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Monitoring of human papillomavirus vaccination

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Summary

Persistent infection with oncogenic human papillomavirus (HPV) is a necessary causal factor in the development of cervical cancer. Moreover, HPV, predominately type 16 and to a lesser degree type 18, is linked causally to varying proportions of other anogenital cancers (vulva, vagina, penis, anus) as well as cancers elsewhere in the body (oropharynx, larynx, conjunctiva). HPV types 6 and 11 cause most of genital warts and recurrent respiratory papillomatosis. Effective prophylactic vaccines have been developed. In this review, we address briefly the immunological aspects of HPV infection and the results of HPV vaccination trials. Internationally standardized monitoring and evaluation of prophylactic HPV vaccination programmes will be essential for arriving at the most cost-effective strategies for cancer control.

Keywords: cancer prevention, effectiveness, genotyping, surveillance

Immunity against human papillomaviruses (HPV)

Humoral immunity

HPV infection is restricted to epithelial cells; therefore, presentation of viral antigens to the host immune system is limited. Natural HPV infection of the genital tract gives rise to a slow and modest but measurable serum antibody response in most, but not all, infected individuals [1,2]. The intensity of the antibody response depends upon viral load and persistence [3]. The presence of HPV antibodies is long-lasting but does not contribute to the clearance of established infections [4]. HPV serology is an important tool in epidemiological studies to assess past exposure [5–8].

The capsid of papillomaviruses is composed of two viral proteins: the major capsid protein, or L1, and the minor capsid protein, or L2 [9]. Virus-neutralising anti-L1 antibodies are essentially type-specific [2,10,11]. The L2 protein is situated more internally in the capsid, but a small segment is exposed at the surface and can also be recognized by virus-neutralizing antibodies [12–14]. These anti-L2-antibodies are less potent than anti-L1 antibodies [12,14,15], but they show cross-reactivity to heterologous HPV types [16–18].

The discovery that the L1 capsid protein could be expressed in eukaryotic cells and could self-assemble into so-called virus-like particles (VLPs) was a critical step in the development of HPV vaccines [19]. Correct conformation of the capsid proteins is necessary to elicit protective antibodies [20]. Denaturation or improper folding of the L1 protein alters the presentation of epitopes, resulting in induction of antibodies that are not protective. HPV L1 VLPs contain the same conformationally dependent neutralizing epitopes that are present on infectious viruses.

Cellular immunity. Clearance of a naturally acquired HPV infection is triggered by a specific cell-mediated immune (CMI) response (reviewed in [21]). Dendritic cells, also known as Langerhans cells, present in the cervical epithelium play an important role in recognizing HPV-infected cells. These cells stimulate T helper type 1 (Th1) helper cells that in turn elicit the production of cytotoxic T lymphocytes (CTL) [22]. These cytotoxic effector cells attack infected cells, resulting in resolution of the infection [23]. However, little is known about how to modulate these immune responses.

HPV vaccination

Prophylactic vaccination. Vaccination with VLPs gives rise to virus-neutralizing antibodies in serum. Vaccination by intramuscular injection of L1 VLPs has been shown to be highly immunogenic and well tolerated in Phase I trials [24–27]. Three randomized placebo-controlled Phase II trials with, respectively, a monovalent HPV16 vaccine, a bivalent HV16/18 vaccine and a quadrivalent HPV6/11/16/18 vaccine

candidate have consistently demonstrated almost complete protection against persistent infection with the targeted HPV types [28–32]. Moreover, these trials confirmed the safety of the vaccines and showed strong immunoresponses that were several orders of magnitude higher than those observed after natural infections.

Two pharmaceutical companies [Merck Sharp & Dohme (MSD) and GlaxoSmithKline (GSK)] have completed large multi-centre Phase III vaccine trials in all continents except Africa [33–35]. In addition, the National Cancer Institute (United States) is conducting a population-based trial in Costa Rica using the bivalent vaccine [36]. These Phase III trials demonstrated that vaccines protect against histologically confirmed high-grade cervical intraepithelial neoplasia (CIN) and adenocarcinoma *in situ* (AIS) associated with the targeted HPV types under the condition that subjects were not infected with one or more vaccine types at baseline [33–35].

