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Meeting Report

The Second WHO HPV Laboratory Network Meeting **WHO Headquarters, Geneva, Switzerland**

17-19 November 2008



EXECUTIVE SUMMARY

In anticipation of the implementation of new prophylactic Human Papillomavirus (HPV) vaccines, the World Health Organization (WHO) is supporting the establishment of a global HPV Laboratory Network (LabNet) whose mission is to "contribute to improving the quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact through enhanced, state-of-the-art laboratory support". To date, two Global Reference Laboratories (GRL) and eight Regional Reference Laboratories (RRL) have been assigned to the WHO HPV LabNet.

WHO convened a meeting at its headquarters in Geneva, 17-19 November 2008 to review progress since the last meeting in January 2008, to identify priorities and assign roles and responsibilities for future activities. The objectives of the meeting were to: 1) review how the HPV LabNet could contribute to the implementation of WHO policy on HPV vaccination; 2) review progress in standardization projects to develop International Standards (IS) for HPV DNA and antibodies and their use in assay standardization; 3) review data/results from HPV LabNet collaborative studies on HPV genotyping and serologic assays. Progress and workplan in the development of the first edition of HPV Laboratory Manual was also discussed. In addition, the achievements and progress made in HPV LabNet and in each reference laboratory over the year were reviewed along with proposed activities for the coming year. Activities of other WHO laboratory networks were discussed along with input from WHO Regional Offices in order to further develop the role of HPV LabNet in supporting HPV surveillance and vaccination impact monitoring.

Upon the conclusion of the meeting, recommendations were identified to assist the HPV LabNet in fulfilling its mission. In addition to general recommendations to WHO about developing strategic plan and sustainable funding for the HPV LabNet, these included: 1) sourcing and developing critical reagents including HPV virus-like particles (VLP), monoclonal antibodies and human sera samples for use in and control of VLP-based serology assays; 2) developing ISs and reference materials for use in standardizing HPV enzyme immunoassays (EIA), neutralization and genotyping assays; 3) planning the next round collaborative studies towards standardization of DNA genotyping and enzyme immunoassays and proficiency studies; 4) reinforcing

communications within the HPV LabNet and with other partners; and 5) finalization of the HPV Laboratory Manual.

Background

The WHO HPV LabNet was established in 2006 "to harmonize and standardize laboratory testing procedures and create a global HPV laboratory network worldwide and to contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact". This activity is part of a WHO initiated project funded by Bill & Melinda Gates Foundation for a 5-year period.

Following up the recommendations made in the WHO meeting on standardization of HPV assays and the role of HPV LabNet in supporting HPV vaccine introduction, 23-25 Jan 2008 (1), the HPV LabNet has been conducting a series of collaborative studies to evaluate assays for HPV genotyping and HPV serology. Based on results of these studies, the HPV LabNet is developing an HPV Laboratory Manual that will provide basic guidance to the laboratories in the world on harmonized quality control, HPV standards and examples of HPV assays. To facilitate the standardization and harmonization of HPV testing, WHO is developing ISs and Reference Reagents (RRs). The HPV LabNet has also organized proficiency studies to evaluate HPV genotyping assays. This second HPV LabNet meeting was convened to review and conclude the results from these studies and standardization projects, to identify gaps, and to develop HPV LabNet workplan for the next year.

Opening Remarks

Dr I Knezevic [Quality, Safety and Standards (QSS)/ Immunizations, Vaccines and Biologicals (IVB), WHO] welcomed meeting participants. She summarized HPV work in the context of WHO Biological Standardization program by presenting a brief overview of ongoing activities of WHO standardization projects and provided a perspective of HPV related standardization work from a long term point of view. Setting norms and standards and promoting their implementation are WHO core activities. These WHO norms and standards are the basis for the regulation of biologicals worldwide. Specific to HPV related standardization, the use of currently available ISs and RRs for HPV vaccines e.g. HPV 16 antiserum, HPV 16 and 18 DNA, should be promoted.

These norms and standards are the basis for standardization of assays for quality control and clinical evaluation of HPV vaccines. The HPV laboratory manual currently being developed by the HPV LabNet, is part of the support for countries beginning HPV surveillance. The HPV LabNet is a long term approach for which a long term strategic plan is being considered by WHO.

Dr TQ Zhou (QSS/IVB, WHO) told the participants that this meeting, which was attended by all HPV LabNet members, was convened to review progress since the last meeting in January 2008 (1) and to identify priorities and assign roles and responsibilities for future activities. The objectives of the meeting were to

- Discuss how HPV LabNet would be able to contribute to implementation of WHO policy on HPV vaccination which is being developed through WHO Strategic Advisory Group of Experts (SAGE), the WHO's leading immunization advisory body, and to share existing challenges identified
- Review progress in development of ISs (HPV DNA and antibody) and their use in assay standardization
- Review achievements & progress made in HPV LabNet and in each reference lab over the year and identify gaps/challenges in undertaking HPV LabNet tasks
- Review data/results from HPV LabNet collaborative studies on HPV genotyping and serologic assays conducted in 2008
- Discuss content of the first edition of HPV Laboratory Manual which aims to be submitted for publication in 2009
- Exchange laboratory experience from countries in supporting studies on HPV surveillance and vaccination impact monitoring
- Share experience from other WHO laboratory networks, communicate with WHO Regional Offices & other partners, discuss the role of HPV LabNet in supporting HPV surveillance and vaccination impact monitoring

Drs J Dillner and **E Unger** agreed to chair the meeting. **Dr M Ferguson** served as rapporteur.

Session 1 Update on the global HPV vaccine introduction strategies/progress

Dr K Irwin [Initiative for Vaccine Research (IVR)/IVB, WHO] gave an update on WHO's strategic plan in facilitating HPV vaccine introduction. Consultations in all WHO regions during 2007-2008 demonstrated support for HPV vaccines as an important option for preventing cervical cancer. All consultations expressed concern about vaccine affordability and the need to develop new systems to monitor the impact of HPV vaccination programmes and long-term safety, including safety during pregnancy. In July 2008, the WHO HPV Vaccine Advisory Committee (HVAC) recognized that the capacity to monitor vaccine impact varies by country and recommended that tiered monitoring approaches based on country income and capacity will be needed. Requests for technical assistance are first expected from middle-income countries that will be early adopters of HPV vaccine (e.g. in Latin American countries). Many high-income countries, however, are also uncertain about how to monitor vaccine impact and may seek WHO guidance. As of January 2008, 15 high-income countries had issued recommendations about use of HPV vaccines in national immunization programmes. Eight of these 15 recommendations specifically noted the need to monitor vaccine coverage, adverse events, HPV incidence and type replacement as well as incidence of cervical pre-cancers and cancers, but these recommendations did not provide detailed monitoring guidance and have not considered quality and international comparability. Recently, more high-income countries and middle-income countries (e.g. Mexico and Panama) have recommended inclusion of HPV vaccination in national immunization programs and may wish to launch systems to monitor vaccine coverage or impact. HVAC emphasized that lack of monitoring systems in a given country should not delay vaccine introduction and that, as a minimum, all countries should monitor vaccine coverage by age and district. Population-based or sentinel monitoring activities should be sustainable and well-designed. HVAC recommended that HPV LabNet should prioritize HPV DNA genotyping to support monitoring. HVAC also stressed that stable, long-term funding is needed for the HPV LabNet.

At its meeting in November 2008, SAGE recognized the importance of preventing cervical cancer and other HPV-related diseases as global health problems. SAGE recommended that routine HPV vaccination should be included in national immunization programmes, subject to programmatic and financial qualifications. SAGE recommended that after introduction of national or regional HPV vaccination programmes, managers should measure vaccination

coverage by age and district, preferably through routine immunization monitoring systems. SAGE also recommended and elaborated on systems for monitoring of the effectiveness of the programs, where feasible. Dr Irwin noted that the HPV LabNet activities will need to be complemented with additional funds and staff at WHO to design monitoring strategies and support programs over the long haul. She urged development of appropriate capacity/resource within WHO to lead the development of WHO guidance on methods to monitor the impact of HPV vaccination programmes.

