EPISODES OF GENITAL WARTS AND THE LIFETIME RISK OF HPV-RELATED CANCERS

You have reported an increased lifetime risk of cancer in individuals who have had an episode of genital warts. Are such episodes a clinical marker of higher susceptibility to HPV?

Genital warts could be a marker of a higher susceptibility to HPV and/or to consequences of an HPV infection. Most of us will acquire HPV at some point during our lifetime, but as most HPV infections are transient and symptomless, the development of genital warts could indicate that the immune system has not been able to control the HPV infection. These immunological differences between individuals could, in theory, predispose some of them to a higher tendency towards persistence of the HPV infection and, thereby, to an increased risk of cancer.

Which cancers are associated with clinical episodes of genital warts and what is the interval between the two episodes?

In our study of the risk of cancer subsequent to genital warts, which included almost 50,000 individuals diagnosed with genital warts in the period 1978-2008,[1] we found that cancers known to be associated with HPV were most strongly related to previous, clinical episodes of genital warts (SIR=3.1; 95% CI: 2.8-3.5) (Fig. 1). Although mainly anal and vulvar cancers were in excess, the risk of penile, vaginal, cervical and HPV-related head and neck cancers, particularly tonsillar cancer, was also higher among individuals with a previous diagnosis of genital warts. In addition, we also found that the incidences of non-melanoma skin

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cancer and Hodgkin and non-Hodgkin lymphoma were higher in individuals with a previous diagnosis of genital warts than in the general population. Our results therefore support the hypothesis that some head and neck cancers and non-melanoma skin cancer, for example, could also be associated with HPV. Interestingly, the risk of most of these cancers remained significantly elevated more than 10 years after the episode of genital warts.

**Did the risk include both genders?**
The increased risk generally applied to both genders but with a variation in the strength of association. For instance, we observed a higher relative risk of HPV-related cancers in men, driven primarily by a noticeably higher risk of anal cancer. However, the large gender difference in risk of anal cancer could be confounded by male homosexual behaviour, which is known to increase the risk of both genital warts and anal cancer. In women, the risk of HPV-related cancers was lowered by the estimate for cervical cancer, for which there is effective screening. Moreover, the risk of non-Hodgkin lymphoma was significantly elevated among men but not among women, while women were at higher risk of HPV-related head and neck cancers and squamous cell carcinoma of the skin.

**Did other non-HPV-related cancers also show an increased risk?**
We also found significantly increased risks of smoking-related cancers (Fig. 1). Thus, the risk of lung cancer was significantly increased in both genders (SIRmen+women=2.1; 95% CI: 1.9-2.4), thereby indicating a greater proportion of smokers in our cohort of individuals with a history of genital warts compared with the general population. Non-melanoma skin cancers were also in excess, potentially suggesting an association of this cancer with HPV or, alternatively, with smoking. Finally, we found an elevated risk of Hodgkin and non-Hodgkin lymphoma, which has also been reported in a previous cohort study of individuals with a diagnosis of genital warts.[12]

These findings may support the hypothesis that specific immunological differences predispose an individual to genital warts, persistent HPV infection and cancer since patients who have undergone organ transplantation (and thereby are immunosuppressed) are at increased risk of both Hodgkin and non-Hodgkin lymphoma and many of the same cancer types that were in excess in our cohort (anogenital cancer, cancers of the oral cavity, oesophagus, lung and bladder, and non-melanoma skin cancer).[5]

**Genital warts are related to low oncogenic risk HPV types 6 and 11. Which HPV types caused the subsequent cancers? How do you explain this?**
Infection with multiple HPV types is common. It could therefore be hypothesized that individuals with genital warts also have a higher likelihood of having high-risk HPV types as well, and thereby also an increased risk of developing cancer compared to the general population.

**Genital warts are rapidly decreasing in Australia following generalized HPV vaccination. Does this predict a subsequent reduction in cancers caused by the HPV types in the vaccine?**
Based on the rapid decrease in genital warts seen in both Australia and Denmark, a comparable decrease in HPV-16 and -18-related precancerous lesions and cancers could be expected. As long as vaccine coverage rates are high, this should be reflected at the population level.

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**Figure 1.** SIR=1 (red line) reflects that the observed incidence is equal to the expected incidence of cancers in the general population. SIRs above one indicate excess risk and the 95% CI indicate that the observed excess are all statistically significant.
In 2006, when the first HPV vaccines were licensed, the guidelines for recommendations included, and were limited to, concepts such as:
1. a vaccine for cervical cancer
2. a vaccine for women only, and
3. a vaccine recommended in priority before average age at sexual debut to minimize vaccination of subjects already exposed to, or persistently infected with, the relevant HPV types.

Consequently, HPV vaccination has been funded and massively implemented amongst pre-adolescent girls in most developed countries and in pilot programs in developing countries. Catch-up vaccination programs have extended the target age groups in a range from a few additional cohorts (i.e. many countries in Europe), to age 18 (i.e. the UK) or, for a limited period, to age 26 (i.e. Australia). The high price of the vaccines was a strong deterrent to their generalized introduction and the cost-benefit analyses using such high prices repeatedly advised against extending the benefits of vaccination to all women at risk of cervical cancer.