Both vaccine formulations have a good safety profile. Neither has noted any therapeutic effect, as women who test positive for HPV DNA prior to vaccination show no protection against disease end-points associated with that type. Modest cross-protection to closely related high-risk types HPV 31, 33, 45 was found with bivalent vaccine [Cervarix(R)] [37] and also to some extent with the quadrivalent vaccine [Gardasil(R)] [38,39].

Therapeutic HPV vaccines. Development of cervical precursors, their maintenance and progression to invasive cancer requires the continued intracellular expression of the viral oncoproteins E6 and E7 [40,41]. Therefore, therapeutic vaccines have been directed towards stimulating T cell responses against these viral early oncogenes. The approaches include administration of peptide antigens or recombinant proteins, plasmid DNA vaccines, viral vector vaccines and administration of E7-pulsed dendritic cells, but despite being variably immunogenic have not shown an impact upon invasive cancer but appear to induce some degree of clearance of cancer precursors or anogenital warts [23,42–44].

The addition of early antigens (E6 or E7 in particular) to the L1 VLP vaccines is also being investigated to determine if a cell-mediated immune response could be elicited along with the antibody response to the L1 VLP component [16]. If so, this would open the way to development of chimeric vaccines with a therapeutic component included for combined use in treatment and prophylaxis [45,46].

Licensure of VLP vaccines

As of September 2008 Gardasil has been licensed for sale in 105 countries and Cervarix in 71 countries. In November 2008 the WHO Strategic Advisory Group of Experts on vaccines recommended HPV vaccination (http://www.who.int/wer/2009/wer8415/en/index.html). National immunization programmes have been established in 15 high income countries and one middle-income country, Mexico [47,48] (http://www.ecca.info). National recommendations vary, but all focus upon vaccination of girls before infection, the specific age range dependent upon the population. Some countries also include interim recommendations for vaccination of older women as well (see below).

Current HPV vaccination issues

Vaccination against non-oncogenic HPV. HPV types 6 and 11 jointly cause approximately 90% of genital warts [49]. These types also cause some of the low-grade dysplastic cervical lesions. Moreover, in rare circumstances HPV types 6 and 11 can cause serious disease. HPV6 and in particular HPV11 are the major causes of recurrent respiratory papillomatosis, a rare disease with significant morbidity due to repeated surgeries that is occasionally fatal. So-called giant condylomas or Buschke–Löwenstein tumours of the vulva, penis and anus are also associated with these HPV types [50]. These tumours rarely metastasize, but may sometimes be fatal. The quadrivalent vaccine manufactured by Merck contains L1 VLPs of both HPV6 and HPV11. High clinical and statistically significant protection was confirmed in Phase III trials regarding protection against genital warts [34].

Intermediate end-points. Prevention of cervical cancer is the most important expected clinical benefit of HPV vaccination. Trials have used surrogate end-points because cancer develops slowly and cancer as an end-point requires unrealistically large and lengthy studies. In addition, current cervical cancer screening and clinical management requires that premalignant lesions are treated so, ethically, invasive cervical cancer could not be used as an end-point in a clinical trials [51]. Protection against infection seems to be an obvious end-point for an infectious disease. However, HPV infection is extremely common, with a majority of the entire female population having experienced HPV infection at some point in their lives, but with most infections resolving spontaneously. Because HPV-induced cancer occurs in only a small proportion of exposed individuals, estimates of vaccine efficacy against infection cannot be extrapolated to be valid against cancer unless the protection against infection is virtually complete. In addition, detection of HPV is dependent upon sampling and testing methods and use of infection as an end-point in vaccination trials would have required an internationally standardized quality assurance of the HPV testing methodology, which was not available at the time these trials were designed.