Session 2 Update on development and implementation of International Standards & Reference Reagents for HPV testing

Dr DE Wilkinson [National Institute for Biological Standards and Control (NIBSC), UK] gave an update on the development of ISs for use in HPV DNA and serology assays. ISs for HPV-16 and 18 DNA were established by the WHO Expert Committee on Biological Standardization (ECBS) at its meeting in October 2008. Each IS has an assigned unitage of 5×10^6 International Units (IU)/ ampoule or 1×10^7 IU/ml when reconstituted as directed in 0.5ml distilled water. It was agreed that information on the use of these standards to calibrate secondary standards would be included in the Instructions for Use. Human DNA to serve as diluent in such calibrations is also being prepared by NIBSC. ECBS also endorsed a proposal for the development of a panel of five additional high risk types of HPV DNA, namely HPV types 31, 33, 45, 52 and 58. Since each of the candidate HPV DNA standards are plasmid-based, it is proposed that the assignment of unitage be achieved using one of the established HPV DNA IS as calibrator (e.g. the IS for HPV-16 DNA). Unitage will be established in a collaborative study employing a quantitative polymerase chain reaction (PCR) method that targets plasmid backbone sequences common to all of the recombinant HPV high risk panel candidates as well as to the ISs. All members of the high risk HPV DNA panel will therefore be traced to a single value assignment traceable to an IS instead of to five separate arbitrary value assignments. A pilot study demonstrating proof of principle of this approach has been undertaken using the data for the HPV-16 and 18 DNA standards. This approach will save time and be less costly for participants. During discussion, HPV LabNet members also proposed that ISs be prepared for HPV types 6 and 11 DNA and it was agreed that this will be added to the NIBSC program of work. In order to determine who has ordered the standards and how they are being used, it was agreed that NIBSC will review the use

of ISs for the next HPV LabNet meeting. It was noted by Dr R Sahli (RRL, Switzerland) that the cloning site within the HPV genome could affect the performance of some assays and it would be helpful if a map of the recombinant HPV plasmid was included in the Instructions for Use. Dr Wilkinson stated that although a map is not provided, the Instructions for Use does provide the GenBank Accession number as well as the cloning site of the HPV genome. It was also suggested that the use of sheared C33A cellular DNA might give more reproducible results in the preparation of dilutions. However, this has not been observed as an issue in studies to date.

Dr Wilkinson next gave an update on the stability data on the WHO RR for anti-HPV-16 antibodies (NIBSC reference 05/134) which was established by ECBS in 2007. As reported at the 1st HPV LabNet meeting in January, 2008 (1), quality control tests indicated that ampoules of 05/134 had variable and higher oxygen content and residual moisture content than expected thus raised concerns about the long-term stability of the WHO RR.

Using non-destructive testing, 10 ampoules with low oxygen content and residual moisture content and 10 ampoules with 20% oxygen and high residual moisture content have now been selected for antibody assays. If these give homogeneous results we can conclude that the antibody content in all ampoules stored at -20°C can be considered as of comparable stability.

Dr M Ferguson (NIBSC) then gave an update on the sourcing of qualified HPV VLPs and preparation of monoclonal antibodies for HPV LabNet use in HPV serological assays. High quality VLPs and/or pseudovirions (PsV) are required for serology assays to assess seroprevalence, vaccine immunogenicity and vaccine implementation, but most laboratories are unable to produce these material. At the 1st HPV LabNet meeting in January, 2008, representatives from companies who were producing VLPs on a commercial scale indicated that they were prepared to enter into discussion with WHO on the provision of VLPs for use by the WHO HPV LabNet. Dr Ferguson then described the criteria which would be included in a protocol for determining whether VLPs are of good quality for use in serology assays. These criteria include electron microscopy, protein content, purity and intact monomer, antigenic reactivity with neutralizing monoclonal antibodies and reactivity with panels of positive and negative human sera. A panel of monoclonal antibodies for standardized quality control of VLPs and pseudovirions has been provided by Dr ND Christensen (Penn State Milton S. Hershey Medical Center, USA), namely H16-V5 which has HPV 16 neutralizing activity, H18-J4 which

has HPV 18 neutralizing activity and H16-D9 which reacts with denatured VLPs. These reagents will be made available to HPV LabNet members in due course.

Session 3 Progress and challenges in the development of WHO HPV LabNet

Dr TQ Zhou summarized the progress made and challenges being faced by the HPV LabNet and gave an overview of the projects undertaken so far and those planned. Detailed results of HPV LabNet studies were presented by coordinating laboratories in later meeting sessions. In general, progress and achievements in the year are encouraging in line with the workplan agreed in the January meeting (1) and the defined Terms of Reference (TOR) of the HPV LabNet. Issues which arose during discussion included the recognition that the HPV LabNet needs to expand to include laboratories already designated by governments as national HPV reference laboratories for HPV surveillance, e.g. in Canada and the UK where HPV national immunization programs have been implemented. Dr A Bharti (RRL, India) indicated that in India there was no policy at the national level for quality-assured HPV assays in relation to vaccinology, as clinical trials were being undertaken by the vaccine manufacturers and samples are sent outside of the country for testing. Dr AL Williamson (RRL, South Africa) stated that this is also the case in South Africa. It was suggested that this reinforce the need for development of the laboratory infrastructure for research and implementation of HPV vaccination. It was also noted that the criteria for HPV LabNet membership need to be further developed.

Each HPV LabNet member then presented an update on progress during the year and proposals for next year. These reports addressed the key TOR of membership of the HPV LabNet namely, active participation in the HPV LabNet studies, scientific and technical advice, quality assurance and international standardization, testing capacity building, training and communication. Each member also had specific TOR and undertook projects individually. Issues that arose included the size of some of the reference laboratories whose overall throughput was somewhat limited.

Although many HPV LabNet laboratories had actively contributed to development of HPV monitoring studies in their regions, not all HPV LabNet laboratories have had work generated through their designation as an HPV LabNet reference laboratory. This may be because some of the members are research laboratories without established contacts with public health authorities. Strong links to public health initiatives are required for success. The issue of whether WHO and the WHO regional offices could assist in establishing such contacts was discussed. Future

addition of members to the HPV LabNet should in particular evaluate links to public health initiatives.

It was noted that the demands on the HPV assays to include extensive and accurate HPV genotyping are important for HPV surveillance, but less important for clinical HPV diagnostics. Laboratories in the HPV LabNet should therefore be involved in public health surveillance activities and not only in clinical diagnostics.

Session 4 HPV LabNet activities- laboratory manual, newsletter

Dr J Dillner (GRL, Sweden) gave an update on the development of the HPV Laboratory Manual including the rationale for its development and an outline of its content and timelines. The manual will include chapters on surveillance; nucleic acid amplification technique (NAT) assays and how to assess their performance and make data internationally comparable through the use of international standards; serology assays including EIA and PsV neutralization assays; quality assurance (QA) as well as standard operating procedures (SOP); and guidance on some of the specific techniques which had been evaluated through collaborative studies in which HPV LabNet members had participated. It is anticipated that the manual will be finalized in the second half of 2009.

Dr Ferguson then outlined a proposed chapter on determining the acceptability of assays including quality control (QC) and validation. She indicated that guidance for the validation of NAT assays for the detection of viruses in plasma pools is available in the European Pharmacopeia and that this chapter will reflect the principles described in these documents. In addition, this chapter will reflect the general guidance on the validation of analytical assays as described in International Committee on Harmonization (ICH) (2).

Dr E Unger (GRL, USA) described issues relating to quality in laboratory testing including quality management systems which cover QA, quality assessment, quality improvement, quality indicators and QC in individual assays. There will be a chapter discussing these aspects in the laboratory manual, which will be based on and refer to general checklists and documents available from other sources such as the College of American Pathologists. However, Dr Unger indicated that it is also required to develop and document the procedures for the specific system. She also indicated that regular review of testing results and control values are useful to monitor trends. Laboratory inspections also have a role. For the HPV LabNet she suggested that each

HPV LabNet member prepare a QA/QC overview for their laboratory and share QA/QC tips that are found to be helpful through the WHO HPV LabNet SharePoint site. For example, how potential problems are addressed and how often problems are uncovered as this would help others avoid the same pitfalls.

The group agreed that the manual is in good shape but need further expansion and revision of some sections. The need for QA guidance was discussed and it was agreed that the first edition should focus on basic guidance. Dr Unger indicated that the principles followed by the Centers for Disease Control and Prevention (CDC), United States, are suitable for any environment and emphasized that "a bad test is worse than no test". It was agreed that the chapter on surveillance needs to be updated and the chapter on general issues of QA and ISs also needs to be updated and expanded. It was further agreed that the chapter on neutralization assays should include general concepts but not details, in the current version, until the assay protocols are evaluated by the HPV LabNet. The chapters on EIA and genotyping should include protocols (SOPs) evaluated by the HPV LabNet this year and an introduction should be added indicating that they are described as examples. Other protocols and more extensive information will be posted on the HPV LabNet SharePoint. The group agreed that all chapters should be finalized by HPV LabNet by June 2009. Focal points (drafters) and timeline were agreed (see Recommendations and Conclusions of this report).

Dr S Garland (RRL, Australia) updated HPV LabNet members on issues relating to the HPV LabNet newsletter which is produced every six months in order to "promote and participate in the exchange of information/activities between national, regional, and reference laboratories, and the HPV LabNet". The contents of the third edition, which was due to be distributed early in 2009, was drafted.