Now, at the end of 2013, many important contributions have been added to the rather simplistic views that have guided cervical cancer prevention initiatives for the past six years. Thus,
1. HPV is recognized as a cause of several other cancers in both genders,
2. the burden and social impact of genital warts has been recognized,
3. HPV vaccine efficacy is as high as 80–90% in adult women (to ages 45/50) who are HPV DNA negative at the time of vaccination,
4. high vaccine efficacy has also been proven among HPV-negative males for genital warts and anal pre-neoplastic lesions,
5. a growing body of evidence indicates that HPV vaccines are effective against all HPV-16-related cancers, possibly including oropharyngeal cancers,
6. the consolidation of evidence regarding the potential of HPV screening programs to dramatically reduce the prevalence of HPV-related lesions and, finally,
7. a dramatic reduction in the cost of vaccines for public programs and GAVI-eligible countries is underway.

Furthermore, the concept that HPV vaccination and HPV screening could and should work in an integrated manner has been recognized by several working parties and review panels. The objective of such an approach is to make unified and consistent proposals to health authorities that facilitate decision-making and budget allocations. In addition, these proposals should be cost-effective for the population and should attempt to extract the greatest benefit from the extraordinary potential of these two preventive options.

In light of this new body of evidence, future actions may include proposals to initiate male vaccination programs, such as that launched in Australia in 2013, and extend the offer of HPV vaccination to women of a screening age in association with HPV screening campaigns. The latter should benefit from the high sensitivity of a single HPV test to identify prevalent lesions and help in the management of HPV-positive women. The concurrent vaccination of HPV-negative women would prevent additional new HPV infections from occurring, thereby accelerating the reduction in the incidence and mortality of invasive disease.

The format of the new protocols and trials required to substantiate these proposals are currently the subject of intense discussions amongst scientific and public-health societies and institutions.
GENITAL WARTS AND CANCER RISK – A DANISH STUDY OF NEARLY 50,000 PATIENTS WITH GENITAL WARTS

INTRODUCTION

Although HPV types 6 and 11 are the dominant HPV types in genital warts, co-infection of genital wart lesions with high-risk HPV types is common. To investigate whether patients with genital warts have an increased risk of subsequent HPV-related cancer, we compared the risk of cancer among individuals with genital warts to that of the general population.

We used the unique personal identification numbers, which are assigned to all Danish residents, to accurately retrieve and link nationwide data. The personal identification numbers are used universally in Danish society, including all registries.

We identified a cohort of 16,155 men and 32,933 women who were diagnosed with genital warts in a hospital or out-patient clinic in Denmark from 1978 to 2008. This cohort was followed for up to 31 years, the mean follow-up time being 12.5 years.

The number of primary cancer cases (identified from one month after the genital wart diagnosis until death, emigration, or 31 December 2009) among these individuals was compared with that expected for the general population. Standardized incidence ratios (SIR) for cancer were calculated as estimates of relative risks and stratified for follow-up time.

KEY FINDINGS

With a total of 2363 identified cancer cases and only 1806.6 expected, individuals with a genital wart diagnosis were at significantly increased risk of all cancers combined (SIRmen+women: 1.3, 95% CI 1.3-1.4, SIRmen: 1.5, 95% CI 1.4-1.6, SIRwomen: 1.2 95% CI 1.2-1.3). The risk was caused primarily by HPV-related cancers.

For men, the SIR of 7.2 (95% CI 5.5-9.2) for HPV-related cancers covered a strongly increased relative risk of anal and penile cancer and a moderately elevated risk of HPV-related head and neck cancers (Table 1).

For women, the SIR for HPV-related cancer was 2.8 (95% CI 2.4-3.1), which covered a strongly increased risk of vulvar and anal cancer, a moderately increased risk of vaginal and HPV-related head and neck cancer, and a slightly, but still significantly, elevated risk of cervical cancer (Table 1).

For head and neck cancers, the ones with expected HPV association (based on the literature) showed the highest risk estimates, with the risk of tonsillar cancer being substantially increased (SIRmen: 4.6, 95% CI 2.7-7.2, SIRwomen: 4.7 95% CI 2.3-8.4). In addition, significantly increased risks were observed for smoking-related cancers (especially of the pharynx, larynx and lung), non-melanoma skin cancer, and Hodgkin and non-Hodgkin lymphoma (Table 1).

Both anogenital cancers and tonsillar cancers were in excess more than 10 years after the genital wart diagnosis. Although this did not reach statistical significance for the rarer cancers (penile and vaginal cancer), a significantly increased risk was found for vaginal cancer after 5-9 years of follow-up (Table 2).
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genital warts

This study has the advantage of a large cohort size and a long follow-up period, which enabled us to get enough statistical power to study rare cancers subsequent to genital warts. Several hypotheses can be proposed to explain our results. A recent study of swab samples from genital wart-like lesions in 621 individuals found that 35% were infected with high-risk HPV types.[1] Co-infection with high-risk types may therefore be one of the reasons for the excess risk of cancer. In addition, immunological differences between individuals could make some individuals particularly susceptible to HPV infection and less likely to clear the infection, thereby increasing their risk of both genital warts and cancer.

