What is the PREHDICT consortium?
PREHDICT, coordinated by the Free University of Amsterdam group of Chris Meijer, is a multidisciplinary consortium bringing together leading European scientists in the fields of epidemiology, mathematical modeling, virology, vaccinology and cancer prevention. It is third in a series of a number of EU supported HPV networks. From my perspective it all started as biobank-based research on the epidemiology and population attributable fraction HPV in various human cancers in the early 2000s, but together with the Nordic population-based HPV vaccine efficacy/safety trials, has formed a basis for evidence based decision making in the EU for synergistic implementation of HPV vaccination and HPV screening programmes.

How is it supported?
The PREHDICT Network was funded by the 7th Framework programme of DG Research (Brussels, Belgium), and through the ECGC (European Cooperation on development and implementation of Cancer screening and prevention Guidelines, via IARC, Lyon, France). It was also funded by the Directorate of SANCO (Luxembourg, Grand-Duchy of Luxembourg) and The Belgian Foundation Against Cancer, Brussels, Belgium. It is and an example of the European networking

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on HPV and cancer prevention research. Some national sources also contributed to support the country specific components of the activities.

**PREHDICT includes several work packages. Which are the global objectives of the project?**
The ultimate question is to model (predict) how to combine the new possibilities in vaccination and screening not only in the EU but also in the developing country context. If this challenge is not met the gap between affluent and developing countries will rapidly grow even wider when the interventions are implemented in a synergistic manner in the former but left drifting in the latter.

**Which are some contributions in terms of understanding HPV vaccination? (i.e. modeling herd immunity)**
Now, that new indications to vaccinate males per se are emerging, the modeling data, which supports the possibility to substitute low vaccine coverage in females (outside school-based vaccination programs) by vaccinating both girls and boys, are becoming important. Furthermore, as the last deliverable of the modeling work package we will be able to verify the model-predicted herd effects from the different vaccination strategies by a community randomized trial data by the end of next year.

**What would be the recommendation of the consortium for an integrated vaccination and screening program in Europe?**
From my point of view the recommendation of the consortium is to implement the new intervention measures (HPV vaccination and HPV screening) as comparative effectiveness research of EU public health policies. This not only includes surveillance but surveillance of randomized interventions to provide earliest possible data on the (most synergistic) impact of the best intervention combinations.

**Which are the forthcoming projects of the consortium?**
In the new CohearHr Project we evaluate whether cervico-vaginal self-sampling or vaccination of screened adult women will improve performance of these interventions are work packages of the consortium. I am leading a work package on randomized evaluation of the least frequent (approaching "once-in-a-life-time-screening") vs. current frequent screening of women vaccinated as early adolescents since 2007. The aim is to provide earliest possible data to stop unnecessary (or even harmful) screening in the vaccination era.

**EUROPEAN PARTNERS IN THE PREHDICT AND COHEAHR CONSORTIUMS**

- Finland
- Sweden
- Denmark
- UK
- Germany
- The Netherlands
- Belgium
- France
- Italy
- Slovenia
- Spain

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**Interview**

Matti Lehtinen  
University of Tampere, Finland
EDITORIAL

Jorma Paavonen
University of Helsinki, Finland

HPV- VACCINATION AND GENDER EQUITY

The HPV vaccine is the first vaccine mandated for only one gender. Yet men have equally high HPV rates and are as likely to transmit the infection to their partners. Reducing HPV prevalence among men would decrease transmission of HPV to women. Although gender distinction may be justified based on the available evidence of the vaccine efficacy, lack of gender equity is an ethical problem. It is not fair that young women are vaccinated within vaccination programs, but young men are not. Unfortunately here is the common perception that HPV is a women’s health issue in the first place. HPV vaccine trials have shown high efficacy against high grade CIN (CIN3+) in adolescent HPV-naive women. Vaccine efficacy against vulvar and vaginal intraepithelial neoplasia has also been demonstrated. Recent HPV trials in men have shown efficacy against persistent HPV infection and related anal genital disease in men as well. This is important since most genital infections in men are symptomless and subclinical. Also, each year almost 650,000 patients received the diagnosis of head and neck cancer, and HPV is a significant contributor to these cancers. HPV also causes genital warts, the most common sexually transmitted viral disease in both genders.