Session 5 HPV LabNet progress in HPV genotyping assays

Dr R Sahli (RRL, Switzerland) described the transfer of the PGMY- reverse hybridization typing assay (CHUV assay) to other HPV LabNet laboratories and presented the results of the subsequent collaborative study. Considering the questionable affordability of commercial kits, the HPV LabNet had decided to evaluate an alternative, non-commercial assay for possible inclusion in the HPV Laboratory Manual (1). The evaluation included validation of the assay, technology transfer to laboratories without prior experience of performing the assay,

improvement of the SOP following experience in collaborative study and identifying training needs. The technique, which involves a general primer PCR and typing by reverse blot hybridization, was attempted to be transferred to 8 laboratories and encouraging results were seen from 5-6 laboratories; although they may not yet be considered as proficient. Additional trouble-shooting and/or training was necessary for 2-3 laboratories. However, considering the "technical expertise" involved in this method, its transfer was better than expected. It must be stressed that the hands-on time and expertise needed to set up the assay requires considerable training in comparison to implementing commercial assays like Roche Linear Array. The CHUV assay was further evaluated with the first HPV LabNet DNA proficiency panel, and the results were encouraging considering the recent implementation of the assay.

The assay was also evaluated with the second HPV LabNet DNA proficiency panel. Excluding HPV types 39 and 68 that were not adapted to the CHUV assay and other assays, some types were missed by some laboratories, underscoring the necessity of further training to optimize the performance of such an in-house technique in specific laboratories.

The issue of QC of primers and probes was raised and Dr Sahli indicated that this was covered in the SOP. Although 30% of laboratories trialing this had had some problems, it was emphasized that RRLs must be able to have at least one full HPV genotyping assay established in order to qualify as a RRL. It was concluded that the pros and cons of the use of commercial and in-house assays be discussed in the HPV LabNet manual along with guidelines on maintaining and monitoring competence in performing assays. Dr Sahli concluded that at around 4\$ per typing, considering that it had a comparable performance to the most commonly used commercial complete HPV genotyping test (Linear Array), the CHUV assay is a viable alternative to commercial assays provided it is used under specific, quality-assured conditions. The selection and use of appropriate assays in real epidemiological work will depend on the setting, e.g. the purpose and need of studies, available laboratory resource etc. It was suggested that the possibility of negotiating lower costs for commercial kits or membranes be investigated and central supply of critical reagents could be considered if there is a demand. CDC, for example, had developed PCR reagents for the WHO polio laboratory network. It was emphasized however that this will be a major task for anyone undertaking this project. The group agreed that the non-commercial assay developed at RRL, Switzerland (CHUV assay) should be included in the laboratory manual and that the development, evaluation and technology transfer of the assay

should be published in the scientific literature. Since RRLs may be required to perform HPV genotyping for other laboratories, Dr Sahli was also asked to develop a SOP detailing requirements for sending amplified products to RRLs for genotyping.

Dr Sahli then described the in-house validation of the CHUV assay. This assay had been developed in 1999 and was based on a method for typing mycobacteria. The PGMY primers were disclosed prior to publication by Dr P Gravitt and the CHUV assay can be considered a development of the Roche reverse blotting hybridization assay (RBH), modified to allow for the reuse of the membrane in order to minimize the cost. Different DNA extraction procedures are used for different types of samples. The sensitivity of the assay has been demonstrated through the detection of HPV genomic DNA with known copy numbers in SiHa, CaSki or HeLa cells which were mixed with 1×10^6 293 cells prior to DNA extraction. Performance using the first HPV LabNet DNA proficiency panel and the ISs for HPV-16 and -18 DNA indicated a sensitivity of 5 HPV-16 or HPV-18 DNA molecules per reaction, using PGMY primers and RBH.

Reproducibility of the CHUV assay had been demonstrated through retrospective analysis of DNA samples stored at -20°C for 6 months to two years and using different reagent lots. One sample per patient was selected to increase sample complexity and samples were from patients who had been tested at least three times (N=279). Negatives were included in the retrospective analysis. The results were read independently by two individuals and compared to original data. Most discordant cases were seen with mixed infections and with low HPV load. 41 samples/ types were discordant of which 10 were from single infections which became negative, 31 were from mixed infections of which 21 were weak positives (9 originally, 12 on repeat testing). To further evaluate the CHUV assay against a commercial assay, two-hundred samples previously tested by the Roche Linear Array HPV genotyping assay were analysed with the CHUV assay retrospectively using stored DNA (-20°C , < 6 months) purified with the bioMérieux EasyMAG system. It was concluded that the CHUV assay is comparable to the commercial assay: 99% type-specific concordance was obtained. Most discordant cases were seen with mixed infections and with low HPV load. Technical issues noted were that the CHUV assay needs more hands-on time and careful QC. There are also limitations on throughput as the RBH cannot be automated and technical expertise is also required. However, where cost is an issue, this assay is competitive with costing around 4 CHF compared to the Roche Linear Array

assay, which costs 80 CHF including PCR. As this assay has been validated and performed well, yet not perfectly, in the proficiency studies in several laboratories, the group agreed that the description should be included in the HPV Laboratory Manual.

Session 6 Review of the 2nd HPV LabNet DNA proficiency study and confirmatory testing

Dr J Dillner summarized the results of the 2nd HPV LabNet proficiency study to evaluate HPV DNA genotyping methods. He emphasized that participation in external proficiency studies is a basic quality requirement and a prerequisite for accreditation. Various proficiency panels are manufactured by a large number of different organizations and companies. However, when panels contain different samples for each study, it is not possible to identify improvements directly as data are not comparable against previous proficiency panels and laboratories using different proficiency panels can not compare performance against each other. When the panel is composed of individual plasmids or mixtures of plasmids traceable to ISs, the composition of the panels are defined and the problem of relying on the consensus of the results from the "best" laboratories to evaluate sample composition is avoided. The WHO proficiency panels were prepared from plasmids of 14 oncogenic and 2 benign HPV types that are the types most likely to be of interest for HPV vaccination for the foreseeable future. Sensitivity requirements are particularly high for the current major vaccine types HPV 16 and 18, but somewhat less important for other types. Assays should also be able to detect multiple infections and plasmids were therefore both included separately and in mixes, to evaluate the sensitivity of assays for single and mixed infections. HPV LabNet members were required to participate in the 2nd HPV DNA genotyping proficiency study and external HPV laboratories worldwide were invited to participate free of charge by announcing of the study on the WHO website. Eighty-four different data sets were delivered from 54 laboratories, using fourteen major HPV genotyping assays. Dr Dillner described the agreement from the previous HPV LabNet meeting that for a laboratory to be considered proficient: no mis-typing or false positives were allowed and that assay sensitivity of 50 IU for HPV 16 and 18 and 500 genome equivalents for other HPV types (both in single and in mixed infections) should be obtained. Following discussion, it was now agreed that one mistyping/false positivity per data set would be allowed (corresponding to a >97% specificity).

Of the assays used in the proficiency study, the Roche Linear Array HPV genotyping assay was the most widely used assay with adequate performance. Several other very high quality data sets were obtained with assays that were used in only one or a few laboratories (e.g. PCR-Luminex; multiplex PCR-Arrayed Primer Extension [PCR-APEX]; Type-specific PCRs; PCR-microarray). It was agreed that the report of the study should be published in the scientific literature.

The use of ISs and proficiency panels in relation to run controls was discussed. Dr Unger emphasised that the inclusion of a low level positive control in every run is required to detect if a run is valid. ISs and proficiency panels are not in supply to be used as run controls, but it is desirable if run controls are traceable to ISs. Monitoring for changes in titration curves are also useful to detect performance changes in quantitative assays.

The group agreed that the next annual proficiency study should be limited to HPV LabNet members, due to insufficient resources to perform a worldwide open proficiency study every year. It was agreed that the out-sourcing of this activity to an organization with regular catalogue, ordering, filling and billing capacity should be investigated.

Dr T Gheit from the International Agency for Research on Cancer (IARC), Lyon, France described the validation and application in field studies of a genotyping assay for detecting multiple HPV infections. He started by discussing the pros and cons of available HPV typing assays. Currently available typing methods use degenerate or consensus primers that have varying affinity for specific HPV types. They have the advantage of requiring a single PCR per sample but the disadvantage is the potential for competition that may affect the detection of multiple types in a single sample. The use of specific primers will increase specificity and sensitivity but has the disadvantage of requiring several PCR reactions that are time consuming, require large sample volume and are prone to cross-contamination. To address these problems, Dr Gheit and colleagues developed a multiplex PCR / APEX assay that uses a set of specific primers in a single PCR reaction tube followed by microarray analysis for determination of HPV types (3).