Table 1. Risk of cancer after genital warts. Figures in black indicate statistically significant excess risk. Figures in grey indicate risk estimates not significantly different from the reference expected value.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>MEN</th>
<th>WOMEN</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Observed</td>
<td>Observed</td>
</tr>
<tr>
<td></td>
<td>SIR</td>
<td>95 % CI</td>
<td>SIR</td>
</tr>
<tr>
<td>All HPV-related cancers</td>
<td>60</td>
<td>7.2</td>
<td>5.5-9.2</td>
</tr>
<tr>
<td>(HPV-associated HNC, anus (ICD-O C21), vulva (C53), vagina (C52), cervix (C53), and penis (C56).)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All smoking-related cancers</td>
<td>255</td>
<td>1.8</td>
<td>1.6-2.1</td>
</tr>
<tr>
<td>HNC (according to anatomical localization)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>117</td>
<td>1.5</td>
<td>1.3-1.8</td>
</tr>
<tr>
<td>Vagina</td>
<td>6</td>
<td>5.9</td>
<td>2.2-12.9</td>
</tr>
<tr>
<td>Anus</td>
<td>29</td>
<td>21.5</td>
<td>14.4-30.9</td>
</tr>
<tr>
<td>Vulva</td>
<td>74</td>
<td>14.8</td>
<td>11.7-18.6</td>
</tr>
<tr>
<td>Penis</td>
<td>11</td>
<td>8.2</td>
<td>4.1-14.6</td>
</tr>
<tr>
<td>HNC (according to HPV relationship)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated</td>
<td>20</td>
<td>3.5</td>
<td>2.2-5.5</td>
</tr>
<tr>
<td>Potentially associated</td>
<td>33</td>
<td>2.2</td>
<td>1.5-3.1</td>
</tr>
<tr>
<td>Unrelated</td>
<td>6</td>
<td>2.0</td>
<td>0.7-4.3</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>143</td>
<td>1.4</td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>10</td>
<td>1.4</td>
<td>0.7-2.7</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>11</td>
<td>1.7</td>
<td>0.8-3.0</td>
</tr>
<tr>
<td>Other</td>
<td>52</td>
<td>3.0</td>
<td>2.3-4.0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HNC, head and neck cancer; HPV, human papillomavirus; ICD-O, International Classification of Diseases for Oncology typology code; SIR, standardized incidence ratio.

DISCUSSION

This study has the advantage of a large cohort size and a long follow-up period, which enabled us to get enough statistical power to study rare cancers and accurately estimate the long-term risk of cancer subsequent to genital warts. Several hypotheses can be proposed to explain our results. A recent study of swab samples from genital wart-like lesions in 621 individuals found that 35% were infected with high-risk HPV types.[11] Co-infection with high-risk types may therefore be one of the reasons for the excess risk of cancer. In addition, immunological differences between individuals could make some individuals particularly susceptible to HPV infection and less likely to clear the infection, thereby increasing their risk of both genital warts and cancer.

Behavioral confounding may influence our results. Our findings of an increased risk of smoking-related cancers suggest a higher proportion of smokers in our cohort. Similarly, individuals who acquire genital warts may, for example, have more sexual partners relative to the general population, which in itself increases the likelihood of HPV infection and HPV-related cancer. Finally, the increased risk of cancer could be due to local immune suppression or could be a result of the inflammatory process itself.

Overall, our results confirm the link between anogenital cancer and HPV and support the suspicion that specific head and neck cancers are associated with HPV. In addition there may be a relationship between HPV and non-melanoma skin cancer, either directly or in combination with other causal factors.


Table 1. Risk of cancer after genital warts. Figures in black indicate statistically significant excess risk. Figures in grey indicate risk estimates not significantly different from the reference expected value.
## Standardized incidence ratios for selected genital cancer sites among men and women who received a diagnosis of genital warts in Denmark during 1978-2008, according to follow-up time.

**Abbreviation:**
CI, confidence interval; SIR, standardized incidence ratio.

**Table 2.** Risk of cancer after genital warts by follow-up time. Figures in black indicate statistically significant excess risk. Figures in grey indicate risk estimates not significantly different from the reference expected value.