In October 2011 the Advisory Committee on Immunization Practices (ACIP) in the US recommended routine use of quadrivalent HPV vaccine (HPV4; Gardasil, Merck) in males aged 11-12 years. ACIP also recommended catch-up vaccination of males aged 13-21, to prevent genital warts. Health economic studies conclude that when vaccination coverage in women is high, vaccination of men is not cost-effective. One cost-effectiveness analysis of including boys in an HPV vaccination program did not show good value for resources compared with vaccinating adolescent girls only.

CANCERS AND PRECANCERS INDUCED BY HPV INFECTIONS AND AMENABLE TO PREVENTION BY VACCINATION

- Cervical cancer
- Vulvar cancer
- Vaginal cancer
- Anal cancer
- Oropharyngeal cancer*
- Genital Pre-cancers
- Genital warts

- Penile cancer*
- Anal cancer
- Oropharyngeal cancer*
- Genital Pre-cancers*
- Genital warts

* Preventive potential of the vaccines to be confirmed by clinical trails
However, the study had limitations and uncertainties. The authors suggested that such analysis should be re-visited as new information emerges. High vaccination coverage in women induces so-called herd immunity, which ultimately protects heterosexual men as well. Herd immunity can be described as the real life impact of vaccination in which the protective effect extends beyond the vaccinated individuals to others in the population. Unfortunately, in most countries where HPV vaccination has been introduced the vaccination coverage remains relatively low. One important target is men who have sex with men (MSM) who then receive little or no benefit from herd immunity and remain susceptible to HPV associated disease. It is not ethical or meaningful to leave men to rely on herd immunity only. Even though health economists demonstrate that male vaccination provides only a small added benefit, such approach certainly is unfair or unjustified from the individual point of view. Women-only vaccination programs for HPV have been introduced in many countries aiming to prevent cervical neoplasia. However, HPV-associated cancers in men are rising and by not vaccinating adolescent boys we certainly fail to gain maximum health benefit. Male HPV vaccination is ethically sound and promotes equality and social responsibility and sexual health in both genders. Australia has been leading the way on HPV vaccination in boys. Such school based immunization program, offering the quadrivalent vaccine to boys aged 12-13 years, with a catch-up program to students aged 14-15 years, was launched in July, 2012.

Consistent use of condoms only partially protects against HPV. Similarly comprehensive sex education including delay in initiation of sexual intercourse, reducing frequency of sex, reducing frequency unprotected sex and reducing the number of sexual partners are unrealistic and is unlikely to be effective in primary prevention. Studies also suggest that HPV vaccination for males is generally well accepted by young men, as well as parents and healthcare providers. Vaccination of males is safe and no vaccine-related serious adverse events had been reported in clinical trials.

**USA: HPV VACCINATION COVERAGE 2013. ADOLESCENTS AGED 13–17 YEARS**

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>57.3%</td>
<td>47.7%</td>
</tr>
<tr>
<td>2 dose</td>
<td>34.6%</td>
<td>23.5%</td>
</tr>
<tr>
<td>3 dose</td>
<td>37.6%</td>
<td>13.9%</td>
</tr>
</tbody>
</table>

Male vaccination is being gradually introduced in many countries as part of the routine public immunization practices or as an individual alternative. Preliminary results from the male vaccination campaign in the US initiated in 2011 indicate a coverage among boys aged 11 or 12 of 35% for one dose and 14% for three doses. Trends in vaccination coverage for both girls and boys are encouraging and clinician recommendation to parents of girls increased to from 61% in 2012 to 64% in 2013. Corresponding encouragement and for parents of boys increased from 28% in 2012 to 42% in 2013. In systems like the US where vaccination rely on parents compliance with clinician advise / recommendation, major efforts in communication and promotion are required with relatively low effectiveness. In contrast in countries were the vaccination program is facilitated by school based programs and centrally endorsed by the health authorities such as in Australia, vaccination of boys occur at a very high rates, similar to the vaccination coverage of girls (J Brotherton 29th IPV society meeting. August 2014 Seattle).
VACCINATING WOMEN AND MEN AGAINST PREMATURE DEATH
Summary of an International Workshop, Helsinki, Finland, 12.01.2012

CONFERENCE REPORT
Selected and prepared by Matti Lehtinen and reviewed by presenters

Exactly twelve years after the landmark trials of human papillomavirus (HPV) vaccination up to the phase III/IV study designs were discussed during the first HPV vaccination symposium in Helsinki. Leading experts in the field gathered together to report and discuss vaccination safety and efficacy data, and effectiveness and impact of HPV prevention strategies during the fourth HPV vaccination symposium, which took place in Helsinki on January 12, 2012. We report here some selected presentations disclosing efficacy and effectiveness of HPV vaccinations and interactions with screening programs.