The multiplex PCR reaction targets a region in E7 using HPV type-specific primers as well as cellular DNA using Beta globin primers. The APEX microarray uses hybridization with HPV type-specific oligonucleotides and the output is read with a Genorama-003 four-color detector: the HPV types are defined by the position of the signals on the microarray chip. Currently,

oligonucleotides for 19 high-risk mucosal HPV types are used on the HPV chip. In a comparison study, several HPV types were found more frequently by the multiplex PCR/APEX method than by the GP5+/GP6+ Reverse Line Blot (RLB) assay, especially in multiple infections. The greatest difference between the two assays in detecting specific HPV types was found for HPV types 16, 33 and 53. HPV types 33 and 53 were better detected by the PCR/APEX method, whereas more HPV16 was identified by the GP5+/6+ PCR RLB assay. A modified version of the multiplex PCR assay has now been made that has a comparable sensitivity to the GP5+/6+ in detecting HPV16 DNA

The latest version of the APEX chips could contain up to 68 papillomavirus types and other infectious agents such like EBV, HSV or Chlamydia trachomatis, expanding the platform to encompass many sexually transmitted infections (STI). The throughput has been increased by adaptation of the APEX microarrays to the bead-based Luminex hybridization assay in collaboration with the DKFZ (German Cancer Research Center of Heidelberg). The multiplex PCR / Luminex method therefore meets the requirements for an assay useful for epidemiological studies as it has high sample throughput with low sample consumption and is time-saving and cost-effective. These assays have been used for the detection of HPV types in different anatomic regions.

Dr E Unger next discussed issues relating to the use of archived samples for HPV detection and typing, in particular formalin-fixed paraffin embedded (FFPE) samples from diagnostic pathology laboratories. The diagnostic FFPE samples (or blocks) are used to make histologic diagnoses, and the excess material remaining after diagnosis provides a way to directly test material from the lesion. In addition, follow-up information about the course of disease may be available. However, sample preparation and adequacy checking needs input from a pathologist. A “sandwich” method of block preparation using serial sections is required. The sections used for PCR or other molecular testing are between the first and last sections, which are stained with hematoxylin and eosin (H&E). If histologic review confirms the lesion is present in the first and last sections, then the intervening sections also contain the lesion. When serial sections are cut, PCR precautions must be used to prevent carryover between samples. These precautions include the use of gloves by the technologist, cleaning the microtome between cases, the use of a new disposable blade for each block, direct transfer of sections for PCR to clean sterile tubes and, most importantly the sectioning and HPV testing from a "blank" paraffin block in-between the

sectioning of each case block. A successful approach is to cut six serial 5- μ sections so that sections 1 and 6 can be stained and sections 2-3, 4-5 placed in two tubes for PCR testing. It was proposed during discussion that some aspects of this be included in the HPV LabNet manual to highlight contamination risks and to emphasize the need to confirm the presence of the lesion in material being tested using the serial section "sandwich" method.

Dr J Dillner then reviewed the need for confirmatory testing by GRLs on samples tested in RRLs. Confirmatory testing had been emphasized in the WHO HPV workshop in 2005 (5) that is the foundation of the HPV LabNet and the actual practicalities of the work had been agreed on at previous HPV LabNet meetings and included as an essential part of the quality control in the TOR of all HPV LabNet members. Only one RRL had submitted such samples as agreed. The need for confirmatory testing was further explained, as it is an important part of the quality control/quality improvement of a reference laboratory to test real patient samples as adequate data on testing of plasmid samples does not fully control for adequacy of testing of real samples. Confirmatory testing facilitates identifying problematic samples and real-life testing problems and finds ways on how to handle them. 5% of positive samples should be submitted (but shipments of less than 100 samples should not be sent). These positive samples would preferably be from cervical cancers or, if not available, from cervical intraepithelial neoplasia (CIN) 2/3. Furthermore, all samples from cervical cancer patients and CIN2/3 patients that test "HPV-negative" should be sent for confirmatory testing. Finally, all samples considered to contain HPV of an unknown type as well as a random sample out of every 50 samples (at most) with "questionable positivity" (grayzone samples) should be submitted. The samples that were submitted for confirmatory testing had been retested at both GRLs and a high concordance was observed. Thirty-six "HPV-negative" cervical cancers had been retested and HPV had been detected in 17 of them, but 19 cases were also HPV negative on retesting in both GRLs.

Session 7 HPV LabNet progress in HPV serology assays

Dr J Dillner presented the report from the HPV LabNet collaborative studies on the VLP-based enzyme-linked immunosorbent assay (VLP-ELISA). This study was designed to evaluate a suggested SOP for HPV 16 ELISA in the HPV LabNet and improve it in light of experiences obtained in the study. Plates pre-coated with VLPs had been evaluated for stability prior to distribution in the study. A shelf-life of 3 months at +4 °C post coating was found. A panel of

coded samples was distributed to study participants. This included 6 samples from women with no sexual experience (negative controls), 11 samples from cervical cancer patients with HPV 16 DNA PCR-positive tumors. Respectively, 5, 2 and 4 of these 11 samples were found previously to be strong positive, positive, and negative for HPV 16 IgG. One strong positive was included twice in the panel with different numbers. The results of the study indicated that the assay had been well implemented by the laboratories, the SOP had been found to work in different settings and the inter-laboratory variation in antibody levels found was reasonable. All samples previously found positive were uniformly found positive by all laboratories. The background among negatives was a bit higher than expected, but if the cut-off value was raised (e.g. from 2 units to 4 units) most laboratories correctly identified negatives as negative. The assay can therefore be included in the HPV Laboratory Manual, after incorporating improvements to the SOP.

The next stage of the serology work will be a phase 2 study on VLP-ELISA and probably a proficiency study, for which qualified VLPs available in larger amounts need to be obtained, preferably from more than one source. Some further optimization of the assay could be undertaken by the GRLs. The group agreed that the goal of this planned collaborative study on VLP-ELISA using a standardized source of VLPs, is to accomplish that standardized and high quality serology assays that could be used for large scale serology in vaccination studies are established and ready to use at all HPV LabNet laboratories. An international definition of the cut-off value should also be agreed upon. The group agreed that a call for VLPs and human sera for use in the international collaborative study should be published on the WHO website and in the next edition of the HPV LabNet newsletter. Dr Dillner also reported that sourcing of sera for use in the preparation of the anti-HPV18 standard had so far not been successful and that any laboratories able to help with identifying suitable donors should contact him.

The group agreed that the VLP-ELISA should be included in the HPV Laboratory Manual. Considerations for defining the cut-off should also be described in the manual. Parameters such as dilution series and cut-off when testing sera from naturally infected individuals and vaccinees will be described. Validation requirements and the use of run controls will also be elaborated upon, including testing for antigenic units using the monoclonal antibody panel donated by Dr N Christensen. The stability studies that found plates need to be kept moist at +4 °C will also be included.

The HPV LabNet members discussed the workplan for the coming year. They agreed that calls should be made for donation of VLPs and sera for use in collaborative studies aimed at standardizing the serology assays. 1mg of VLPs (i.e. sufficient for 15,000 tests) would be appropriate for the evaluation phase and minimum 4ml of positive and negative sera would be required. Negatives should be individuals with no sexual experience or children between 2-10 years old. Positives should be from patients with cervical cancer or CIN with unequivocally detected HPV16 or HPV18 DNA. For anti-HPV18 standard serum sourcing it would be helpful to receive samples from individuals who would be prepared to be re-bled so that sufficient serum could be accumulated for the preparation of the IS samples. The GRL/USA agreed to prepare secondary standards for use by HPV LabNet members, following guidance from NIBSC, if such need is identified and prioritized.

It was hoped that the serum samples to serve as a proficiency panel could be characterized in the two GRLs and that the phase 2 study on VLP-ELISA could start in May 2009 and finish in September 2009. The issues relating to potential bias in assaying vaccinee serum on different VLPs used to produce the vaccine were discussed. In due course when commercial assays become available, HPV LabNet will want to evaluate them. Serology assays are essential for several aspects related to HPV vaccination. Serology is used to learn about the epidemiology of the infection, in particular in pre-adolescent populations. Serology is also used to define susceptible populations in vaccine research and in immunogenicity studies bridging different populations and checking immunogenicity of different vaccine batches/administration methods. The ongoing research for correlates of immunity is also critically dependent on high quality serological methods.

Standardization of the neutralization assay has not been a priority of HPV LabNet work, but neutralization assays are important as confirmatory tests and in the research for correlates of protection after HPV vaccination. In addition, standardizing a neutralization assay is part of the activities defined in the HPV Gates project and was emphasized in WHO workshop in 2005 (5) that forms the task for the HPV LabNet and thus should be implemented. The issues involved in standardization of the neutralization assay were discussed and the need to undertake a collaborative study was agreed. Several members of HPV LabNet received training from Dr John Schiller (National Cancer Institute, USA) and have implemented the assay following protocols from his group (4). This PsV-based method is therefore the one most appropriate to standardize

for HPV LabNet use. The group agreed that such assays do not need to be implemented by all HPV LabNet members, the members with such assays already established can provide sufficient testing capacity for the entire HPV LabNet. It was also agreed that those who have implemented the assay will participate in a collaborative study to evaluate the SOP described in the previous draft HPV Laboratory Manual. The study will include testing of the WHO RR of anti-HPV16 sera.