<table>
<thead>
<tr>
<th>Follow-up time, by cancer site (years)</th>
<th>MEN</th>
<th>WOMEN</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>117</td>
<td>1.5</td>
<td>1.3-1.8</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>6</td>
<td>1.8</td>
<td>0.7-3.9</td>
</tr>
<tr>
<td>1-4</td>
<td>17</td>
<td>1.1</td>
<td>0.6-1.8</td>
</tr>
<tr>
<td>5-9</td>
<td>32</td>
<td>1.6</td>
<td>1.1-2.2</td>
</tr>
<tr>
<td>≥ 10</td>
<td>62</td>
<td>1.6</td>
<td>1.3-2.1</td>
</tr>
<tr>
<td>Vulva total</td>
<td>74</td>
<td>14.8</td>
<td>11.7-18.6</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>14</td>
<td>90.6</td>
<td>49.5-152.0</td>
</tr>
<tr>
<td>1-4</td>
<td>12</td>
<td>17.2</td>
<td>8.9-30.0</td>
</tr>
<tr>
<td>5-9</td>
<td>32</td>
<td>1.6</td>
<td>1.1-2.2</td>
</tr>
<tr>
<td>≥ 10</td>
<td>62</td>
<td>1.6</td>
<td>1.3-2.1</td>
</tr>
<tr>
<td>Vagina total</td>
<td>6</td>
<td>5.9</td>
<td>2.1-12.9</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>0</td>
<td>0.0</td>
<td>0.0-9.8</td>
</tr>
<tr>
<td>1-4</td>
<td>0</td>
<td>0.0</td>
<td>0.0-9.8</td>
</tr>
<tr>
<td>5-9</td>
<td>4</td>
<td>18.2</td>
<td>4.9-46.6</td>
</tr>
<tr>
<td>≥ 10</td>
<td>2</td>
<td>3.4</td>
<td>0.4-12.2</td>
</tr>
<tr>
<td>Penis total</td>
<td>29</td>
<td>21.5</td>
<td>14.4-30.9</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>9</td>
<td>190.2</td>
<td>53.9-777.0</td>
</tr>
<tr>
<td>1-4</td>
<td>3</td>
<td>14.7</td>
<td>3.0-42.9</td>
</tr>
<tr>
<td>5-9</td>
<td>7</td>
<td>25.6</td>
<td>10.2-52.6</td>
</tr>
<tr>
<td>≥ 10</td>
<td>10</td>
<td>12.2</td>
<td>5.8-22.4</td>
</tr>
<tr>
<td>Anus total</td>
<td>29</td>
<td>21.5</td>
<td>14.4-30.9</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>9</td>
<td>190.2</td>
<td>53.9-777.0</td>
</tr>
<tr>
<td>1-4</td>
<td>3</td>
<td>14.7</td>
<td>3.0-42.9</td>
</tr>
<tr>
<td>5-9</td>
<td>7</td>
<td>25.6</td>
<td>10.2-52.6</td>
</tr>
<tr>
<td>≥ 10</td>
<td>10</td>
<td>12.2</td>
<td>5.8-22.4</td>
</tr>
<tr>
<td>Tonsils total</td>
<td>18</td>
<td>4.6</td>
<td>2.7-7.3</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>0</td>
<td>0.0</td>
<td>0.0-31.0</td>
</tr>
<tr>
<td>1-4</td>
<td>1</td>
<td>1.9</td>
<td>0.0-10.6</td>
</tr>
<tr>
<td>5-9</td>
<td>4</td>
<td>5.7</td>
<td>1.5-14.7</td>
</tr>
<tr>
<td>≥ 10</td>
<td>13</td>
<td>5.0</td>
<td>2.7-8.6</td>
</tr>
</tbody>
</table>

**Acknowledgement:** This work, including the tables, is reproduced from the original article: Blomberg M, Friis S, Munk C, Bautz A, Kjaer SK. Genital warts and risk of cancer: a Danish study of nearly 50 000 patients with genital warts. J Infect Dis 2012; 205(10): 1544-53.

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KEYS TO THE SUCCESS OF HPV VACCINATION IN DENMARK

In Denmark the HPV vaccine has been integrated into the pre-existing and well-functioning program for childhood immunization by general practitioners and has obtained a coverage of more than 83%* for HPV3.

HPV vaccination was introduced into the Danish immunization program in October 2008, with a two-year catch-up program for three birth cohorts of adolescent girls (13-15 years old) and routine vaccination for 12 year old girls in January 2009. Vaccination is state-funded, voluntary and free of charge. The vaccine used, Gardasil®, was chosen by tender.

General Practitioners (GPs) occupy a central position in the Danish health-care system and perform all childhood vaccinations in the program, including the MMR2 vaccine at age 12 for the oldest cohorts. It was therefore a natural choice to also use this normal and trusted system for HPV vaccination. Although school-based vaccination was considered during the planning process, this would have required a major effort to set up a new organizational structure for HPV vaccination in schools (trained health workers, cold chain, side effects, monitoring, communication, etc.) instead of building on the existing system.

A health-technology assessment[1] in 2007 formed the basis for decision making, along with articles in the epidemiological bulletin EPI-NEWS[2] for health professionals. The fact that information was provided to GPs at an early stage, and before being made available to the public, was crucial as doctors are key actors and should be prepared to answer questions from both girls and their parents. A month before starting the program, an information package was sent to all GPs and school health services. Shortly thereafter a direct letter with a folder on HPV vaccination was sent to girls eligible for vaccination and their parents. The girls were identified by a unique identifying number given to everyone in Denmark at birth.

The information material was based on research into parents’ and adolescents’ knowledge of, and attitude towards, HPV vaccination, which showed little awareness of HPV infection but a positive attitude to a vaccine.