A World Health Organization (WHO) expert group consensus report proposed histologically confirmed high-grade CIN and adenocarcinoma *in situ* (AIS) or worse (i.e. including cervical cancer) associated with one of the target vaccine types as an acceptable surrogate end-point for Phase III vaccination trials [51]. Type-specific persistence of infection, defined as presence of the same HPV type at two or more

consecutive visits separated by 6–12 months, is another interesting outcome measure that is a later and thus more informative end-point than protection against any infection [52].

Duration and consistency of the antibody response to VLPs. Type-specific L1 VLP-antibodies reach maximum titres at month 7, i.e. 1 month after administration of the third dose. Titres decline until month 24 and remain rather stable thereafter [30,53]. At 3 years, antibody titres remain two- to 20-fold higher than in placebo controls [53]. Complete protection against HPV16 associated CIN lesions was observed over the whole follow-up duration of two Phase IIb trials: 6 years for the monovalent HPV16 vaccine, 5·5 years for the bivalent HPV16/18 vaccine [54,55] and 4 years for the quadrivalent vaccine (abstract presented at the 25th International Papillomavirus Conference, available at http://www.hpv2009.org). Follow-up is continuing, and continued protection against HPV 16/18-associated disease end-points has been shown for the entire available observation time, even when specific antibody titres fall [55].

Optimal target age range for vaccination. The incidence of HPV infection is very high among sexually active women [56–58]. Therefore, vaccination before initiation of sexual contacts is the safest strategy for complete protection. However, vaccination programmes targeting 12-year-olds will, compared to programmes targeting 15-year-olds, delay the cancer prevention gains by 3 years [59]. The highest HPV incidences are between 16 and 20 years of age, with a peak incidence at 18 years [59]. 'Catch-up' vaccination programmes that target the age groups that are spreading the infection most actively will be required for effective infection control. Large cancer-preventive gains are expected from catch-up vaccination up to 18 years of age and diminishing, but still noteworthy, gains are seen up to 24 years of age [59,60].

In the vaccination trials, women who were vaccine-type HPV DNA- or seropositive at enrolment or who became HPV DNA-positive during the vaccination period were not part of the per-protocol population. Preliminary analysis of the large Phase III trial with the quadrivalent vaccine observed that protection against HPV16/18-associated $CIN2^+$ was absent among women who were baseline HPV DNA-positive and seropositive for HPV16 or 18 and was reduced strongly [efficacy of 31·2; 95% confidence interval (CI): <0–54·9%] for women who were HPV DNA-positive but seronegative at the time of vaccination. While these data suggest a potential utility of testing for the HPV DNA and antibody status before vaccinating older women who have already initiated sexual contacts [61], current guidelines do not recommend screening with HPV testing because very few women have been exposed to all types in the vaccine, and protection against other vaccine types is not affected by the presence of infection with one vaccine type. Moreover, there is no evidence of clinical utility for HPV genotyping at young ages (<25 years), as nearly all HPV infections will clear spontaneously and unnecessary HPV testing could generate over-diagnosis and treatment [62,63].

Immunization of males. Immunization of boys with VLPs elicits a serum immune response similar to that in girls. Because genital HPV infection is sexually transmitted, immunization of men may help to prevent infection of women. Modelling studies on herd immunity, i.e. indirect protection of those who remain susceptible, owing to a reduced prevalence of infections in the risk group for disease, have been published [64–66]. The utility of immunization of males depends upon the assumed population coverage of vaccination, with successively smaller additional benefits seen in scenarios with high population coverage [67]. Modelling of programmes with high population coverage (90%) have found that addition of male vaccination gives a more rapid infection control and have suggested that both sex vaccination programmes may be required to achieve an ultimate eradication of the infection [60].

