions or gaps that need to be assessed before developing guidance on HPV vaccine coverage monitoring
1. Should monitoring be based on vaccine delivery strategy?
   - Routine immunization through public providers (EPI clinics, MCH/FP clinics)
     i. Through routine reporting
     ii. Through sample reviews of immunization registries or immunization information systems
   - School-based vaccine coverage monitoring
   - Campaign; child health days; catch-up approach
   - Private practice - How much vaccine is administered in the private sector?
     With current price of vaccine, private sector may be where more vaccine is currently being administered. Routine reporting by private sector may be feasible in some settings.
2. Should monitoring be based on vaccine recipients?
- Monitor by surveys such as DHS and MICS but since these have modules that focus on children < 5 yrs, men, and women 15-49 yrs, would need to modify the surveys. What needs to be done?
- Perform young girl/adolescent girl specific surveys through schools or households
- Need to see whether other public health partners are already surveying this population for other health needs (e.g., UNICEF, UNAIDS, others)

3. How should the denominator for HPV vaccine coverage be defined?
- Does one want to monitor coverage of vaccine delivery programs or to monitor coverage of the population recommended for the vaccine? If the latter, for school-based delivery of HPV vaccine, will need to be able to quantify and describe non-school attendees - the uneducated girl likely overlaps with the unimmunized child
- Follow cohort of target age group (use country estimates, UNDP population statistics)
- Cross-section of vaccinations performed divided by target age group size
  Use of Ministry of Education or school enrolment data

4. Reporting and assessing the data: ability to aggregate or make sense of the data may be more difficult at the regional or global level due to the variety of vaccine delivery approaches and possibly different denominators
  - Program (dependent on vaccine delivery strategy)
  - Country
  - Regional/global - Joint Reporting Form

5. What is the role of the adolescent immunization or health card?
6. Consider monitoring whether HPV vaccine is being delivered with other interventions (other immunizations, commodities, etc.) (may need to do this as part of implementation or as part of post-introduction evaluation rather than as part of routine coverage monitoring)
Appendix 4 - Agenda for Work Group 4

HPV vaccine safety monitoring
Date: 7 May 2009
Room: M421
Facilitator: Aleksandra Caric
Rapporteur: Julia Brotherton

Objectives of the workgroup session
1. Identify existing mechanisms (systems) and challenges for safety monitoring of HPV vaccines
2. Identify next steps for the improvement of HPV vaccines safety monitoring

Background documents
1. Siegrist CA et al. Human Papilloma Virus Immunization in Adolescent and Young Adults: a Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions. Pediatric Infectious Disease Journal 2007; 26(11)

Proposed discussion areas
1. Review existing capacities for routine AEFI monitoring in countries:
   - Existing monitoring systems: developed vs. developing countries;
   - WHO initiatives: Global Network for Post-marketing Surveillance of Newly Pre-qualified Vaccines, Global Advisory Committee on Vaccine Safety (GACVS)
2. Technical data issues:
   - Case detection and reporting: serious/non-serious events, denominator data, sentinel or comprehensively, public/private providers
   - Data collection and validation: specify core data/ additional data, timelines for symptoms onset, criteria for validation of the system (syncpe?)
   - Data management and analysis: capacities for investigation and causality assessment evaluation of records (retrospective/prospective), retrospective solicited surveillance?, availability of relevant background data, expected rates of AE vs. reported rates of AE, comparison with base-line rates (validation of base line reported rates of medical conditions in the specific age group, e.g. autoimmune diseases, infertility), use of standardized case definitions, international coding of reported events to ensure data comparability, linkages with registries (pregnancy, specific diseases registries)
   - Data ownership and data sharing: global data base (UMC) - confidentiality issues
3. Communication issues: response to public inquiries and media requests, risk communication plans.