*Minimum coverage as not all vaccinations are registered.
against cancer and vaccination in general. This material contained the key message “HPV vaccination for the prevention of cervical cancer” and consisted of a poster for doctors consulting rooms and schools, a short folder with basic facts, a public website (www.stophpv.dk), short messages on web sites for teenagers, articles in magazines and press releases. More costly advertising campaigns on TV, radio or cinema were not used and did not appear to be necessary.

The media usually based their articles on this material, thus resulting in more balanced and factual information and the communication of official messages. Introduction of the vaccine benefitted from this positive media attention, which was also a result of the positive attitude and involvement from stakeholders, especially the Danish Cancer Society, the Danish Association of Obstetrics and Gynecologists and NGOs. An open and transparent dialogue with the many stakeholders and the vaccine industry was important and ensured more coherent and consistent information for the public.

Another key factor in its success was careful preparation for the reporting of adverse events and negative press based on rumors and misinformation. Concerns regarding rare and unknown side effects of the new vaccine were addressed by mandatory reporting of adverse events and safety evaluations, which were published quarterly on the website of the Danish Medicines Agency together with information from the European Medicines Agency.

As timely coincidence of the onset of any other condition or disease with vaccination was to be expected, and could be falsely attributed to vaccination, a baseline study of the incidence of autoimmune diseases such as allergy, diabetes, multiples sclerosis, Guillain-Barré etc. was undertaken using Danish registers.[3]

This preparation, and regular meetings between the National Board of Health, the Medicines Agency and the Statens Serum Institut, served as basis for a quick and coordinated response to the press whenever a rumor or public concern arose, thus maintaining public confidence.

HPV-vaccination has reached the same level of coverage as MMR2 vaccination at 12 years. However coverage fell slightly when no direct letters from national level were sent to girls eligible for vaccination after the introductory period. The challenge is to develop a renewed call and recall for vaccination appointments in all regions and to improve coverage in times with less or less positive media attention.

Promoting the health of populations demands the adoption of a perspective that encompasses societal, community, family and individual health determinants. This is particularly relevant, for example, in the case of HPV infection and related diseases, which affect highly vulnerable population groups, in order to reduce health inequalities and support equal access to cancer-screening programs. Indeed, the term “vulnerability” should not be intended merely as an ethnic-geographical profile (i.e. immigrants, refugees or marginalized populations) but should be used to define an inner condition characterized by a lack of the cultural tools needed for an appropriate consideration and awareness of individual health and disease prevention.

HPV infection and related diseases involve many anatomical areas, in both sexes and at different ages, thus representing a clear example of a complex public-health challenge that requires the implementation of interdisciplinary health-care delivery models.

HPV is the most relevant carcinogenetic virus in the human species[1] and is the causative agent responsible for cervical cancer, along with several other types of gynecological cancers (vulva, vagina), as well as anal carcinoma and head and neck cancers in both sexes. In addition, as it is sexually transmitted, the prevention and care of HPV infection and related diseases pose a complex multifaceted challenge for public health. In a recent position paper, the WHO explicitly emphasizes that “HPV-related diseases are a global public health problem” and that “the prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority”.[2]

The different expression of HPV-related diseases places complex demands on HPV teams in terms of both clinical management and the need for a successful prevention strategy, which requires a supportive community, engagement and education. Indeed, there is a “pressing social demand for the scientific, medical and public health communities” to translate correct and unbiased information concerning HPV prevention in both genders to the general population.[3,4] The combination of prevention methods that rely on the targeted use of evidence-based interventions (information/education; counseling; training of healthcare workers), which are necessary for the effective support
INCOMING PATIENTS

Need for specific clinical consultation

- Gynecology HPV-Unit
- Psychology HPV-Unit
- ENT HPV-Unit
- Proctology HPV-Unit
- Dermatology HPV-Unit
- Male STDs HPV-Unit

HPV vaccine

Diagnosis & therapy

Lab of Microbiology

Virology
Microbiology
Pathology IRE
Skin Pathology ISG

Need only for cervical HPV testing

Figure 1. Flow chart of services provided by the HPV unit. IRE: Institute Regina Elena; ISG: Institute San Gallicano.
of research and clinical trials. In this respect, although current prophylactic vaccines have been developed with the primary aim of protecting against HPV-16 and -18, the design and conduct of future clinical trials will be necessary for the clinical development of novel vaccines capable of covering a larger number of HPV types and therapeutic vaccines.[15] Comprehensive multi-sectorial teams for HPV care are formed out of necessity due to the broad range of clinical and psychosocial needs of patients, the range of individuals and families affected, and the great value of education and counseling as regards effective prevention and support.[6,7] In this regard, the services offered by the Unit in the context of the public health system provide an opportunity to promote appropriate interventions and reduce inequalities across the population in terms of prevention, diagnosis, and therapy of HPV-related diseases. As an example, in the first few months after constitution of the HPV Unit, the number of hits for a specific website concerning any kind of HPV-related question increased by almost 40%. This is of particular significance since this increase did not result from a targeted information campaign, but was rather a consequence of proposing an appropriate referral point for both physicians and the general population. The first months of operation have clearly resulted in an increase in the total number of patients visited and/or treated for HPV-related diseases, with a marked (more than 50%) increase in the number of HPV counseling sessions for couples attended by males. In this way we believe that men will become better informed regarding these diseases and will consider the possibility of getting themselves vaccinated. Thus, this approach, which encompasses all aspects of HPV infection and related diseases, as well as prevention, appears most appropriate as regards responding to the needs of the population.