EFFICACY OF HPV VACCINATION AGAINST THE MOST STRINGENT END-POINTS.

EFFECTIVENESS AND IMPACT OF DIFFERENT HPV VACCINATION AND SCREENING STRATEGIES.

Extracts of the lectures and videos of the Symposium can be found at: www.rokotiitus.net

Achim Schneider (Charite, Berlin),
Lutz Gissmann (German Cancer Research Center, Heidelberg) and
Eduardo Franco (McGill University, Montreal)

chaired the sections.
At the beginning of the second session concerning the efficacy of HPV vaccination against the most stringent end-points in females and males, Dr. Kevin Ault from Emory University Vaccine Center gave a talk about the efficacy of the quadrivalent vaccine against human papillomavirus (HPV) types 6/11/16/18 against the stringent end-points in females. At the beginning he noted the importance to distinguish clinical trial defined vaccine efficacy (VE) from effectiveness in the “real world” setting. He also noted that in the unexposed, baseline naïve population the quadrivalent vaccine has shown excellent (99 to 100%) VE against external genital warts, cervical, vaginal and vulvar dysplasia, as well as against cervical adenocarcinoma in situ.[1-3]

Regarding the most stringent end-points of the combined FUTURE I/II study with 17 622 subjects (approximately 10% enrolled from Finland) he noted, that in the baseline naïve cohort VE against HPV16/18 positive CIN3 was 100% (95%CI 90.5-100). The VE against any CIN3 was 43% (95%CI 13.5-63.2, Table). Corresponding VE results in the intention-to-treat population were 43.5% (95%CI 27.3-56.2) and 16.4% (95%CI 0.4-30.0), respectively.[4] Long-term follow-up of the Finnish FUTURE cohort and a concomitant cohort of >15 000 unvaccinated females of the same age, exploiting the population-based Finnish Cancer Registry is ongoing with CIN3+ as the most stringent end-point.[5]

In conclusion, Dr. Ault noted the consistency of the high vaccine efficacy verified for the quadrivalent HPV6/11/16/18 vaccine against different clinical end-points, including the most definitive precancerous end-points.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 3 due to HPV16/18, HPV naïve cohort</td>
<td>100%</td>
<td>90.5 to 100%</td>
</tr>
<tr>
<td>VaIN 2/3 or VIN 2/3 due to HPV16, HPV naïve cohort</td>
<td>94.9%</td>
<td>68.3 to 99.9%</td>
</tr>
<tr>
<td>CIN 3 due to HPV16/18, intent to treat cohort</td>
<td>43.5%</td>
<td>27.3 to 56.2%</td>
</tr>
<tr>
<td>CIN 3 due to any HPV type, HPV naïve cohort</td>
<td>43%</td>
<td>13.0 to 63.2%</td>
</tr>
</tbody>
</table>

Table 1. HPV naïve are women HPV DNA negative and HPV antibody negative in serology at the time of recruitment.
Protection against CIN3+ cases related to any HPV type has been reported at > 90% using the bivalent HPV vaccine.

Dr. Allan Hildesheim from the National Cancer Institute talked about the choice of outcome for the post-licensure HPV vaccine studies noting that both the bi-valent and the quadrivalent vaccines have yielded almost identical vaccine efficacy (VE) results against cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in comparable per protocol analyses 98% (95%CI 93-100) and 95% (95%CI 88-98). Reproducibility of the CIN2 diagnosis, which forms the bulk of this end-point is, however, poor. Moreover, a large proportion of the CIN2 lesions regress over time.[6] So far, overall VE results with the bi-valent vaccine on CIN3+, which is a more reproducible end-point, vary a lot depending whether or not baseline HPV naïve only or so called all comers are considered: 93% (95%CI 79-99) vs. 46% (95%CI 29-59), respectively (Table, 2). Since CIN3 cases are reported to cancer registries long-term follow-up the different cohorts is of paramount importance.