Vaccination programme strategies as a randomized health-care policy. Design of HPV vaccination programmes has been based upon estimations of the impact of HPV vaccination on the burden of cervical cancer incidence and mortality using mathematical modelling of projected effects from the observed surrogate endpoint effects [59,67,68]. Whereas clinical end-points are essential for estimates of effects on health economy, the control of HPV infections is a more immediately relevant end-point in models that compare different programme designs [60]. For programme design issues that are ambiguous, notably which age groups should be targeted and whether vaccination of males is required, randomization of vaccination programmes is an interesting option. That the incidence of cervical and other HPV-associated cancers does eventually decrease in vaccinated populations should then be verified by monitoring HPV incidences in sexually active youth groups and incidences of HPV-associated diseases by registry-based follow-up [69–72].

HPV types. Antibody responses elicited by VLP immunization are, in general, specific for the individual HPV type. However, lower titre cross-reactivity is noted for closely related HPV types [31,33,45,52] as well as partial protection against disease end-points associated with these non-vaccine types [35,73]. There are 13–16 different HPV types that have been proposed as oncogenic [50,74]. It is technically feasible to add additional VLPs to second-generation HPV vaccines, but there is probably a limit for how large amounts of antigen that can be included in combined vaccines without risking deteriorating responses against the major oncogenic HPV type, HPV16.

Table 1. Cumulative proportion of cervical cancers in Europe that are attributed to a ranked combination of human papillomavirus (HPV) types and the number of cervical cancers occurring each year expected to be caused by these types.

HPV types prevented	Proportion of cervical cancers prevented	Number of annual cases prevented in Europe
16	65·4%	34 008
16 + 18	71·5%	37 180
16 + 18 + 33	77·1%	40 092
16 + 18 + 33 + 31	81·2%	42 224
16 + 18 + 33 + 31 + 45	84·1%	43 732
16 + 18 + 33 + 31 + 45 + 56	85·6%	44 512
16 + 18 + 33 + 31 + 45 + 56 + 35	86·8%	45 136
16 + 18 + 33 + 31 + 45 + 56 + 35 + 52	87·8%	45 656
All HPV	100%	52 000

In Europe, 52 000 cases of cervical cancer occur yearly (estimates for 2004). Sixty-five per cent, or 34 008 of cancer cases, are attributed to HPV16; 71·5% (or 6·1% more) can be attributed to HPV16 or HPV18. Almost 88% of cervical cancers are attributed to one of eight HPV types. Adapted from Munoz, 2004 and Arbyn, *Ann Oncol* 2007a,b [75–77].

Table 1 shows the cumulative proportion of the main HPV types present in cervical cancer, estimated for Europe from studies conducted by the International Agency for Research on Cancer (IARC) [75]. Approximately 52 000 new cases of cervical cancer occur yearly in Europe [76,77]. Thus, with vaccination with a 100% effective HPV16 vaccine, 34 000 incident cases of cervical cancer could be avoided. An HPV16/18 vaccine could potentially avoid 37 000 cases per year (71·5%) and an octavalent vaccine could potentially reduce the incidence with 88%. This simple calculation assumes absence of 'type replacement' or cross-protection, which, respectively, should decrease or increase vaccine efficacy.

Type replacement – what is meant and is it likely? There is a theoretical concern that eradication of some HPV types will cause post-vaccination emergence of disease caused by types not included in the vaccine, 'type replacement'.

Type replacement is a viral population dynamics phenomenon and is defined as elimination of some types causing an increase in incidence of other types. This effect can occur only if two conditions apply: (i) there exists partial competition among different types during natural infection and (ii) the vaccine does not afford cross-protection against types affected by this natural competition [78].

Several epidemiological studies have addressed the question of possible competition between different HPV types for infection. Presence of type-specific antibodies (a marker of past or present infection) for one HPV type is associated with a strongly increased risk for also being seropositive for other HPV types, even when adjusted for determinants of sexual behaviour. For example, one study found the odds ratio (OR) for being seropositive for HPV16/18/33 to be 2·9 (95% CI: 1·6–5·3) for women seropositive for HPV6/11 compared to those seronegative, even when the risk was adjusted for sexual behaviour and other sexually transmitted infections [79]. This is the opposite effect to that expected if there had been competition between the types.

