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Review

HPV Technologies Advancing Public Health: Discussion of Recent Evidence

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A B S T R A C T

Effective primary and secondary cancer prevention programmes are key to improve public health. Cervical cancer is preventable if high quality screening programmes, diagnosis and treatment are offered to female populations at high coverage. Nevertheless, it continues to be a public health problem, and screening programmes need improvements. Human papillomavirus (HPV) has been firmely established as the necessary cause of virtually all cervical cancer cases. To date we count two clinically validated and approved HPV technologies, available to prevent cervical cancer, and other diseases caused by these carcinogenic viruses: Prophylactic vaccines for primary prevention, and HPV DNA tests for secondary prevention, to detect life threatening infections by carcinogenic HPV types, allowing timely diagnosis and clinical management of precancerous lesions. The new technologies will help improve the health of the public if made widely accessible. Similar to vaccination programmes, systematic and well organized cervical screening programmes, with high quality validated HPV tests, can save more lives than ever and improve women's health, in an effective manner.

***Key words**: Human papilomavirus, screening, vaccine, cervical cancer*

Introduction

Public health is the approach to medicine that is concerned with the health of the community as a whole: public health is community health. In this context, the mission of public health professionals is assuring conditions in which people can be healthy. This can be achieved through three key public health functions: 1) systematic assessment and accurate monitoring of the health of communities and populations at risk, to identify health problems and their causes; 2) assuring access to appropriate and effective interventions, including health care and disease prevention services, and evaluation of the cost-effectiveness of such services; and 3) formulation of public policies designed to solve identified global health problems in a sustainable manner. These functions can include the provision of personal health care (services at the clinic level, district or referral hospital) or be population-based such as immunization or screening programmes, and may also include legislation (guidelines, mandatory interventions) and economic incentives such as subsidies. Public health professionals are concerned with planning and implementation of activities that fulfil one of the three functions, leading to measurable outcomes and improvements in the health of the public, within reasonable time frame. Primary and secondary prevention programmes have a synergistic effect in improving health.

Cervical cancer is the second most common cancer in women worldwide with about half million new cases every year[1]. Cervical cancer is preventable and readily treatable, still it kills one of two women diagnosed with cancer, and over 250 thousand women die annually. Worldwide, survival rates vary between regions with good prognosis in some regions, e.g. 73% in the United States[2], and 63% showed in European registries[3], where high quality screening programmes have been implemented in large scale.

The Human papillomavirus in the Root of New Technologies for Cancer Prevention

The notion that papillomavirus infection underlies the development of cancer of the cervix in women was

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first described in 1976 by zur Hausen[4]. Since then, on the basis of a variety of scientific assessements, Human papillomaviruses (HPVs) have been firmely established as the major cause of virtually all cancers of the uterine cervix[5]. This breakthrough in knowedge of cancer etiology led to the development of innovative technologies, that can be used as tools to improve health care and strategies to accelerate cervical cancer prevention. For instance, screening to identify precancerous disease states, that can be successfully removed without sequelae, can save lives. Cervical screening programmes have been recommended to targeting women after the age of 25 in some countries, although the target age and screening intervals can be adapted to needs and resources of different countries.

HPVs are small DNA viruses wraped by a shell or viral capsid, composed of two structural proteins expressed late upon viral replication, known as L1 and L2. HPVs infect the stratified squamous epithelia of skin and mucous membranes, where they may cause benign lesions, some of which have the potential to progress to invasive cancer. Most infections are self-limited and asymptomatic, presumably because the host eventually mounts a successful immune response. There are co-factors that increase the risk for cancer development in infected subjects.

While there are over 100 different types of HPVs molecularly characterized[6] about 15 types have been evaluated as highly carcinogenic to humans, and two types among those have consistently been reported as most common in cervical cancer cases, HPV types 16 and 18[7]. The genome of these two common types have been isolated by molecular cloning in 1983[8] and their cloned DNAs served as basis for producing vaccines by biotechnolgy methodology, as well for molecular diagnostic tests as described bellow.

To date we count two prominent clinically validated and approved technologies available to prevent cervical cancer, and some other cancers caused by these carcinogenic viruses: 1) prophylactic vaccines against HPV the two most common carcinogenic types, and 2) molecular HPV DNA tests to detect life threatening infections by carcinogenic HPV types, and to allow timely diagnosis and clinical management of precancers. On one hand, prophylactic HPV vaccines can prevent the infections, and therefore the associated diseases that the infectious viruses can cause. Because they cannot influence the course of already established infections, vaccines may be most beneficial if administered before any infection occurs. On the other hand, HPV DNA tests can identify already existing infections and prompt to early clinical management and treatment, as appropriate, before the early HPV associated precancerous lesions can progresses to invasive cancer. These two available technologies are schematically illustrated in Figure 1, and will be discussed bellow. Understanding the successes and limitations of new technologies will help to make best use of them for improving the health of the public in general.