Dr Hildesheim also discussed the possibilities to use virological end-points, i.e. HPV persistence as alternative outcomes of post-licensure trials noting that HPV testing is highly reproducible. In the major trials (PATRICIA and the Costa-Rica HPV Vaccine Trial) of the bi-valent vaccine VEs against CIN2+ and persistent HPV DNA positivity have been comparable. This enables evaluation also in the context of multiple HPV infections with less concern for false attribution of causality between different (vaccine and non-vaccine) HPV types to the clinical lesion. He also noted that the virological end-points are preferable in studies of the duration of vaccine protection when new HPV-associated cancer end-points like oro-pharyngeal cancers are considered.

### VACCINE EFFICACY RESULTS USING CIN3+ AS OUTCOME ANALYSES IRRESPECTIVE OF HPV TYPE USING THE BIVALENT VACCINE: PATRICIA TRIAL[7]

<table>
<thead>
<tr>
<th>Analytic Cohort</th>
<th>Arm</th>
<th>Women</th>
<th>CIN 3+</th>
<th>Rate/100py</th>
<th>Efficacy (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Vaccinated Cohort - Naïve [44mo FU]</td>
<td>HPV</td>
<td>5,466</td>
<td>3</td>
<td>0.0</td>
<td>93% (77, 99)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5,452</td>
<td>44</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Total Vaccinated Cohort [44mo FU]</td>
<td>HPV</td>
<td>8,694</td>
<td>86</td>
<td>0.3</td>
<td>46% (29, 59)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>8,708</td>
<td>158</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

FU: Follow up time

Lehtinen et al., Lancet Oncol 2011.

Table 2.
Dr. Dan Apter, from Family Federation in Finland, reviewed immunogenicity and efficacy results of the bi-valent and quadrivalent human papillomavirus (HPV) vaccines in males. By month 7 post vaccination, the bi-valent vaccine was in a small study of 270 subjects proven to be equally safe and immunogenic in generating serum IgG antibodies following a three-dose (0, 1, 6 months) regimen in 10 to 18 year-old boys and girls. However, when compared to 15 to 25 year old young women (mean age 20 years) the antibody responses in the early adolescent boys were significantly higher.[8] As for the quadrivalent vaccine, virtually all (97.4%-99.2%) of the 4,065 male vaccine recipients also seroconverted by month 7 following a three-dose (0, 2, 6 months) regimen.[9] Geometric mean titres of the quadrivalent HPV vaccine induced antibody levels were slightly, albeit not significantly lower in males than in females.

Efficacy has been estimated only for the quadrivalent HPV vaccine in the above-mentioned study population. Both persistent infection with the vaccine HPV types 6/11/16/18 and external genital lesions (EGL) were used as the end-points. In an intention-to-treat analysis vaccine efficacy (VE) against persistent HPV6/11/16/18 infection was 47.8% (95% CI 35.0-57.6) and against HPV6/11/16/18 associated EGL it was 65.5% (95% CI 45.8-78.6). In the per protocol analysis, the latter VE was 90.4 (95% CI 69.2-98.1) (Table 3). The vaccine efficacy and safety results were essentially comparable in heterosexual men and men who have sex with men.

In summary, both the bi-valent and the quadrivalent vaccines have proven to be the highly immunogenic also in males, and the quadrivalent vaccine has also proven to be highly efficacious against HPV infection and associated disease outcomes in males.

### Efficacy of Quadrivalent Vaccine Efficacy Against External Genital Lesions (Largely Genital Warts) in the Per-Protocol Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quadrivalent HPV Vaccine</th>
<th>Placebo</th>
<th>Observed Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases of EGL</td>
<td>Rate no./100 person-yr at risk</td>
<td>Cases of EGL</td>
</tr>
<tr>
<td>Any type</td>
<td>6</td>
<td>0.20</td>
<td>36</td>
</tr>
<tr>
<td>Type 6, 11, 16 or 18</td>
<td>3</td>
<td>0.11</td>
<td>31</td>
</tr>
<tr>
<td>Type 6</td>
<td>3</td>
<td>0.12</td>
<td>19</td>
</tr>
<tr>
<td>Type 11</td>
<td>1</td>
<td>0.04</td>
<td>11</td>
</tr>
<tr>
<td>Type 16</td>
<td>0</td>
<td>0.00</td>
<td>2</td>
</tr>
<tr>
<td>Type 18</td>
<td>0</td>
<td>0.00</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3.