Furthermore, studies of multiple HPV DNA types in the same samples have, in general, not found interactions between types, nor clear examples of types of HPV DNA that are not found together, as would have been expected if there had been competition [80]. If anything, past infection with HPV appears to increase the likelihood that a new infection will be acquired. For example, Mendez *et al.* [81] reported on a cohort study where baseline HPV6/11 DNA positivity was associated with a 14·1-fold (95% CI 2·1–95·4) increased risk for incident infection with HPV18 at subsequent visits, where baseline HPV16/18 DNA was associated with a 5·7-fold (95% CI: 2·2–15·1) risk for HPV58 acquisition and no statistically significant decreased HPV incidences.

Viral dynamics could also be affected if the duration of infectivity is affected, i.e. if prior infection with one HPV type would affect the time it takes to clear infection with another HPV type. In a population-based cohort study of >6000 women, baseline HPV seropositivity did not affect the clearance rate of other HPV types [82].

Thus, it seems that the first prerequisite for type replacement – natural competition – does not apply and that type replacement is therefore unlikely. However, it should be pointed out that most of the studies that have investigated viral type competition effects on incidence and/or clearance have had limited statistical power to detect small effects, particularly for rare HPV types.

Viral escape mutants. Apart from the risk of changes in population dynamics of already existing types, it is possible that viral mutations could occur to generate new variants that are equally oncogenic but not recognized by vaccine-induced antibodies. However, the fact that HPV replicates using the cellular DNA polymerases and thus has a very slow mutation rate suggests that this risk is low. This is also indicated by the fact that viral variants of HPV16 from all over the world are neutralized by the same HPV monoclonal antibodies [83].

Attributable proportion/number of healthy women at risk. Because vaccination with HPV16/18 will prevent many women from dying of cervical cancer, there will be more women who will be at risk for cervical cancer caused by other HPV types. The proportion of cases prevented if an HPV type is eliminated is therefore not exactly the same as the proportion of positive cases, but is given by S*(1-1/RR), where S is the proportion of positive cases and RR is the relative risk. When HPV-related relative risks for cancer are increased about 100-fold, this effect is so small that it is usually ignored. However, for specific rare 'oncogenic' HPV types, the relative risks are not so high when compared to a

reference category of all women without that specific HPV type. However, regarding the impact on HPV16/18 vaccination on cervical intraepithelial lesions, in particular low-grade lesions, RR is substantially lower, as they are caused proportionally more by other types. Therefore, HPV vaccination will have a smaller impact on low-grade abnormalities than the prevalence of HPV16/18 in these lesions [84,85]. Consideration of attributable proportions is therefore of particular relevance when discussing benefits and caveats of including additional HPV types in second-generation HPV vaccines.

Monitoring of HPV vaccination programmes. HPV differs from most other vaccine-preventable diseases in that the major diseases to be prevented occur many decades after infection. Whereas clinical trials have documented prevention of infection and intermediate disease end-points (condylomas and precancers), surveillance following vaccine implementation will be required to document the expected gains in cancer prevention if there is appropriate population coverage. Surveillance will also provide data to indicate if type replacement or escape mutants occur. Other important tasks for the HPV surveillance include monitoring of the duration of protection, long-term safety and actual effects on health-care cost consumption. Monitoring the impact of vaccination on type-specific infection could be important as it is the earliest change that could be anticipated, and failure to detect protection from infection will indicate failure to impact cancer in the decades that follow and allow appropriate changes in strategy to be introduced. As countries differ in their health-care priorities and infrastructure as well as in their incidence and prevalence of various HPV infections, their HPV vaccination strategies are also likely to differ.

What should be monitored?