We anticipate that those systems that successfully implement interdisciplinary collaboration will be ahead of the curve in providing high-quality care with a more favorable cost/efficacy ratio for public health systems, improving health education and, in the meantime, setting the stage for the development of clinical and basic research in critical medical and social areas.

Competing interests:
The authors declare that they have no competing interests.

Authors’ contributions:
LM, AV and FE all conceived the project, participated in its design and coordination and drafted the manuscript. All authors read and approved the final manuscript.

Authors’ information:
LM is Coordinator of the HPV UNIT. AV is Coordinator of the HPV UNIT and Acting Head of the Virology Laboratory. FE is Head of the Pathology and Microbiology Laboratory.

Composition of HPV-UNIT:
- **Regina Elena National Cancer Institute**
- **San Gallicano Dermatological Institute**

THE ABBOTT RealTime HIGH RISK HPV TEST: 
A REVIEW OF VALIDATION STUDIES

The Abbott RealTime High Risk HPV test (RealTime) (Abbott GmbH & Co. KG, Wiesbaden, Germany) is a next-generation real-time polymerase chain reaction (PCR) based assay for concurrent individual genotyping of HPV-16 and HPV-18 and pooled detection of 12 other “high-risk” HPV (hrHPV) genotypes. The assay has an internal control based on a housekeeping gene (136-bp region of human beta-globin) and a proprietary algorithm for amplification curve validation (Figure 1).

RealTime was launched on the European market in January 2009 and is currently used in many laboratories worldwide for routine detection of hrHPV. The test is performed on the m2000rt real-time PCR instrument using a modified GP5+/GP6+ primer mix consisting of three forward and two reverse primers.[1]

The test is configured so that it uses four channels for concurrent detection as follows:

- **Channel 1:** HPV-16.
- **Channel 2:** HPV-18.
- **Channel 3:** 12 pooled hrHPV types (-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68).
- **Channel 4:** A separate beta-globin control to ensure specimen adequacy.

The assay turnaround time is 6-8 h for 96 samples, depending on the method used for DNA extraction. The highly automated high-throughput m2000sp instrument or smaller m24sp instrument, can be used for DNA

![Figure 1. Example of the result of the Abbott RealTime High Risk HPV test in a cervical sample in which both HPV-16 and HPV-18 were detected. The assay uses four channels for the detection of fluorescent signals, one for the detection of an internal process control for sample adequacy and DNA extraction and amplification, a second for the detection of HPV-16, a third for the detection of HPV-18, and a fourth for the aggregate detection of the 12 HPV types. The assay’s clinically validated threshold is set at a fixed cycle threshold (Ct) value of 32. Positive result for HPV-16 is visible as orange curve (positive in cycle number 14.37) and positive result for HPV-18 as green curve (positive in cycle number 13.45). Internal process control based on amplification of housekeeping beta-globin gene gave positive signal in cycle number 19.51 (red curve). Result for the aggregate detection of the 12 HPV types is negative (no specific curve present).](image-url)
extraction or, alternatively, DNA can be prepared manually. The assay is officially validated for use with cervical specimens collected using ThinPrep PreservCyt Solution, SurePath Preservative Fluid (both original and post-gradient sample) and the Abbott Cervi-Collect Specimen Collection Kit; however, cervical specimens collected in Digene Specimen Transport Media (STM) are also appropriate. In addition to cervical specimens, RealTime can reliably detect and identify targeted HPVs in fresh tissue, fresh-frozen tissue and in tissue fixed with formalin and subsequently embedded in paraffin or paraplast.[2-6]

**ANALYTICAL VALIDATION STUDIES**

Probit analysis showed that the analytical sensitivity of RealTime is between 500 and 5000 copies of HPV DNA per assay, depending on the HPV type.[1] An analytical specificity study on a panel of 41 bacteria, viruses and fungi that can be found in the female anogenital tract revealed no cross-reactivity with any of the organisms tested, including all relevant low-risk HPV genotypes.[1] The high analytical specificity of RealTime and its lack of cross-reactivity with non-targeted HPV genotypes has been confirmed in all studies performed to date, which have focused on both, the clinical and analytical performance of RealTime.[2,7-13]

Interference or PCR-inhibition was not observed with any of the substances (blood, mucus etc.) that may be present in cervical specimens tested.[1]

**VALIDATION OF RealTime SENSITIVITY FOR CIN3 AND CERVICAL CANCER**

The clinical sensitivity of the RealTime test was initially evaluated in 593 archived cervical specimens from Amsterdam (The Netherlands) and the presence of hr-HPV was detected in 97.2% (246/253) and 98.5% (335/340) of CIN3 and cervical cancer specimens, respectively.[14] Eight of the 12 hr-HPV-negative specimens evaluated further had invalid beta-globin results in the Roche Linear Array HPV Genotyping Test and four contained only low-risk HPVs. In a Slovenian study, HPV was detected by RealTime in 96.4% (245/254) and 98.8% (84/85) of cases of CIN3 and cervical cancer containing targeted hr-HPVs, respectively.[25] As described below, the high sensitivity of RealTime for CIN3+ lesions, including cervical cancer, has been confirmed in further validation studies in referral population and primary cervical cancer screening settings.