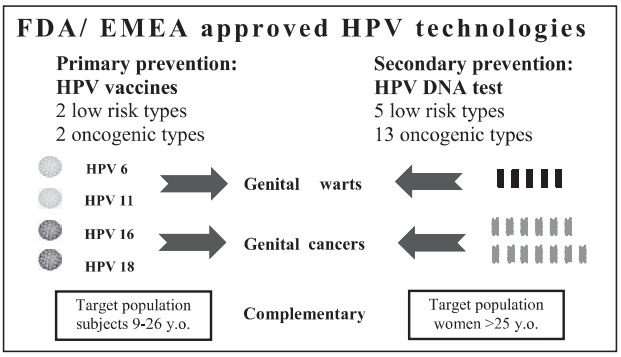

Fig. 1. FDA approved technologies for use in primary and secondary cancer prevention to date. Two health technologies have been so far approved by the US FDA and EMEA, as well as other regulatory authorities, for prevention of neoplasis. For Primary prevention, a prophylactic recombinant quadrivalent vaccine, based on proteinaceous Virus Like Particles against two low risk HPV types, 6 and 11, and two high risk HPV types 16 and 18, is available for administration to subjects 9–26 years of age. For secondary prevention a screening test available as two sets of reagents to detect 5 low risk HPV types, and 13 high risk types, for use in laboratory diagnosis of neoplasias at risk to progress to cancer, and recommended for routine use on women over 30 years. HPV – Human Papillomavirus, y.o. – years old, FDA – Food and Drug Administration, EMEA - European Agency for the Evaluation of Medicinal Products.

HPV Vaccine Technology for Primary Prevention

The vaccines under consideration here are recombinant protein vaccines comprising L1 proteins that self-assembly into particles similar to empty shells of the virus, and are therefore non-infectious and non-oncogenic[9].

The aim of vaccination against HPV is to induce immunity to neutralize HPV infections and later associated diseases and cancers. Clinical data originated in several studies in phase 1, phase 2 and phase 3 have been published[10,11.] Although the primary concern is reduction in cervical cancer cases and deaths, the impact of vaccination on surrogate markers and intermediate diseases can be assessed sooner, and may have implications for design and implementation of effective prevention programmes. This information will also be crucial for planning succesful health policy initiatives that involve both screening and vaccination.

Vaccines that have completed controlled efficacy studies have demonstrated high levels of efficacy against histologically characterized high grade dysplasias associated to the viral antigen types included in the vaccines, namely cervical intraepithelial neoplasias (CIN2-3) or worse, following administration of a three-dose regimen among women who had no evidence of previous infection with HPV[13].

The indications for the use of HPV vaccines in the EU are, so far, for prevention of HPV 16/18 related cervical

TABLE 1
SUMMARY OF STATISTICAL ANALYSES RESULTS FROM CLINICAL TRIALS TO MEASURE THE EFFICACY OF A QUADRIVALENT VACCINE IN PREVENTING CIN 2–3 ASSOCIATED TO HPV INFECTIONS IN THE TRIAL POPULATION OF FEMALES AGED 15–26 YEARS OLD

Source reference	Endpoint	Vaccine cases	Placebo cases	Efficacy
Package insert Gardasil™ (Merck & Co.)*	HPV 16/18 CIN2–3 or worse in Per Protocol efficacy analysis	0 (N=9,342)	53 (N=9,400)	100%
Package insert Gardasil™ (Merck & Co.)*	HPV 16/18 CIN2–3 or worse in the general trial population (MITT-3)	122 (N=9,831)	201 (N=9,896)	39%
Statistical review and evaluation Gardasil™ (Merck & Co.)**	any HPV type CIN2–3 or worse in the general trial population	287 (N=8,814)	328 (N=8,846)	12.2%

Clinical trials analysis to measure the efficacy of a quadrivalent vaccine in preventing CIN 2–3 associated to HPV infections in the trial population of females aged 15–26 years old. Three trial sub-populations considered for analysis are indicated here: the HPV type specific per-protocol-efficacy analysis, the type specific modified intention to treat analysis, and the modified intention to treat analysis as to efficacy against CIN2–3 associated to any HPV type. *Data available in the public domain, at package insert Gardasil label http://www.fda.gov/cber/label/hpvmer060806LB.pdf, and **Interim analysis data adapted from Dr. N. Miller, available at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006–4222S-2.ppt[16]. HPV – Human Papillomavirus, CIN – Cervical Intraepithelial Neoplasia, MITT – Modified Intention-To-Treat.

cancinomas, high grade cervical dysplasias CIN2 and CIN3, high grade vulvar dysplasias, VIN2 and VIN3, as well as prevention of HPV 6/11 related genital warts (condyloma acuminata), and in children and adolescents 9 through 15 years of age, and women 16 through 26 years of age[14].