Levels of protective antibodies in the population. As has been mentioned, the waning in the levels of HPV antibodies post-vaccination appears to plateau after 5 years. It is not known whether waning of HPV antibody levels in the longer term will require a vaccine booster. In addition, antibody correlates of protection have not been defined because there have so far been almost no cases of vaccination failure. If a reliable immunological correlate of protection can be identified, this will help in assessing the requirement for booster vaccinations and greatly facilitate the evaluation of second-generation vaccines.

Population coverage of HPV vaccination. Many countries are likely to implement HPV vaccination registries to determine coverage [86]. Rough estimations of vaccine can be made from health insurance statistics and sales figures [87]. Seroepidemiological surveys could be used to establish the population coverage of vaccination, as well as to monitor the time–course of persistence of titres in the population.

HPV DNA prevalences in sexually active teenage populations. As the type-specific prevalence of HPV infection is very high in young sexually active populations, the effect of a successful HPV vaccination programme should be detected quite rapidly by sentinel surveillance in these populations. The specific design of these sentinel studies will vary, but selecting clinics offering sexual counselling may be more efficient than school-based sampling. Reduction in the prevalence of types targeted by the vaccines as well as no increase in the prevalence of non-vaccine types are important end-points. Baseline data are needed to establish pre-vaccine prevalence as well as to determine the sample size required to observe impact beyond confidence intervals of sampling and testing errors. It is imperative that all HPV DNA prevalence surveys are performed using testing methodology that has been subjected to an international quality assurance, as comparability of data between countries or even before *versus* after will otherwise not be possible.

Condyloma incidence. England and Wales implemented registration of condylomas in the 1970s, but condyloma surveillance has not been conducted in other countries. Consequently, the epidemiology and public health burden of condylomas is not well known. However, symptomatic condylomas appear to be quite common and the age-specific incidence curve of first-attack condyloma appears to be similar to Chlamydia incidence. As the incubation time from exposure to clinical condyloma is between 3 and 12 months, and because some 90% of condylomas are caused by HPV types included in the quadrivalent HPV vaccine, reduction in the occurrence of condylomas in sexually active young populations is the first clinical end-point that can be detected following implementation of the quadrivalent HPV vaccine. In Australia, where rapidly a high coverage with quadrivalent vaccine was built up, a significant decrease in incidence of genital warts was observed among young women ($\leq$26 years) and heterosexual men, but not among older women and homosexual men [88]. If a reduction in condylomas is not seen, then this will serve as an early warning that the control of HPV infection is not adequate and prompt investigation of possible reasons for the failure, such as inadequate population coverage, type-replacement or vaccine breakthrough.

Cervical screening results. For Europe, the proportion of low-grade cervical dysplasia attributable to HPV vaccine types has been estimated to 26% and the proportion of high-grade cervical dysplasia to be greater than 50% [89]. With incubation times from 1 to 4 years, effective control of HPV should result in a significant decline in the burden of screen-detected precursor lesions requiring follow-up and treatment on medium-term follow-up.

To use screen-detected lesions as an end-point for vaccine surveillance requires that screening practices and methods are not impacted by vaccination. In addition, determining the types that are associated with these lesions will be required, and that in turn will rely upon HPV typing of these lesions. Clinical HPV assays differ from HPV assays used in epidemiological studies as well as in vaccine clinical trials in that they have a lower sensitivity and do not commonly provide type-specific results. Therefore, clinical results may not be optimally informative for surveillance. We suggest that strategies using residual clinical samples could be developed, whereby a random sample of positive and negative samples could be retested with quality-assured HPV typing assays.