**CLINICAL VALIDATION OF RealTime IN A REFERRAL POPULATION SETTING**

The clinical performance of RealTime in a referral population setting has been evaluated in several studies. [9-11,15-19] The results of the most important studies with clinical endpoints are presented in Figures 2 and 3. Although these studies differed significantly as regards the composition of the referral population for colposcopy (the majority using women with abnormal

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**Figure 2.** Absolute clinical sensitivity and clinical specificity of the Abbott RealTime High Risk HPV test for CIN2+ (with 95% confidence intervals when available) established in eight studies which evaluated RealTime performance in referral settings and in four studies which evaluated RealTime performance in primary cervical cancer screening in women aged 30 years and older. Whenever appropriate the relevant parameters have been recalculated from the original papers by the author.
Clinical sensitivity and clinical specificity of the Abbott RealTime High Risk HPV test for CIN2+ relative to performance characteristics of clinically validated tests HC2 and GP5+/6+ PCR. Values were established in eight comparative studies which evaluated RealTime performance in referral settings in comparison to HC2 and in four studies which evaluated RealTime performance in primary cervical cancer screening in women aged 30 years and older in comparison to HC2 or GP5+/6+ PCR. RealTime values below 1.00 favorite comparator, values above 1.00 favorite RealTime.

<table>
<thead>
<tr>
<th>Study</th>
<th>Referral Setting</th>
<th>RealTime Relative Sensitivity</th>
<th>RealTime Relative Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang S et al. [15]</td>
<td>Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halfon P et al. [9]</td>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuzick J et al. [16]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Halfon P et al. [17]</td>
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<tr>
<td>Wong OGW et al. [18]</td>
<td></td>
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<tr>
<td>Venturoli S et al. [10]</td>
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<tr>
<td>Szarewski A et al. [19]</td>
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<tr>
<td>Jentschke M et al. [11]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Carozzi FM et al. [6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poljak M et al. [7]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hesselink AT et al. [22]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuzick J et al. [24]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Clinical sensitivity and clinical specificity of the Abbott RealTime High Risk HPV test for CIN2+ relative to performance characteristics of clinically validated tests HC2 and GP5+/6+ PCR. Values were established in eight comparative studies which evaluated RealTime performance in referral settings in comparison to HC2 and in four studies which evaluated RealTime performance in primary cervical cancer screening in women aged 30 years and older in comparison to HC2 or GP5+/6+ PCR. RealTime values below 1.00 favorite comparator, values above 1.00 favorite RealTime.

**Clinical validation of RealTime for use in primary cervical cancer screening in women aged 30 years and older**

RealTime has been clinically validated for use in primary cervical cancer and pre-cancer screening in women aged 30 years and older in four studies (Figures 2 and 3, Table 1).[7,8,22,24] A Slovenian study prospectively evaluated RealTime in comparison with HC2 in 3129 women.[7] Italian[8] and Dutch[22] studies evaluated RealTime following the “Guidelines for HPV DNA test requirements for primary cervical cancer screening in women 30 years and older”[23] in comparison with HC2 and GP5+/6+, on retrospective samples collected from 949 (68 cases, 881 controls) and 927 (68 cases, 859 controls) women, respectively. RealTime fulfilled the cross-sectional clinical equivalence criteria of the international consensus guidelines in all three studies,[23] indicating that RealTime can be considered as clinically validated assay for cervical cancer screening purposes. RealTime also performed well in a multi-HPV assay comparison study [Predictors 3], being among HPV assays with the highest clinical sensitivity for cervical high-grade disease in women aged 30 years and older and showed comparable clinical specificity with other clinically validated HPV DNA assays.[24] This was further confirmed in a recent meta-analysis[21] in which RealTime was listed as one of four currently available commercial HPV assays that can be considered to be clinically
THE ABBOTT RealTime HIGH RISK HPV TEST: A REVIEW OF VALIDATION STUDIES

HPV IN SCREENING AND TRIAGE

validated for use in primary screening.

VALIDATION OF RealTime INTRA-LABORATORY REPRODUCIBILITY AND INTER-LABORATORY AGREEMENT

Intra-laboratory reproducibility and inter-laboratory agreement of RealTime have been extensively validated following the “Guidelines for HPV DNA test requirements for primary cervical cancer screening in women 30 years and older”[25] in three and two studies, respectively.[7,8,22] As shown in Table 1, both intra-laboratory reproducibility and inter-laboratory agreement of RealTime were well above confidence bounds in all studies (>87%, with kappa values >0.5) thereby confirming the exceptional reproducibility and reliability of RealTime for the detection of targeted hrHPV, even in samples stored for more than 3 years.

Table 1. Validation of intra-laboratory reproducibility and inter-laboratory agreement of Abbott RealTime High Risk HPV test.