Dr Unger agreed to coordinate the neutralization assay study. The participants should review the assay protocol and also confirm if sera are available by December 15, 2008 so that the study can take place and results be sent to Dr Unger, GRL/CDC by end of February 2009. Consensus on a SOP for the neutralization assay should be reached for consideration for possible inclusion in the laboratory manual.

Session 8 Country experience in supporting HPV surveillance and vaccination impact monitoring

Dr J Dillner described ongoing pilot projects on the logistics of establishing a monitoring system for HPV infection that the GRL/Sweden is performing. This involved obtaining ethical permission to genotype all HPV-associated cancers in Sweden (about 1000 cancers/year), an HPV typing and reporting system for condyloma acuminata; HPV typing in the cervical screening program; and anonymous HPV testing in the Chlamydia trachomatis screening program. The last group targets sexually active teenagers and will therefore give a very rapid evaluation of effectiveness of the program. An HPV vaccination registry has been established which includes informed consent for registry linkages to HPV vaccination trials and other health data registries, e.g. cervical screening registries. The number of positives identified during cervical screening should decline following vaccination.

As all HPV diagnostic laboratories in Sweden took part in the HPV LabNet DNA proficiency study, it could be useful to collect HPV typing data from quality-assured laboratories for monitoring of HPV type distributions. A standard format for reporting of HPV data has been agreed upon.

Dr E Unger then gave an overview of activities in support of HPV vaccines being conducted by CDC, US under the auspices of the CDC-wide HPV working group. Encouraging the acceptance

of HPV vaccination programs is being facilitated through use of focus groups to test educational messages about HPV and vaccination developed specifically for Vietnamese, Korean, Filipino, American Indian/Alaskan Native populations. Vaccine implementation is being monitored through pilot programs and surveys to evaluate methods to improve delivery. Safety of vaccine is being monitored through the national system Vaccine Adverse Event Reporting System (VAERS) and other groups. Monitoring the disease burden of cancer is undertaken through cancer registries that cover more than 99% of the country. Several state cancer registries are participating in a study to determine the type-specific HPV prevalence in HPV-related cancers from 2004-5. As this is a time-frame prior to vaccination, results will form the baseline with which to compare post-vaccination prevalence. Similar population-based pre-vaccine baseline studies of HPV type-specific prevalence are being conducted in cervical cancer in Alaskan natives, and in cervical cancer precursors, i.e. cervical intraepithelial neoplasia (CIN) 2/3, in the Emerging Infections Program. The disease burden of genital warts is also being assessed and this early outcome will also be used to monitor the impact of the use of quadrivalent vaccines.

Dr S Garland gave an update on the WHINURS (Women HPV prevalence Indigenous, Non-indigenous, Urban, Rural, Study group) HPV study in which HPV vaccination impact will be monitored. This is to model the likely health and economic impact of a quadrivalent HPV vaccine in Australia and inform decision-making on the cost-effectiveness of vaccination in a school based government funded programme. Gardasil was licensed in June 2006 and the national immunization program started on 1st April 2007. The program uses school-based immunization of 12 years old girls with catch-up cohorts of 13-18 year old (school based) and 19-26 years old (general practitioner based). Once catch-up is complete, the on-going cost is estimated to be approximately \$50 million per year. A national HPV vaccination program register has been established. The WHINURS study have recruited 1000 indigenous and 2000 non-indigenous women from around the country. The aim of the study is to estimate prevalence of type specific genital HPV infection prior to vaccination in the Australian female population by age group, indigenous status, cervical Pap smear status, region of residence (urban, rural, remote) and to assess impact of HPV population vaccination strategy through use of disease modelling. Standardised assays are being used for the study. All HPV positive samples are genotyped. The plan is to continue to use surveillance post vaccination and now given that the country is in its third year's cohort of vaccination in schools. The lessons learnt from this study will lead to

improved ongoing surveillance and facilitate monitoring vaccine effectiveness and screening practices.

Dr MA Picconi (RRL, Argentina) presented the work being undertaken at the Argentinian national reference laboratory for papillomavirus which is part of the National Institute of Infectious Diseases - "Dr Malbrán" National Administration of Laboratories and Health Institutes (ANLIS) . This laboratory heads the Argentinian HPV laboratory network, which has been established in order to prepare for the epidemiologic surveillance once vaccination programs are initiated. So far, laboratories in 12 provinces have joined the Argentinian HPV laboratory network. The network laboratories have different degrees of infrastructure, development and experience in HPV. The Pan-American Health Organization (PAHO) and Argentinian Ministry of Health have supported the network through training and technology transfer. A preliminary QC panel has been developed and Argentinian HPV laboratory network workshops have been held annually since 2004. As the regional laboratory for South America Dr Picconi's laboratory aims to support surveillance of infection and disease through the provision of competent national reference laboratories in the region. This will include training and advice to improve accuracy of genotyping and serological measurements and to encourage the interaction of the national reference laboratories with their public health authorities through collaboration in national immunization programs, epidemiologic surveillance, and cancer prevention. Dr Picconi's laboratory performs a range of HPV detection and typing techniques and makes available DNA controls (cell lines and HPV DNA-plasmids). They require assistance in setting up quality assurance and proficiency programs. During the next year they hope to strengthen capacity through training and implementation of currently accepted L1 consensus reverse line blot systems with type specific hybridization.

Dr F Carozzi (Cancer Prevention and Research Institute ISPO , Italy) described a project to monitor HPV vaccination impact in Italy. Data was being collected ahead of vaccination programs to determine the overall and age-stratified prevalence of HPV infection and HPV type distribution on a population level in women. The Ministry of Health financed three different studies: 1) women aged 25-60 participating in a screening program for cervical cancer; 2) women aged 18-24; 3) typing 1000 CIN2+ lesions on tissue samples obtained in Italy in the past 10 years which will be the basis to evaluate in the future potential non vaccine type replacement in the post-vaccine era. The Hybrid Capture 2 assay is performed in 12 different laboratories and HPV

genotyping in three laboratories. ISPO coordinates the laboratory activities and is responsible for quality assurance program. Meetings are held to define and share laboratory protocols. In order to compare results, the typing method used in IARC studies, i.e. Line blot typing with GP5+/GP6+ primers was the assay chosen for use in the national study. An HPV vaccination registry has been created and it is proposed that this will be linked in with health data registries, including screening programs, which will allow monitoring of the total effect of the vaccination programs. An independent pilot study is also being undertaken in the Tuscany Region that will help in understanding the impact of vaccination on regular screening activity; evaluate the compliance at the next screening round; and evaluate the seroprevalence before vaccination and the immunity status after vaccination. Type replacement should also be studied. The HPV status in cervical and in urine samples will be studied to evaluate the possibility of monitoring HPV status using urine testing in younger girls.

The group discussed the role of country-specific national HPV laboratories with respect to the WHO HPV LabNet. It was agreed that the HPV LabNet could benefit from the experiences of laboratories in those countries that have implemented national HPV vaccination programs and are already undertaking HPV surveillance. Dr Zhou recognized the importance of communicating with laboratories in countries with regard to HPV LabNet work and information. However, WHO has established its strategic structure and policy in organizing a global network. The WHO long term strategic plan for the HPV LabNet is under development along with WHO guidelines on HPV surveillance and vaccination monitoring. The WHO regional offices will play a key role in networking national laboratories in a global network if there is the need. Nevertheless, laboratories doing HPV surveillance, particularly those designated as national laboratories by their public health authorities, should be permitted to take part in HPV LabNet activities and be shared with the information. There are several useful tools in place e.g. HPV LabNet website and newsletter that will help. In addition, all HPV LabNet laboratories have the responsibility to provide information and technical help to national laboratories.

Dr A Bharti (RRL, India) described a simple paper smear method for dry collection of cervical samples for HPV-DNA detection that has potential for use in low-resource settings. The ideal HPV test method should be rapid and simple, cost-effective, sensitive and specific, reliable and reproducible. The same is true for sample collection. Current methods for sample collection have various limitations. The dry smear on a filter-paper slide is easily transported at ambient

temperature from field and clinics to the laboratory in a ziplock polythene pouch using ordinary post and takes up little storage space. DNA elution followed by PCR can be performed using a small piece (2-3 mm) of paper-smear in a single Eppendorf tube . This means that it is suitable for use in mass screening of HPV. This method can be employed for collection of almost all cytologic specimens for molecular analysis including blood, cervical scrape/smear, and urine. The technique has already been employed for the collection of cervical and oral specimens from all over the country for HPV screening. During discussion, some members of the group were concerned about the contamination and labeling. These concerns can be addressed through appropriate training. It was agreed that the paper smear method looks promising. Further validation and comparison of results with convention sample collection methods will be required.