One pivotal vaccine trial included over 20.000 females 13–26 years old (median age of 20) enrolled in different geographical regions. The population for the efficacy studies included large proportion of women in Europe (44.1%), mostly from Nordic countries, 25.3% women in North America, 27% in Latin America and only 3.6% in Asia (available under Food and Drug Administration [FDA] and European Agency for the Evaluation of Medicinal Products [EMEA] websites[15–17]). It was noted that of the females in the trial population aged 13–26 years overall 12% had an abnormal baseline Pap test with squamous intraepithelial lesions. The majority of these were low grade SIL and atypical squamous cells of undetermined significance (ASC-US). In addition, 27% of these subjects had been previously exposed to one or more of the vaccine HPV types (sero+ and/or PCR+).

Different subpopulations among the randomized females enrolled in the studies were considered for analyses of efficacy (Table 1)[15–17]. Per-Protocol Efficacy (PPE) included subjects who received all 3 vaccinations, were seronegative to the appropriate HPV type(s) at day 1 and PCR-negative to the appropriate HPV type(s) day 1 through month 7, and generally did not deviate from protocol. Modified Intention-To-Treat (ITT-1) analysis included subjects who received all 3 vaccinations, were seronegative to the appropriate HPV type(s) at day 1 and PCR-negative to the appropriate HPV type(s) day 1 through month 7, and included general protocol violators. Modified ITT-3 included all subjects who received at least 1 vaccination, regardless of initial serology and PCR status.

Per Protocol HPV type-specific analyses indicated a very high level of efficacy in naïve subjects, while the efficacy for all HPV related disease on a population basis, especially if given to many females who already have an HPV infection, appear to be lower, as summarized in Table 1. For subjects naïve for the relevant vaccine HPV type(s), the measured vaccine efficacy against HPV 16 and/or 18 related CIN2/3 or worse was 100%, and for all randomized trial population, the vaccine efficacy was about 40%, due to the fact that about a quarter of women had evidence of previously been infected with HPV. Noteworthy, data was analysed in a HPV type specific manner. Hence, females naïve to the four vaccine HPV types are expected to benefit most from vaccination.

Furthermore, vaccinated subjects naïve to all four vaccine HPV types could still develop disease related to an HPV type not included in the vaccine. In one case scenario, vaccination of naive populations shows that approximately 50% reduction in cervical cancer mortality could be achieved by vaccination in over many years[12,13]. Combination of vaccination and screening strategies are likely to offer the most effective prevention to cervical cancer.

HPV DNA Test Technology for Secondary Prevention

An independent study conducted by the International Agency for Research on Cancer (IARC), and a independent Advisory Group concluded there is *sufficient evidence* that screening for cervical cancer by cytological examination of Pap smear cell samples does prevent death[18]. The experts, however, emphasized that in order to achieve this goal optimally, an organized programme with quality control of every key step of the entire process is a prerequisite. Tests for the presence of viral DNA in a sample of epithelial cells have been established as a step toward

TABLE 2
OVERVIEW OF RESULTS OF SOME EUROPEAN STUDIES COMPARING CYTOLOGY AND MOLECULAR METHODS DETECTION RATES FOR HIGH GRADE CERVICAL DISEASE

Source reference	Study site and size (N)	Any HR HPV type CIN2+ or worse Number of Cases		Clinical Sensitivity CIN2+ or worse Endpoint	
		HC2**	Cytology	HC2**	Cytology
Cuzick et al.[26]	United Kingdom (N=10,358, 30–60 years)	87	69	96.8%	76.9%
Petry et al.[27]	Germany Tuebingen/Hannover (N=8,967; 30–87 years)	52	22	97.5%	48.9%
Clavel et al.[28]	France (N=14,123)	199	120	98.1%	62%
Ronco et al.[29*]	Italy (N=33,364)	73 (16,706)	51 (16,658)	97.3%	74%
Cuzick et al.[24]	United Kingdom (N≥60.000)	513	283	96.1%	53%

*Randomized trial, **The HC2 assaw shows consistenly higher rates of disease detection in large studies, including randomized trials, HR HPV – High Risk Human Papillomavirus, CIN – Cervical Intraepithelial Neoplasia, HC2 – Hybrid capture 2 assay.

identifying potentially precancerous conditions. In this context, the IARC expert Group concluded that there is also *sufficient evidence* that the HPV test for women 25–65 years *can* reduce mortality from cervix cancer[18]. If high quality screening test is provided to the public it will likely have an immediate impact on disease burden, in contrast to prophylactic vaccination, because it is designed to identify and avert cases in the women who already have some precancer pathology and are at high risk of progression to invasive cancer.