Giuliano et al. NEJM 2011

Protection against genital warts in males was > 80% using the quadrivalent vaccine
Dr. Joakim Dillner from Karolinska Institute began by explaining why monitoring human papillomavirus (HPV) vaccination is especially important to assure that the vaccination program works much before its impact on the remote cancer end-points (due to the long incubation time between infection and cancer) can be seen in e.g. 2022 (the earliest). Not only because the infection is asymptomatic, but also to monitor type-replacement based on lab testing is required. He stressed the importance of comparable evaluation systems which should comprise:

1) HPV Vaccination Registry;
2) Condyloma Surveillance with HPV typing, and
3) Quality-assured HPV testing and typing in the target age-groups.

In Sweden the national HPV vaccination program has started in the beginning of 2012 targeting 11-12 year old girls with a catch-up up to the age of 18 years. The Swedish health care infrastructure yields two options to monitor HPV vaccination in the context of 1) the cervical screening starting at the age of 23 years, and 2) the free Chlamydia trachomatis (Ctr) testing programme, which has high coverage among sexually active teenagers with 80 000 samples collected in a population of 1.2 million adolescents and young adults. The Ctr-samples from females are a mixture of first void urine and self-sampled vaginal swabs, and have been used to establish the baseline HPV prevalences of 14 oncogenic and 2 benign HPV types: HPV16/18/31/33/35/39/45/51/52/56/58/59/66/68 and HPV6/11 exploiting a PCR followed by MALDI-TOF mass spectrometry.[10] The semi-automated, high-throughput system has reduced the costs down to 2.2 Euro/sample. While the testing is more sensitive in females than in males, the HPV prevalences peaked at 54.4% in 21 year-old women and 14.9% in 23 year old men. The role of WHO Global HPV LabNet is pivotal in the quality assurance. The annually issued HPV DNA genotyping proficiency panel, which includes all the above-mentioned HPV types[11] is important in assuring laboratories (using all known HPV DNA tests) ability to detect multiple HPV infections and to identify typing errors. A comparable HPV serology panel has recently been launched.[12]

**In summary**, Dr Dillner described three ambition levels (Table 4) in the internationally standardized post vaccination surveillance and effectiveness evaluation: low (coverage and safety), medium (HPV DNA testing, HPV immunogenicity testing and monitoring of HPV-associated diseases), high (registry-based follow-up systems).

### POST VACCINATION SURVEILLANCE: THREE AMBITION LEVELS

<table>
<thead>
<tr>
<th>Level</th>
<th>Coverage and safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Effectiveness surveillance systems</td>
</tr>
<tr>
<td></td>
<td>• HPV DNA testing (in teenager surveys or in cervical screening program);</td>
</tr>
<tr>
<td></td>
<td>• Immunogenicity;</td>
</tr>
<tr>
<td></td>
<td>• Monitoring of HPV-associated diseases.</td>
</tr>
<tr>
<td>Medium</td>
<td>Registry-based follow-up system</td>
</tr>
</tbody>
</table>

The session: Effectiveness and impact of different HPV vaccination and screening strategies was started by Dr. Marion Saville from Victoria Cytology Register, Melbourne, who described the Australian National HPV vaccination program, which started in 2007. This consists of ongoing vaccination of 12 to 13 year girls and a two year catch up program extending to young women up to the age of 26. Girls aged up to 17 or 18 years were vaccinated in schools whilst young women aged 18 to 26 were vaccinated by their general practitioners. Three dose coverage of approximately 70% has been achieved in the school aged girls, whilst coverage in the young women in general practice was lower ranging from 66% in 18 year olds down to approximately 30% in 26 year olds.