Session 9 Role of HPV LabNet in supporting HPV surveillance and vaccination impact monitoring

Dr D Featherstone [Expanded Programme on Immunization (EPI)/IVB, WHO] updated the group on the developments in other WHO Viral Vaccine Preventable Disease (VPD) Laboratory Networks. These have a tiered structure with Global Specialized laboratories, Regional Reference laboratories, National and Sub-national laboratories. There are now 145 polio laboratories globally and 679 laboratories for measles and rubella. These laboratories perform cell culture based assays, IgM EIAs and molecular assays as appropriate. There are also 23 yellow fever laboratories in the African region performing IgM ELISA most of which are integrated with measles and rubella laboratories. In South-East Asia and Western Pacific regions there are now over 20 members of a Japanese encephalitis network who also perform IgM ELISA. Each level of laboratory has different levels of responsibility. All laboratories are involved in training of the laboratories tiered below themselves. The networks also have very clear goals. As examples, the polio programme strives for global eradication and the measles programme, mortality reduction and regional elimination. The yellow fever network has regional focus relating to rapid detection of outbreaks so that there can be an immediate vaccination response. The role of the Japanese encephalitis network is less well defined but covers sentinel surveillance, monitoring disease burden and the impact of vaccine introduction. There are guiding principles for developing laboratory networks such as for the standardization of testing and reporting and establishing a quality assurance programme. All of the existing networks started with small numbers and grew

progressively. Regular communication is important through meetings as well as on an ad hoc basis if trouble shooting is required. Funding for laboratory networks is important. National funding is obtained for the polio and measles networks for the salaries and the majority of infrastructure costs. External funding is required for other items including equipment and consumables for low resource countries, meetings, training workshops, quality assurance, accreditation, assay development and validation and transportation of samples at all levels. Costs vary by region and disease, with Africa and South East Asia most dependent on external resources. It is essential that funding is sustainable. At present it is not clear how the HPV LabNet will fit into the current structures. The current 700 network laboratories have broad technical and functional capacity and are open to further integration, but only after consideration of impact on current laboratory-based surveillance activities, funds and personnel.

Participants of the meeting asked for advice on how to get governments to contribute to the HPV LabNet. Governments are lobbied through regional meetings which are attended by Ministry of Health (MOH) officials and EPI experts. The role of the WHO Regional Office is to give technical support so that countries can demonstrate the cost benefit of vaccine introduction. They provide terms of reference so that countries can identify suitable candidate laboratories to serve as national laboratories and then they propose to WHO that a laboratory fulfils the conditions. Other laboratory networks now have clear goals and sustainable funding although the funding was not sustainable in the beginning. This is not yet the case for HPV LabNet but once it is shown that a network is effective, funds should become available. A recommendation from SAGE was that countries should monitor prevalence and clinical outcomes, including typing of viruses, to see the effect of vaccine programs. EPI cannot be a focal point for HPV surveillance until HPV is included in the EPI programs. Guidelines for such studies need to be developed including how long they will last and how many individuals will need to be tested to assure that the impact of vaccination programmes can be monitored.

Dr H Ahmed [Regional Office for the Eastern Mediterranean (EMRO), WHO] presented on the potential role of EMRO/WHO in facilitating HPV surveillance and vaccination impact monitoring. Gardasil is licensed in 7 countries and Cervarix in 5 countries. The countries in the region comprise low-, middle- and high-income countries. One of the first issues to address is how to link HPV to other programmes and a meeting had been convened to discuss this issue. Information was shared and draft country work plans addressing HPV related disease burden and

comprehensive prevention strategies, including HPV vaccine introduction, were discussed. The need for a regional surveillance network for building country capacity to give the decision-making process on HPV vaccine introduction was also discussed. Main observations and concerns identified include: 1) cervical cancer prevention programmes are far from optimal in the EMRO countries; 2) although HPV vaccine is perceived as being valuable, its high cost could have an impact on other priorities; 3) data of HPV related disease burden is needed to support evidence-based decision-making. The meeting concluded that there was a consensus to build a comprehensive approach to the prevention and control of cervical cancer and that screening, treatment and HPV vaccination should form the basis of the national comprehensive cervical cancer prevention and control programmes. A range of recommendations were presented and it is hoped that, with the assistance of WHO and other partners, national action plans can be developed in early 2009 for HPV vaccine implementation. The global laboratory network could assist in identifying validated and standardized assay with appropriate protocol that could be used by national laboratory in the region to conduct HPV surveillance of disease burden and to monitor the impact of HPV vaccine after introduction.

Dr Y Jee [Regional Office for the Western Pacific (WPRO), WHO) presented the extensive activities in other networks already underway in the region. She also described a project on HPV genotyping being undertaken in Fiji. Samples are being examined in Dr Garland's laboratory (RRL, Australia) and this study will give good baseline data before the introduction of vaccines. So far 6 countries in the region have introduced HPV vaccine in national programmes. Challenges for the HPV LabNet are to have better communication with MOHs in these countries. WHO Regional Offices are not yet fully engaged. It may also be difficult to utilize the existing VPD network which is based on public health laboratories. Quality indicators for laboratory performances need to be established along with a WHO accreditation checklist to evaluate the performances of Regional or Global HPV LabNet laboratories. WPRO needs to collect information on HPV diagnosis and genotyping in the region to identify laboratory capacity so that WHO National HPV Laboratories in the region can be designated. Information sharing is a key issue including the activities of the regional laboratories.

Dr AM Bispo de Filippis (PAHO, WHO) presented the challenges and needs of South America with respect to HPV. In May 2008, the region has held a meeting in Mexico City, Mexico on cervical cancer prevention and control with the objective to strengthen national capacity for

informed public health decision-making regarding the introduction of HPV vaccines within a framework of comprehensive cervical cancer prevention and control, including screening and treatment. All countries have some type of cervical cancer prevention and control program, although the organization, quality, effectiveness and completeness of these programs varies. Some countries have already adopted alternative screening and treatment and others will be exploring the use of traditional or alternative cytology methods. All countries would implement HPV vaccination programs if the cost was affordable and it is therefore important to update policy makers on the importance of preventing cervical cancer and of the resources that are required to be in place on a sustainable basis. Countries would like the assistance of PAHO/WHO to conduct operational studies related to HPV vaccine introduction and in the strengthening of cervical cancer information systems, cancer registries, cytology quality assurance systems, etc. Countries would also like to acquire HPV vaccines through the PAHO Revolving Fund for Vaccine Procurement to assist in the purchase of vaccines, syringes/needles, and cold chain equipment. HPV LabNet can assist in monitoring the impact and effectiveness of HPV vaccine introduction through making available standardized and validated low-cost assays and facilitating appropriate QA/QC activities.

Dr G Lipskaya [Regional Office for Europe (EURO), WHO] indicated that this region is very diverse. A paper on HPV vaccine introduction describing general strategy and laboratory integration had been prepared. Both vaccines are licensed in many countries. Countries that would benefit from HPV immunization programs do not have HPV screening programs in place and will need assistance from WHO. There are however no funds although Global Alliance for Vaccines and Immunization (GAVI) will fund three pilot studies and the related surveillance for HPV. There are no resources to deal with HPV related work at EURO at present as the current priorities concerned are with rotavirus and meningococcal disease. Countries who wish to have laboratories designated as "WHO HPV national laboratories" should contact EURO for consideration.

Dr E Unger described potential objectives and approaches to HPV surveillance and vaccination impact monitoring. There are unique features of HPV vaccine impact monitoring as the problem is chronic rather than acute and the cost of vaccination, screening and testing is high. The possible goals of surveillance vary before and after HPV vaccine introduction and are dependent on the needs of the country e.g. knowledge of disease burden, infrastructure for cervical cancer

screening and treatment and availability of population-based cancer registries and cytology/histology banks or registries for CIN. HPV surveillance requires integration of efforts and the HPV LabNet can contribute to this along with academia, public health bodies, industry and Non-Governmental Organizations (NGOs). Harmonization of HPV laboratory testing procedures and implementation of quality assurance systems and proficiency testing among HPV LabNet members will allow inter-laboratory comparisons and facilitate assessment of HPV vaccine efficacy and provide a network for testing surveillance samples. Options exist for tiered monitoring that could address vaccine coverage, safety, cancer incidence and HPV typing in cancers and HPV types in the population. A plan to develop consensus on HPV vaccination impact monitoring is being considered by WHO, CDC, GRLs and other partners. Opportunities for surveillance will be specific to a country so HPV LabNet needs to develop general guidelines on what should be done. In addition, HPV LabNet could play a role in HPV DNA typing in cancer and CIN in sentinel urban centers and national/regional populations. The HPV LabNet should generate an enabling environment through piloting of combining screening/surveillance. Dr Irwin commented that even SAGE had indicated that all countries should consider a range of activities. However, even high-income countries were looking to WHO for guidance. If monitoring is implemented in high-income countries, this can be tailored to the needs of others. The group agreed that a review on HPV vaccine surveillance written by HPV LabNet members actively involved in these issues would have a lot of influence and Dr Dillner agreed to coordinate this.