It is important to understand the difference between analytical and clinical sensitivity in order to allow effective use of HPV technology for clinical diagnostics. While analytical sensitivity relates to the amount of analyte or genome equivalent or copy number of viral particles present in a given sample, the clinical sensitivity relates to the degree of agreement of a positive test result with a positive disease status. Generally a test with high analytical sensitivity, detecting down to 10 viral copies per sample, would give positive results to all infected individuals, irrespective if this is a transient subclinical infection or an infection associated to neoplasia. Tests that detect only higher levels of viral DNA, eg. more than 5000 copies per sample, give positive results that are more likely associated to neoplasias at risk to progressing to cancer, and so are clinically relevant[19].

New diagnostic assays must be validated using data regarding prediction of risk of cancer and CIN3 from large representative study populations. In addition to targeting the correct genotypes, HPV tests must have clinically validated viral load cut points, ie. analytical sensitivity[20]. Hybrid Capture 2 (HC2) is FDA-approved, CE-marked, clinically validated, and commercial HPV test available worldwide. The test is available with two sets of reagents, one set to detect five low-risk types HPV, and another reagents set to detect 13 high-risk types HPV[21]. The analytical detection level of HC2 HPV has been set at 1.0 HPV DNA pg/mL (5000 genomes/assay) based on multiple clinical trials over a long period of time with high grade cervical intraepithelial neoplasia (CIN 2+) as the disease endpoint[22].

Primary screening with combined cytology and HPV testing is already an accepted and approved option in North America. The HPV HC2 test is recommended in the United States as adjunct to cytology screening for women over the age 30, or for triage of inconclusive cytology results in women under 30-years old[23].

In the European guidelines to be released now, evidence for HPV testing is accepted for two clinical applications: triage of equivocal cytology (ASCUS), and follow-up of treated lesions to predict failure or success of the offered therapy[24]. HPV triage of LSIL is recommended for women over 30 years of age, where the specificity of HPV test is higher than in young women[25]. In Europe a high level of confidence on primary HPV screening from randomized trials is awaited to complement the guidelines. At present, there are five randomized trials under way in Europe, to assess the effectiveness of HC2 as primary screening test for public health programmes. Similarly to endpoints used in vaccine studies, screening studies considered detect prevalent CIN2–3 in long follow-up periods. In general interim studies results showed that HC2 clinical performance in the field, as measured by biopsy confirmed cervical histopathology, is consitently higher than cytology based methods (Table 2)[24,26–29]. A meta-analysis of the various studies conducted in Europe and in North America involving over 60.000 women over 35-years old, confirmed that HC2 performance in the field to detect women with cervical premaligant lesions, is higher than cytology. With cytology triage, the specificity improves to the level of repeated conventional cytology. The studies also showed that combining HC2 with cytology maximizes the clinical benefits of large cervical screening programmes[22].

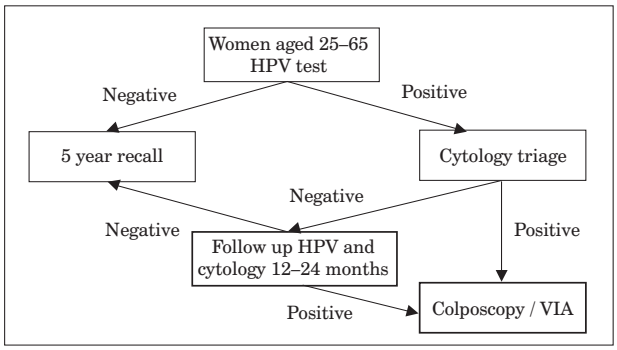

Fig. 2. Schematic representation of a possible algorithm for the use of HPV testing as the primary screening method followed by triage using cytology based methods, for women eligible for cervical cancer screening. The age group targeted for screening may vary in different countries and the interval considered for recall and follow-up,ay also be adapeted to national needs. Adapted from Cuzick et al. 2006[34]. HPV – Human Papillomavirus, VIA – Visual Inspection using 4% Acetic acid.