Whilst socioeconomic status is related to participation in screening, no such relationship has been observed for the vaccination programme. It is thought that this greater degree of equity in vaccination is due at least in part to the school's based delivery programme. Although there is no ongoing type specific HPV surveillance underway in Australia, two independently funded research activities have examined type specific surveillance. The first of these the WHINURS study[13] was undertaken prior to the implementation of the vaccine program and aimed to estimate the prevalence of type specific genital HPV infection in sexually active Australian females aged 18 to 40 presenting for a Pap test to a variety of health services.

**IMPACT OF HPV VACCINATION IN AUSTRALIA: RAPID REDUCTION OF CERVICAL HIGH-GRADE ABNORMALITIES**

*Figure 1. A relative reduction of ~50% was observed in this age group, post vaccination vs. pre vaccination, barely 3 years after the introduction and the trend continues*
Subsequently the same researchers are undertaking the Vaccine Impact in Population study.[14] This is a study of 1,300 women aged 18 to 24 presenting to family planning clinics for a Pap test. The study has been undertaken as a sentinel site model using baseline data from the large sites involved in the WHINURS study. Preliminary results indicate a modest reduction in the presence of any HPV type but a substantial (approx. 75%) reduction in the likelihood of identifying HPV types 6, 11, 16 and 18. Dr Saville went on to outline substantial reductions in presentation to sexual health clinics by young people with genital warts. Among women who were age eligible for vaccination there has been a 73% reduction in presentations with genital warts with no change seen in the older cohort of women. A 35% reduction in presentations with genital warts has been recorded amongst heterosexual men with no change being demonstrated amongst men who have sex with men.

Dr Saville then went on to describe a profound reduction in histologically confirmed high grade abnormalities amongst women under 18 years in Victoria. There was a fall from 0.85% in 2006 to 0.22% in 2009. By 2010 this reduction could also be seen in women to the age of 20. Reductions have also been seen at the national level in Australia. Australia is fortunate in having a system of jurisdictional Pap test registers and a national HPV Vaccine Register. The next step in surveillance will be to undertake data linkage studies between these registers.

In summary five to six years after introduction, the Australian national HPV Vaccination Program is already showing a remarkable reduction of the HPV disease burden.
Pekka Nieminen, from the University of Helsinki Central Hospital described the Finnish Organized Cytological Screening programme, which starts at the age of 30 and continues 35 years with 5 year intervals. The programme started in 1963 and following its full implementation from the beginning of the 1970’s reduced the incidence of and mortality from cervical cancer by 80%. Since the 1990’s, however, considerably low participation among 30/35 year-old women of about 60% together with the preceding increase of background exposure to high-risk human papillomaviruses (hrHPVs) has resulted in an outbreak of cervical cancer epidemic in Finnish women under the age 40.[15] The incidence of cervical cancer in this age-group is now similar to the pre-screening era. However, overall 530 000 cytological samples (with a 4:1 ratio of opportunistic and organized screening samples) have an impact on cervical cancer incidence and mortality in older women in whom 85% of the cancer cases are diagnosed.[16] This has high cost. Using a dynamic model Finnish expert group of the National Institute for Health and Welfare has evaluated the joint cost of conventional Pap screening, and reviewed the possibilities to reduce the cost by implementing HPV vaccination and modifying screening. While the current screening and treatment cost up to 35 MEuros, minimizing opportunistic screening using sensitive and specific HPV screening for HPV vaccinated birth cohorts would bring annual savings of 20 MEuro, and major reduction in quality assured life-years lost (Fig. 2).

In conclusion, while older women are protected effectively by screening, HPV vaccination and screening rapidly prevents CIN3+ cases of younger women.

**Figure 2.** Under no vaccination and no screening programs (green dot number 1) the social costs of cervical cancer would be low (i.e. some 11ME) and the quality adjusted years of life lost very high (close to 5,000). Vaccination programs with a range of screening options (red dots 8,9,10 or 11) would have a similar cost but the number of QALYs lost would be reduced to around 500.
Dr. Iacopo Baussano from Imperial College London (presently International Agency of Research on Cancer) defined dynamic transmission systems of infections as mechanistic models based on assumptions that infectious agent transmission results from the dynamic interaction between populations of the agents, possible biological vectors and human hosts within a specific and changing environment. Thereafter Dr. Baussano presented his compartmental deterministic SIR/SIS model where individuals change from susceptible (S) to (human papillomavirus (HPV) infected (I) and further to recovered susceptible (S) or immune (R). While the infection incidence is determined by contact rate, transmission probability, duration of infectiousness and fraction of susceptibles, vaccination acts on it by decreasing the fraction of susceptibles. The impact of vaccination, in terms of vaccine coverage required for the reduction of endemic HPV prevalence is largely dependent on whether or not natural infection induced immunity is assumed to take place (high coverage, low herd-immunity in the SIR-model) vs. (low coverage, high herd-immunity, in the SIS-model). On the other hand, trends and assortativeness of sexual behaviour, and its geographical heterogeneity have an impact on the epidemic state (incidence trends) of HPV types and HPV vaccination induced herd effect.[17]