Dr J Dillner described a proposed data reporting and collection mechanism that should be trialed in the HPV LabNet as this is an essential part of the work of every laboratory. Such systems will be described in the HPV LabNet manual. Every HPV LabNet reference laboratory needs to report the results to those submitting the specimens, produce reports of its work to their director and national disease control agencies as annual reports or progress reports and produce annual summary reports to WHO to justify why the reference laboratory should continue to receive funding. These data should include the number and type of tests performed as well as the HPV type distribution in "healthy" subjects and in subjects with HPV-associated diseases. The first step for this will involve compiling data in a common, standardized format. GRL/CDC is piloting the suitability of the approach described in the draft chapter of HPV laboratory manual. These data have to be managed effectively and databases such as ACCESS are suitable. HPV LabNet

member laboratories willing to exchange experiences in data reporting and jointly working towards defining a common format were asked for. Dr Sahli, Dr Garland, Dr, Unger and Dr Jerbi agreed to participate. Data will need to be sent to local authorities as well as to WHO and the HPV LabNet. This will be restricted to the HPV LabNet initially but should be designed to be suitable for all relevant laboratories.

Recommendations and Conclusions

At end of the meeting, recommendations and conclusions were reviewed and agreed.

General recommendations

- 1) WHO should find a solution for long term sustainability of the WHO HPV LabNet.
- 2) WHO international guidelines on HPV surveillance and vaccination monitoring need to be developed. This is essential for the HPV LabNet to develop appropriate infrastructure, testing formats and testing capacity.

Sourcing reagents and serology study (VLP-ELISA)

- 3) NIBSC will continue discussions with companies in order to source VLPs for use by HPV LabNet members. The VLPs sourced must be possible to be made available to all HPV LabNet members, at least as coated plates.
- 4) WHO will post calls for donation of VLPs and human sera samples on the HPV LabNet website as well as in the 3rd edition of HPV LabNet newsletter. A time limit of 4 weeks for responses should be included. All HPV LabNet members should help in sourcing these materials. In particular, Dr Bharti agreed for contacting the local scientist who has developed indigenous VLPs and Ms Sukvirach agreed to help in sourcing sera samples.
- 5) Drs Dillner, Unger and Kukimoto agreed to investigate the availability of in-house VLPs (>1mg) and reply to Dr Wilkinson within 2 weeks as to whether a supply is available.
- 6) The first HPV LabNet study on VLP-ELISA serology gave promising results and HPV LabNet members agreed that the method should be included in the HPV Laboratory Manual. Considerations about cut-off calculation and assay validity should be written in the SOP.
- 7) The second HPV LabNet study on VLP-ELISA (HPV type 16 & 18) is planned to be initiated in May, 2009 and coordinated by GRL/Sweden. The aims are to ensure that

prime HPV serology is established at all HPV LabNet laboratories with a standardized supply of VLPs and establishing an internationally accepted standard "cut-off" value. Sera panel should include naturally infected sera, vaccinees' sera as well as positive and negative control sera.

- 8) As it will be necessary to evaluate different sources of VLPs, the characterization of VLPs, including the use of the monoclonal antibody panel and human serum panels, should be performed by NIBSC and the two GRLs. 250µg VLP is required for these studies.

Neutralization assay

- 9) Both GRLs, the RRLs from Switzerland and GRL from Japan, have agreed to evaluate, on behalf of the HPV LabNet, the "generic" neutralization assay protocol which is currently described in the draft HPV Laboratory Manual using the residual serum samples provided for the first study of VLP-ELISA by GRL/Sweden. In-house PsV should be used in this pre-study. This study will be coordinated by the GRL/USA. These 5 laboratories should review the current SOP and provide any comments to Dr Unger by 15 Dec 2008. The study results should be submitted to Dr Unger by the end of February, 2009.
- 10) The use of a single supply of PsV in a later study will be discussed based on the data generated from the neutralization assay pre-study. If necessary, this will be conducted together with the phase 2 study of VLP-ELISA.

Proficiency studies for HPV genotyping

- 11) The report of the 2nd HPV DNA typing proficiency study should be published as soon as possible. Feedback to participants on identity of samples should be done immediately with a detailed report to follow. The two GRLs are to coordinate preparation of the detailed report and publication.
- 12) HPV DNA proficiency studies should continue. The 3rd study will be restricted to the HPV LabNet due to limited resources. The 3rd study will be coordinated by the GRL in Sweden and dispatched in September 2009.
- 13) The proficiency studies organized under the auspices of the HPV LabNet needs support by an administrative organization. Options for administrative support are to be investigated. CDC has previously coordinated Laboratory Performance Evaluation modules to evaluate laboratory harmonization on testing specific analytes of interest. The

GRL in the US will contact them to solicit their interest in including HPV typing as a module. Other offers of involvement in administrative support for handling of the proficiency panels will also be sought.

Genotyping assay

- 14) HPV LabNet members agreed that the PGMY-reverse hybridization blotting assay developed at CHUV had performed satisfactorily in the evaluation studies. This method should be included in the HPV Laboratory Manual. Users of the CHUV assay for technology transfer should review the SOP and indicate where they deviated from the SOP and where they had problems so that these issues can be addressed and incorporated in the HPV Laboratory Manual.
- 15) The genotyping assays which have been shown to perform satisfactorily in multiple laboratories under a range of conditions in the proficiency studies should be identified and listed with the actual data in the HPV Laboratory Manual, e.g. the Roche Linear array HPV genotyping assay.

Role of RRLs in confirmatory testing

- 16) RRLs must send samples to GRLs for confirmatory testing.
- 17) WHO will send letters to RRLs requesting that samples for confirmatory testing be sent, citing the need for continuous quality monitoring within HPV LabNet laboratories. Such a correspondence from WHO is seen by several HPV LabNet members as required for expediting ethics review. This letter should be sent before 25 December, 2008.

Assay performance

- 18) Sensitivity of HPV genotyping assays undertaken within the HPV LabNet should be at least 50 IU/5µl for HPV-16 and -18 DNA and 500 copies /5µl for other types. Specificity should be >97%.
- 19) All assays used to generate data in the HPV LabNet should be validated in a proficiency study performed under the auspices of the WHO HPV LabNet.

Commercial assays for HPV genotyping

- 20) Dr Dillner will provide WHO with a list of kits that performed well in the genotyping proficiency studies. The performance criteria to consider are sensitivity, specificity, cost and ease of use. Dr Zhou will then discuss with WHO colleagues on the next step to move forward.

Communication

- 21) HPV LabNet members are encouraged to use the WHO HPV LabNet SharePoint.
- 22) Laboratories in the HPV field should be made aware of the WHO HPV LabNet website.
- 23) HPV LabNet members should contribute regularly to the Newsletter.
- 24) HPV LabNet members should make contact with national health authorities in their region.
- 25) WHO Regional Offices should facilitate RRLs in contacting national health authorities in their region.
- 26)** Laboratories designated as national HPV reference or surveillance laboratories by governments and who are doing surveillance should be identified by the WHO Regional Offices and invited to future HPV LabNet meeting as observers, so that the HPV LabNet can gain from their experience.

Development of International Standards (IS)

- 27) Current proposals for development of high-risk types DNA panel of standards and human DNA diluent are to be pursued. [Types 31, 33, 45, 52 and 58.](#)
- 28) Development of ISs of HPV-6 and -11 DNA is to be added to the NIBSC program of work. This will be presented in a NIBSC-WHO joint standards review meeting in March 2009.
- 29) Guidance on how to use ISs for the calibration of secondary standards will be included in the "Instruction For Use" by NIBSC.
- 30) HPV LabNet members will advise NIBSC of suitable DNA levels for use as working standards/run controls, and advise on how these should be used, i.e. frequency of inclusion in assays. NIBSC to develop a unified "survey form" by requesting this information and send to HPV LabNet laboratories for input by June 2009.
- 31) For monitoring usage of HPV DNA and antibody standards, the ordering and dispatch of ISs will be reviewed by NIBSC and presented at the next HPV LabNet meeting.
- 32)** The development of IS of HPV-18 antibody should be pursued. In addition to Drs Dillner and Unger, other HPV LabNet members will assist in sourcing material.