Another advantage of HPV test is that women with a negative result have an extremely low probability of having a CIN in the following 10 years. The longitudinal sensitivity to predict CIN3+ over a period of 10 years is 66% for HC2 whereas only 35.4% for baseline cytology defined as ASCUS+, while the positive predictive value of cytology remains higher than HC2[30–31]. Importantly, the positive predictive value of HPV test can be significantly increased by typing for HPV 16 and 18[32]. These observations indicate that HPV testing is safe and could be cost-effective allowing longer screening intervals, as opposed to methods such as Pap smears. In addition it may decrease significantly psychological anxienty associated with screening practice. Positive results for HPV 16 and 18 may warrant a shorter follow-up period.

A proposed new paradigm for cervical screening management is schematically illustrated in Figure 2. If resource constrains need to be respected, a HPV test would be a possible option because it is based on the higher sensitivity consistently demonstrated using HPV test, and high sensitivity could be achieved using cytology triage, for example[34].

Conclusion

To date, two HPV technologies reviewed and approved by regulatory authorities in North America and Europe for use in populations are at hand: HPV vaccination and HPV testing. Both technologies are derived from the cancer causing virus, and represent effective interventions to eliminate cervical cancer. Vaccines are tools for primary prevention strategies, i.e. to prevent the life treatening infection of establishing, and HPV tests are tools for secondary prevention strategies, i.e. prevent infections and neoplasias of progressing to invasive cancer.

There are some limitations that need to be acknowledged: vaccines to date target two out of fifteen carcinogenic types of HPV, and will likely prevent 70% of potential cancer cases in vaccinated subjects, so screening will need to continue in order to prevent those cases not protected by these vaccines. The vaccines are essentially prophylactic and have no effect on the course of already acquired infections, therefore screening needs to continue ensuring the population that previously acquired infections will be prevented of developing to cancer. Vaccination may have a lag of decades between the intervention and a reduction in cancer incidence at population level. Nevertheless, these limitations could be surmounted by vaccines that would be effective against most of the HPV carcinogenic types.

There are also limitations to HPV testing, as HC2 HPV test detects the 13 carcinogenic types identified, and has the potential to identify 95% of cases at an early stage to allow timely treatment. Cases caused by some HPV types not included in the test may not be detected. Notably, this can be overcome if the test is combined to cytology where is has demonstrated to be able to achieve 100% sensitivity. Negative HPV test results may warrant an assessment for appropriatness of sampling, such as cellular DNA content.

In an ideal public health service primary and secondary prevention strategies implemented in parallel will have a synergistic effect and solve the public health problem faster, than each strategy isolated. Noteworthy the key for success in vaccination programmes lies on the systematic and well organized approach to vaccinate the populations at high coverage, in addition to use quality products. Similarly, only screening programmes conducted with quality products, implemented in a systematic and well organized manner at high coverage, while targeting the female population at risk, can save lives and improve women's health, and will impact on the health of their families and communities.

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POMACI U JAVNOM ZDRAVSTVU ZAHVALJUJUĆI NOVIM METODAMA VEZANIM UZ HPV: RASPRAVA O NEDAVNIM DOKAZIMA

S A Ž E T A K

Učinkoviti primarni i sekundarni programi prevencije raka vrata maternice su ključni u poboljšanju javnog zdravstva. Rak vrata maternice je moguće spriječiti ukoliko se ženama ponude kontrolirani visoko-kvalitetni programi probira, dijagnostike i liječenja. Unatoč tomu, ovaj rak i dalje predstavlja javno-zdravstveni problem, a programe probira treba poboljšati. Humani papilomavirus (HPV) se smatra neophodnim uzročnikom gotovo svih slučajeva raka vrata maternice. Danas postoje dvije klinički potvrđene i odobrene metode vezane uz HPV, dostupne u prevenciji raka vrata maternice i drugih bolesti uzrokovanih ovim karcinogenim virusima: profilaktička cjepiva za primarnu prevenciju te HPV-DNK-testovi za sekundarnu prevenciju, detekciju infekcija karcinogenim tipovima HPV-a opasnih po život, što omogućuje pravovremenu dijagnozu te kliničko liječenje stadija prije raka. Nove metode će pomoći pomacima u javnom zdravstvu ukoliko budu široko dostupne. Slično programima cijepljenja, sustavno i dobro organizirani programi probira raka vrata maternice, sa visoko-kvalitetnim važećim HPV-testovima, mogu spasiti više života nego ikad te poboljšati zdravlje žena na vrlo učinkovit način.