Finally, Dr. Baussano estimated the interaction of HPV vaccination and screening in an integrated cervical cancer screening programme showing that with increasing vaccine coverage (up to 90%) the interval between screening rounds can be increased up to 20 years with the same net result. In addition to cost-efficacy estimation in the absence of empirical data, the dynamic models can be used to estimate sample sizes for community randomized effectiveness trials of combined interventions.

Increased HPV vaccine coverage allows a significant reduction of the screening requirements

INTEGRATED CANCER CONTROL PROGRAMMES

Figure 3. Given a specific screening algorithm, coverage and accuracy and given a cervical cancer incidence reduction target (constant), the intervals between screening rounds (isoclines blue lines) are identified as a function of the proportion (%) of HPV vaccinated women among screened (x axes) and unscreened (y axes) women. The random vaccination line scenario (yellow diagonal) assumes that the proportion of vaccinated among screened and unscreened women is the same.
Dr. Matti Lehtinen from the University of Tampere started by describing the consequent (11 years interval) HPV16 and cervical cancer epidemics, which took place in < 30 and < 40 year old Finnish women, and started in the middle of 1980’s and 1990’s indicating that the states of hrHPV epidemics (and their consequences) are far from stable. Due to mostly low HPV vaccination coverages, widening scope of HPV associated diseases preventable both in females and males, and remarkable decrease of vaccine prices there is a need to re-evaluate impact of different HPV vaccination strategies. According to an established dynamic model 50% vaccine coverage among girls and boys results in up to 25% free, herd effect in the reduction of HPV prevalence (Fig., 4).[18]

In order to verify the modeling results a community randomized phase IV trial was started in Finland in 2007-2009. In 11 A-communities 90% of both 12-15 year-old girls and boys received the bi-valent HPV16/18 vaccine, in 11 B-communities 90% girls received the bivalent vaccine, while 10% girls and 100% of boys received hepatitis B virus (HBV) vaccine, in 11 C-communities all vaccinated early adolescents received HBV vaccine. Vaccine coverages were approximately 50% for girls in all the communities, and between 20-30% for boys. With half of the altogether 22000 HPV vaccinated, and 5000 HPV un-vaccinated girls attending the follow-up visit at the age of 18.5 years (both cervical cytological sample and a cervico-vaginal self-sample taken) the study is powered to identify differences not only in the overall effectiveness of the different vaccination strategies but, with a narrow marginal, also in the impact of herd effect (Lehtinen et al., submitted).

