INTERNATIONAL QUALITY ASSURANCE OF HUMAN PAPILLOMAVIRUS TESTING

Lena Dillner, Joakim Dillner
WHO HPV LabNet Global Reference Laboratory, Malmö, Sweden

Address for correspondence: L. Dillner, Clinical microbiology, University Hospital MAS, 205 02, Malmö, Sweden. E-mail: lena.dillner@med.lu.se

Summary
To contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact, WHO has initiated a global HPV LabNet. The LabNet tasks are to facilitate implementation of standardized, state-of-the-art HPV laboratory methods by introducing international standards, proficiency testing reagents/methods, standard operating procedures and quality assurance (QA) programs in order to make results comparable across laboratories worldwide. The LabNet is also intended to form the basis for development of a global network for HPV surveillance by using standardized and harmonized laboratory methodologies in order to provide sound data to policy-makers.
The LabNet is composed of 2 global reference laboratories (GRL) and 1–2 regional reference laboratories (RRL) in each WHO region. The GRL provide coordination of the network, lead development of QA programs and perform confirmatory testing of samples from regions. The GRL also oversee the HPV prevalences and vaccination impact worldwide through collaboration with RRL.
Eventually, a formalized global HPV laboratory network will provide HPV surveillance and vaccination impact evaluation in an internationally harmonized way. Effective HPV surveillance programs will be an essential component of appropriately implemented HPV vaccination programs. Such surveillance should be based on internationally standardised and quality assured laboratory methods in order to make results comparable across laboratories in the world.

Key words: quality assurance, HPV, proficiency panels, vaccination, HPV LabNet

INTRODUCTION

A Quality Assurance (QA) system is a continuous process that aims at measuring, evaluating and continuously re-evaluating the quality of the diagnostics procedures. Continuously improving the quality and when required changing the procedures is part of the process. In order to do so, the quality assurance work must have an aim (plan of activity and schedule for work) that covers all activities of the laboratory. All the employees at the laboratory must be involved in the QA system and results must be followed up, reported and analysed. Corrective measures must be carried out based on the analyse. The aim is to never make the same mistake twice!

The QA system must guarantee that the sample handling and analyse have the quality that corresponds to the intended use. Coverage of all activities of the laboratory means that the QA system should cover e.g. purchasing of material, selecting contractors, licensing the staff to perform different assignments, sample collection, transporting, analysis and storage of samples, handling of data and reporting of data. It is important to be able to define the quality of the individual sample/piece of information and to ensure that all activities (including mistakes) of every sample/piece of information can be tracked down and documented. Traceability is very important and essential for QA.

A laboratory with a high QA system implemented can apply for accreditation. Accreditation is issued by a recognized accreditation body. Part of the accreditation requirement is annual participation in proficiency panel testing.

Proficiency panel results is one type of Quality Indicator (QI). A QI should always be relevant for the intended use. It is very important to measure quality in the same manner, otherwise results from different laboratories or results within a laboratory over time can not be compared. Measured quality indicators typically will improve, whereas unmeasured ones will not change.

HPV testing may be used in assisting in vaccine development, vaccination implementation and surveillance of HPV as part of vaccine program evaluation/monitoring. The uses may differ between different countries and may also change with time.

With the rapid development of new and improved tests on the market it will most likely be difficult to have consensus on and recommend use of the same HPV tests in all laboratories worldwide. Different laboratories may also have different contracts with the many companies providing different assays and it could very complicated and costly to try to use the exact same assay in all laboratories.

Internationally agreed Quality indicators for HPV testing will therefore be the key to arrive at internationally comparable results from different laboratories. Results can be compared only if they relate to the same quality indicator (e.g. are traceable to a biological standard or proficiency panel results).

The HPV LabNet will promote that Standard operating procedures (SOPs) can be shared between different laboratories in order to help the laboratories in the quality work. SOPs should contain the internationally standardised procedures used to measure quality indicators. The exact procedures used in the SOP can of course differ, as long as the methods used arrive at traceable results of high quality, documented using agreed QI.

MAJOR VACCINE-RELATED USES OF HPV ASSAYS

For ongoing and future clinical trials (e.g. phase IV/V trials and trials of second generation vaccines) it is essential to define susceptible (naive) populations, which requires both serology & HPV DNA testing and typing. The endpoints of the trials should be internationally standardised, requiring quality assured HPV DNA testing and typing. Finally, there should exist internationally comparable methods for evaluating immunogenicity, which requires quality assured HPV serology reporting antibody levels in international units.