HPV-associated malignancies. A recent IARC review concluded that essentially all cervical cancer is HPV-associated; the proportion of cancers in other anatomic sites that are HPV-associated varies: penis 40%, anus 90%, vulva/vagina 40% and oropharynx 12% [90]. While HPV16/18 are responsible for only about 70% of cervical cancers, the type diversity in the non-cervical HPV-associated cancers is less. HPV16 and 18 are responsible for about 90% of the HPV-positive anal, vulvar/vaginal and oropharyngeal cancers [90], although the estimates are less reliable for cancers other than cervix because the number of high quality HPV typing observations is much lower. It seems likely that routine HPV typing of all cases of HPV-associated cancer forms will become an essential part of the long-term evaluation/monitoring of HPV vaccination programmes in most countries.

Combination of HPV vaccination and screening programmes

Current HPV vaccines include only the major oncogenic types, responsible for only 70% of cervical cancers. Moreover, as the vaccines are aimed at protecting HPV-naive individuals, and the effect on already exposed women is questionable, screening will continue to be necessary [91].

Nevertheless, the reduced background risk may, after just a few decades, allow an increase of the screening intervals. It has been estimated that conventional cytological screening every 5 years starting at 30 years of age results in a 67% reduction in lifetime cervical cancer risk. Adding HPV16/18 vaccination to this programme would result in a risk reduction of 89% [92]. Obviously, several aspects of monitoring and evaluation are the same or strongly interrelated for screening and vaccination, arguing that these complementary strategies need to be co-ordinated in a comprehensive cervical cancer prevention programme [91,93,94].

Internationally comparable methods for monitoring of HPV vaccination programmes. The global HPV LabNet has been launched by the WHO as an initiative towards global quality assurance and standardization of HPV testing methods used in follow-up of HPV vaccination programmes (http://www.who.int/biologicals/vaccines/hpv/en/index.html). International collaborative studies have been performed for both HPV serology [95] and HPV DNA testing and typing [96]. The results indicate that methods are comparatively robust, provided that measurements are related to the same international standard serum that is assayed in parallel [95].

For both HPV antibodies and HPV DNA tests, WHO reference reagent of anti-HPV 16 antibody and the first WHO international standards for HPV types 16 and 18 DNA are available from the WHO International Laboratory for Biological Standards in the UK (http://www.nibsc.ac.uk/products.aspx); other biological reference standards that will facilitate interlaboratory comparison and harmonize laboratory testing via defining an international unit of measurement are being pursued. For quality assurance, and as a basis for certification, global proficiency panels will be made available. An 'HPV laboratory manual' that will provide quality assurance/quality control guidance, basic validated assay protocols and examples of state-of-the-art methods is being developed at WHO.

Conclusions and recommendations

L1 VLP HPV vaccines have been found to be safe, well tolerated and to offer HPV-naive women a very high level of protection against HPV persistent infection and cervical intra-epithelial lesions associated with the types included in the vaccine.

The reduction in background risk of cervical cancer by elimination of the most important HPV types will affect cost-effectiveness of screening programmes and may, in the long term, allow increasing screening intervals. Co-ordinated quality assurance/monitoring of HPV vaccination and cervical screening is advisable for finding the most efficient strategies for cervical cancer control.

Data on vaccination coverage will be essential for every country performing HPV vaccinations. HPV vaccination registries are preferable, but sales statistics and serosurveys may be alternatives.

For rapid assessment of vaccine programme efficacy, the continuous monitoring of which HPV types are spreading in the population will become necessary for early monitoring of 'type replacement' phenomena, inappropriate vaccination strategies or other reasons for vaccination failure. Surveys in sexually active teenagers and/or in younger participants of cervical screening programmes should be contemplated.

As HPV-associated cancers and condylomas are now vaccine-preventable diseases from now onwards they should be subject to similar surveillance strategies as other vaccine-preventable diseases. The recent WHO recommendation on HPV vaccination (http://www.who.int/wer/2009/wer8415.pdf and http://www.who.int/immunization/documents/positionpapers/en/index.html#hpv) includes information

that will help countries make decisions about how HPV vaccination fits into their strategy for cervical cancer control.

Disclosure

The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization or the funding agencies. The findings and conclusions in this report are those of the authors.

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