Verification of the mathematical models with modification vaccination programmes based on data from a randomized controlled trial is likely to lead to a new era in the comparative effectiveness research.
Dr. Lutz Gissmann from the German Cancer Research Center gave a talk about HPV vaccines for developing countries, and noted that the vast majority of HPV associated disease burden, e.g. 85% of the incident cervical cancer cases affects the developing countries which lack resources to implement screening and treatment. While the Global Alliance for Vaccines and Immunizations (GAVI) estimates that by 2015 2 million girls in nine developing countries will be vaccinated the two existing licensed vaccines have shortcomings precluding their wide use in the developing countries: the vaccines are costly, do not prevent all cases of cervical neoplasia, have no therapeutic value, require multiple invasive immunizations, and have low stability. On the contrary, an HPV vaccine for developing countries should be robust, multivalent, immunogenic by non-invasive application and provide long-term protection without boosting. Dr. Gissmann first described experiments done with a recombinant adeno-associated virus, where the HPV16 L1 gene had been constructed under an efficient cytomegalovirus promoter. Following intra nasal immunization the construct efficiently produced long lasting neutralizing antibody and cytotoxic T-cell responses in mice.[19] While adeno-associated viruses are non-patogenic in humans they cause persistent infections, and offer a venue for prophylactic and/or therapeutic immunization. While production of “edible” HPV vaccines in plants (potato, tobacco) is possible,[20] but hard to standardize. In the latter part of his presentation Dr. Gissmann focused on the HPV capsomer (pentamer of single L1 proteins), 72 of which are needed for the assembly of HPV capsids/VLPs. Capsomers can be easily purified after expression of L1 in *E.coli* (Fig. 5). The ability of different L1 mutants to assemble into larger particles, comprising up to 7 capsomers, correlated with their immunogenicity.[21] Since these constructs are stable as precipitated powder and highly immunogenic both in intranasal and i.m. immunization they may form a basis for HPV vaccines for the developing countries.[22]
Dr. Marc Arbyn from the Unit of Cancer Epidemiology, IPH Brussels described two Cochrane reviews: one on Cervical Cancer Screening in developing countries and another on Safety, immunogenicity and efficacy of prophylactic HPV vaccines (Fig.).

Literature search from 1982 to present had identified 27 studies from developing countries evaluating different modes of visual inspection of the cervix (with acetic acid, VIA or with Lugol’s iodine, VILI) against comparative tests (conventional cytology and Hybrid Capture 2, HC2) with two outcome measures, i.e. cervical intraepithelial neoplasia (CIN) grade 2+ and CIN3+. As for the diagnosis of CIN2+ the relative sensitivity of conventional cytology vs. VIA was worse 0.77 (95%CI 0.71-0.84) but the relative specificity was slightly better than that of VIA, i.e. 1.12 (95%CI 1.09-1.16). On the other hand, VIA was less sensitive and less specific than HC2 testing. Surprisingly VILI testing appeared to perform a little better than VIA testing. However, in conclusion Dr. Arbyn noted that colposcopy based confirmation of the outcomes inflates the visual screening tests, and that assessment of the tests or a completely new screening test for the developing countries would require a longitudinal randomize setting with CIN3+ as the only acceptable surrogate marker for invasive cancer incidence and mortality.[23]

Regarding the latter, estimates from early, first line publications of the clinical phase II/III trials were presented without conclusive comparison of the efficacy of the two licensed vaccines. It was also considered unacceptable to pool the bi-valent and quadrivalent vaccine efficacy data in the same meta-analysis.

References:
On June 28, 2014 Mario Sideri MD, Director of the Preventive Gynecologic Division at the European Institute of Oncology of Milan, Italy, passed away at the age of 61. A deadly accident took him while he was riding his motorbike in the winding roads of Aveto valley, a place of charming beauty that he loved. He left his adored wife and colleague Daniela and his talented son Matteo. Mario was a nice chap, a good man and an excellent mentor and doctor. His educated humor, kindness and culture were apparent at a glance. He had the wisdom of the experienced gentleman, but the soul of a teenager and was able to solve difficult situations with the strengths of a smile. He firmly believed in true solidarity, without borders. In Madagascar he had launched a sound program on the prevention and treatment of gynecological malignancies, and had offered his services for free in many developing countries. He was an excellent teacher. His lectures were always sound and precise, without being tedious or weary. He was an enthusiast and a visionary scientist. He had understood before others the importance of HPV in the development of cervical cancer and was keen in implementing viral screening as a more effective alternative of cytology. He knew that simplicity was the key of success and was a pioneer in proposing easier means of cervical sampling, more understandable nomenclature of lower genital tract premalignant disease and more affordable and convenient screening intervals. He highly respected women and their potentials, and had the courage of proposing conservative management of early endometrial and cervical cancer, where hysterectomy was the rule. He was a fierce believer in the strengths of primary and secondary prevention. His eagerness on the molecular diagnosis of women at high risk of ovarian cancer prompted his participation in innovative and rigorous research protocols, which received recognition by the medical community. Mario, dearest SuperMario, you will remain our special friend and we already miss you for what you have been and for what you could have done, if you were here. Ride the sky, sail with the trade winds, and dispute with the angels. While you look after us from Heaven, we’ll try to follow your railway line on earth.
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