In monitoring of implemented vaccination programs, it is essential to follow how the HPV immunity persists over time as one essential data item to consider when evaluating if a booster vaccination may be required. This requires quality assured HPV serology reporting antibody levels in international units.

Another potential use of HPV serology is in assessing population vaccine coverage/population immunity in population-based serosurveys.

The prime method for assessing the efficiency of the HPV eradication strategy chosen (including checking for “escape mutants” and ”type replacement”) will most likely be HPV DNA testing sexually active teenage groups and/or younger women starting their participation in cervical screening programs. This requires quality assured HPV DNA testing and typing (traceable to international HPV DNA standards) with the ecological studies investigating “type replacement“ requiring that the HPV tests have a broad capacity for detection of a variety of HPV types.

Finally, both quality assured HPV serology and HPV DNA testing and typing are required for understanding the HPV epidemiology for design of vaccination trials and designing which vaccination programs are likely to be most effective for a given population (1).

QUALITY INDICATORS OF HPV TESTING

Quality indicators for HPV DNA testing and typing should **not** change over time. The same quality indicators should work also for new methods, decades later. The purpose of the quality indicators is that the result should have a quality corresponding to the intended use.

An HPV DNA test could be said to have a quality corresponding to the intended use if it can correctly classify HPV types of interest for HPV vaccination, when present at levels that would be relevant to detect for an HPV vaccination monitoring program. It should be mentioned that proficiency panels test only one step in the analysis chain. Other essential steps are e.g. epidemiological design of surveillance sampling, sample handling-(transportation, pre-treatment, safety measures against mix-up) and data handling.

The first WHO HPV DNA proficiency panel study has recently been completed. The panel included fourteen oncogenic HPV types and 2 benign HPV types (most likely everything that will be of interest for HPV vaccination for the foreseeable future). The panel was designed to have high capacity to detect wrong typing (cross-hybridisation et c) and therefore related HPV types were

systematically separated into different pools. The panel was also intended to work for all HPV DNA detection systems known today (and as far as possible also for conceivable improvements).

The recommendation for a laboratory performing HPV testing is that sensitivity and specificity should be evaluated at least annually using a blinded proficiency panel issued by the WHO HPV LabNet. Results should at least conform to what is considered useful for the intended purpose (HPV surveillance). Mis-typing and false positives should not occur and there should be sensitivity at an acceptable level [50 genome equivalents (GE)]. GE will be replaced with the corresponding amount of international units of HPV DNA, which is expected to be defined during 2008 (2).

THE WHO HPV LabNet

Sharing of experiences is very useful in the QA system. The HPV LabNet aims to define and agree on quality indicators for HPV testing and how they should be measured and share experiences and documents (Standard Operating Procedures) in the quality work. The mission of the WHO Global HPV LabNet is to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact, through enhanced, state-of-the-art laboratory support as well as to support the introduction of HPV vaccines and surveillance of disease and infection. Although the activities of the HPV LabNet may be of use for HPV-based screening programs, the mission of the LabNet does not include improved screening but is focussed on the need of HPV testing for the furthering of HPV vaccination (2).

Progress so far is that a proficiency panel for HPV DNA testing and typing has been prepared and a first proficiency study has been completed.

A reference standard for unitage of HPV-16 antibodies has been prepared and assigned a WHO unitage of 5 units. The reference standard can be ordered from the National Institute for Biological Standards & Controls in the UK.

Guidelines Standard and Quality Indicators, examples of SOPs etc “The WHO HPV laboratory Manual” is in progress. At the GRL Sweden, we have as part of our WHO assignment performed several pilot projects on how to design HPV vaccination surveillance systems. A pilot project on HPV typing of condylomas at sentinel STD clinics has been implemented. A national HPV Vaccination Registry has been implemented and we have received ethical permission for nationwide linkages with pathology/cytology biobanks to retrieve specimens for HPV typing and to determine if the HPV-type-specific burden of disease changes after vaccination. We also have permission to link with the population-based serum biobanking system to allow for a random sample to assess if titers wane (population coverage of immunity) and to find serum samples taken before breakthrough cases, to assist in determining a serological correlate of protection.

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