HPV Laboratory Manual

33) The current version of the draft HPV Laboratory Manual is available on the HPV LabNet SharePoint. All HPV LabNet members should prepare and/or review the draft according to the following assignments:

- All chapters are to be sent to Dr Unger by the end of February, 2009 for overall review and editing.
- The final version of the HPV Laboratory Manual approved by the HPV LabNet for publication will be send to Dr Zhou by the beginning of June, 2009 so that she can proceed with the required WHO procedures for publication.
- Outline and assignment of chapters in the manual:

Topic	To be drafted by
Surveillance	Drs Garland, Dillner and Unger
NAT chapter / general assay chapter – how to assess performance of assays including NIBSC guidance on calibration of secondary standards for HPV DNA	Drs Ferguson and Wilkinson
Serology and assays – introduction , references	Drs Dillner, Nardelli-Haefliger and Garland.
Chapters 5 and 6 DNA – overview of methods – typing and DNA Information from 2 nd proficiency study for genotyping- indications	Drs Unger and Sahli Dr Dillner
Quality Assurance	Drs Unger and Eklund All LabNet members to review current draft of the chapter and give feedback to Dr Unger with comments/suggestions. This will help in refining the chapter.
Paraffin embedded samples particularly highlighting contamination risk. SOP to include a recommendation of hematoxylin and eosin staining of	Dr Unger

sections before and after those samples	
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QC/QA

- 34) Dr Unger agreed to place the CDC's QA/QC overview onto the HPV LabNet SharePoint. All HPV LabNet members should read and give feedback/comments to Dr Unger.

Surveillance activities

- 35) HPV LabNet members will write a review paper on surveillance as this could be influential. This will be coordinated by Dr Dillner.
- 36) Led by Dr Dillner, Drs Unger, Sahli, Bharti, Jerbi agreed to participate in a pilot HPV LabNet study on data reporting for HPV testing. Dr Dillner to contact Dr Garland to determine her laboratory's interest in participating.

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MEETING AGENDA

Monday, 17 Nov 2008 - Day 1 (Chair: Dr Joakim Dillner)

- 9:00 Opening Remarks I Knezevic
Introductions Participants
Selection of Chairpersons & Rapporteur
Objectives and expected outcomes of the meeting TQ Zhou
- Session 1: Update on the global HPV vaccine introduction strategies/progress**
- 9:30 Global strategies/recommendations on HPV vaccines K Irwin
- Report from SAGE and HVAC meeting in 2008
Discussion
HPV in the context of WHO Biological Standardization I Knezevic
Discussion
- Session 2: Update on development & implementation of International Standards & Reference Reagents for HPV testing**
- Update on development of ISs for HPV 16/18 and other high risk types DNA, HPV 16/18 antisera M Ferguson /
D Wilkinson
Discussion & Feedback on use of ISs
- 10:30 COFFEE BREAK**
- 11:00 Progress in sourcing qualified VLPs and preparation of M Ferguson
monoclonal antibodies for LabNet use in HPV serological
assays
Discussion
Recommendations on the next step
- Session 3: Progress and challenges in the development of WHO HPV LabNet**
- 12:00 Update of HPV LabNet work in 2008 and Perspectives for TQ Zhou
2009
Discussion
- 12:30 LUNCH**

14:00	Progress review in HPV LabNet laboratories (Lab presentation & Discussion: ~ 20 minutes each lab)	J Dillner (Global) E Unger (Global) AL Williamson (AFR) E Jerbi (EMR)
15:30	COFFEE BREAK	
16:00		D Haefliger (EUR) S Sukvirach (SEAR) A Bharti (SEAR) I Kukimoto(WPR) S Garland (WPR) M Picconi (AMR)
	Conclusions: challenges & gaps identified; Recommendations for the next year plan	J Dillner & E Unger to lead
18:00	Adjourn	

Tuesday, 18 Nov 2008 - Day 2 (Chair: Dr Elizabeth Unger)

Session 4: HPV LabNet activities- Laboratory Manual, Newsletter, etc

9:00	Development of HPV Laboratory Manual	
	<ul style="list-style-type: none"> • General issues about development of "HPV Laboratory Manual" - rationale, content, timeline • Acceptability of assays- Quality Control, Validation • WHO HPV LabNet Quality Assurance program- concept & critical issues; indication in Laboratory Manual 	J Dillner M Ferguson E Unger
	Discussion & Agreement on the next step	
	Development of the 3rd HPV LabNet Newsletter - main issues Discussion	S Garland

10:30 COFFEE BREAK

Session 5: HPV LabNet progress in HPV genotyping assays

- 11:00 Report from LabNet collaborative study on evaluating HPV genotyping assay R Sahli
- Discussion and feedback from laboratories; Agreement on publication of study report
- In-house validation study of PGMY- reverse hybridization assay (CHUV assay) R Sahli
- Discussion
- Discussion on PGMY- reverse hybridization assay Led by J Dillner
- 12:30 LUNCH**
- 14:00 **Session 6: Review of HPV LabNet Proficiency Study and Confirmatory Testing**
- Report of the 2nd HPV LabNet proficiency study to evaluate HPV DNA typing methods J Dillner
- Discussion: J Dillner/
- Feedback from individual laboratories; Follow-up actions; Agreement on publication of study report E Unger to lead
- Invited presentation:
- A genotyping assay for detecting multiple HPV infections-validation and application in field studies T Gheit
- Discussion
- Consensus on the protocol & criteria for inclusion of PGMY- reverse hybridization assay in the WHO HPV Laboratory Manual? J Dillner/ E Unger to lead
- How do the outcomes from the 2nd HPV DNA Proficiency Study contribute to the HPV Laboratory Manual?
- 15:30 **COFFEE BREAK**
- 16:00 Formalin-fixed paraffin-embedded (PFPE) samples for HPV testing E Unger
- Discussion
- Planning for the 3rd HPV LabNet DNA Proficiency Study in 2009: J Dillner & E Unger
- Timeline, panel composition; workplan, etc
- Discussion & Agreement

Review & discussion: Potential perspectives for commercial assays- use in HPV surveillance & monitoring	E Unger to lead
Discussion	
Confirmatory testing - critical issues	J Dillner/
Discussion on the next step	E Unger
Summary & conclusions of the session	J Dillner/
	E Unger to lead
WHINURS HPV study: A project to monitor HPV vaccination impact, Australia (Women HPV prevalence Indigenous, Non-indigenous, Urban, Rural, Study group)	S Garland(TBC)
17:30 Adjourn	

Wednesday, 19 Nov 2008 - Day 3 (Chair: Dr Elizabeth Unger)

Session 7 : HPV LabNet progress in HPV serology assays

9:00	Report from HPV LabNet collaborative studies on VLP-ELISA	J Dillner
	Discussion: Consensus on the protocol & criteria for the VLP-ELISA and inclusion in the WHO HPV Laboratory Manual	Led by J Dillner
	Plan the next:	
	Proposed LabNet workplan on HPV serology	J Dillner/Beth
	Discussion & Agreement on actions & timeline	

10:30 COFFEE BREAK

Session 8: Country experience in supporting HPV surveillance and vaccination impact monitoring - laboratory support

11:00	Pilot project to establish a monitoring system for HPV infection in Sweden	J Dillner
	Overview of HPV epidemiological studies conducted by CDC/US	E Unger
	A National HPV Laboratory Network in Argentina- experience & challenges	M.A Picconi

Invited presentation: National project to monitor HPV vaccination impact, Italy F Carozzi

A simple paper smear method for dry collection of cervical scrapes for HPV-DNA detection - potential use in low resource settings A Bharti

Discussion & comments

13:00 LUNCH

Session 9: Role of HPV LabNet in supporting HPV surveillance and vaccination impact monitoring

14:00 Invited presentation: Development of WHO Viral Vaccine Preventable Disease (VPD) Laboratory Networks D Featherstone (30min)
Discussion

Optional presentation from Regions: (10min/per) WHO Regional

Potential role of WHO/RO in facilitating HPV surveillance & vaccination impact monitoring- challenges & needs Offices

EMRO (confirmed)

WPRO (confirmed)

AMRO/PAHO (confirmed)

Discussion & Recommendations

Potential objectives & approaches to HPV surveillance & vaccination impact monitoring E Unger

Discussion & Recommendations

15:30 COFFEE BREAK

16:00 Potential role of HPV LabNet in supporting HPV surveillance & vaccination impact monitoring E Unger/
J Dillner to facilitate

- Proposed HPV LabNet workplan in monitoring (pilot study)

Discussion & Agreement on the next step

Proposed data reporting & collection mechanism trialed in LabNet J Dillner

Discussion & Agreement on the next step

17:30 **Wrap up**

Summary of Conclusions & Recommendations

Chair & Rapporteur

Closure of the meeting