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Type of study</th>
<th>Number of samples</th>
<th>RealTime overall reproducibility (95% CI)</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carozzi FM et al[8]</td>
<td>Intra-laboratory reproducibility</td>
<td>521</td>
<td>98.5% (97-99)</td>
<td>0.97 (0.95-0.99)</td>
</tr>
<tr>
<td>Poljak M et al[7]</td>
<td>Intra-laboratory reproducibility</td>
<td>500</td>
<td>100.0% (99-100)</td>
<td>1.00 (0.90-1.00)</td>
</tr>
<tr>
<td>Poljak M et al[7]</td>
<td>Inter-laboratory agreement (first round)</td>
<td>500</td>
<td>100.0% (99-100)</td>
<td>1.0 (0.98-1.0)</td>
</tr>
<tr>
<td>Poljak M et al[7]</td>
<td>Inter-laboratory agreement (second round)</td>
<td>500</td>
<td>99.8% (98.7-99.9)</td>
<td>0.99 (0.98-1.0)</td>
</tr>
<tr>
<td>Hesselink AT et al[22]</td>
<td>Intra-laboratory reproducibility</td>
<td>504</td>
<td>98.4% (97.2-99.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hesselink AT et al[22]</td>
<td>Inter-laboratory agreement</td>
<td>500</td>
<td>99.8% (99.1-99.9)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

CONCLUSION

RealTime has been extensively evaluated over the past 4 years and can be considered to be clinically validated for triage in referral population settings and for use in primary cervical cancer screening in women aged 30 years and older.

References:
What are the most important findings of your study regarding self-sampling for HPV DNA testing?
The most significant findings of our pooled analysis are that self-sampling HPV DNA testing is more sensitive and less specific than VIA and liquid-based cytology, and that the sensitivity and specificity are in moderate agreement with those of physician-sampled HPV testing in a total of 13,140 rural Chinese women aged 17-56 years across four regions in China, we observed that self-sampling HPV DNA testing based on HC2 had 86.2% sensitivity and 80.7% specificity for detecting cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN 2+), and 86.1% sensitivity and 79.5% specificity for detecting CIN grade 3 or worse (CIN3+) lesions.

Our results in China indicate that samples for HPV DNA testing can be successfully obtained by women themselves and self-sampling can be a fairly reliable method for cervical cancer screening. Furthermore, according to the latest guidelines released by the U.S. Preventive Services Task Force and the American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology, co-testing with cytology and HPV DNA testing every five years is recommended for women aged 30 to 65 years old. In line with this recommendation, self-sampling HPV DNA testing, with its potential advantages, may facilitate cervical cancer screening at larger intervals and with wider coverage, if women’s interest in, and willingness to perform, self-sampling can be ensured and education regarding self-sampling procedures is provided.

ACCURACY OF SELF-SAMPLING HC2 HPV DNA TESTING COMPARED TO PHYSICIAN-SAMPLING HC2 HPV DNA TESTING, LBC AND VIA FOR CIN2+ AND CIN3+ (HPV DNA POSITIVITY: RLU/CO ≥1 PG/ML)

<table>
<thead>
<tr>
<th>Screening methods</th>
<th>CIN2+</th>
<th>CIN3+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>Self-HPV</td>
<td>86.2</td>
<td>80.7</td>
</tr>
<tr>
<td>Physician-HPV</td>
<td>97.0 (P &lt;0.001)*</td>
<td>82.7 (P &lt;0.001)*</td>
</tr>
<tr>
<td>LBC</td>
<td>80.7 (P =0.015)*</td>
<td>94.0 (P &lt;0.001)*</td>
</tr>
<tr>
<td>VIA</td>
<td>50.3 (P &lt;0.001)*</td>
<td>87.4 (P &lt;0.001)*</td>
</tr>
</tbody>
</table>

CIN2+: cervical intraepithelial neoplasia grade 2 or more severe; CIN3+: cervical intraepithelial neoplasia grade 3 or more severe; HC2: Hybrid Capture 2; HPV: human papillomavirus; LBC: liquid-based cytology; RLU/CO: relative light units per cutoff; VIA: visual inspection with acetic acid.

* Compared to Self-HPV.

Table 1. Results in the pooled analysis of data from five population-based cervical cancer screening studies, including a total of 13,140 rural Chinese women aged 17-56 years in China. Self-sampling and HPV testing based on HC2 had 86.2% sensitivity and 80.7% specificity for detecting CIN2+, and 86.1% sensitivity and 79.5% specificity for detecting CIN3+. The sensitivity of self-HPV testing compared favorably with that of LBC and was superior to the sensitivity of VIA. Self-HPV testing may complement current screening programs by increasing population coverage in settings that do not have easy access to comprehensive cytology-based screening.

Source: Adapted from Zhao FH et al., JNCI. 2012; 104(3):178-188. Reproduced with permission from Oxford University Press.
What are the downsides of existing screening options in developing countries?

There are some apparent downsides of existing screening options in developing countries. Cytology-based screening programs generally fail to achieve the expected positive impact on women’s health in most developing countries due to dysfunctional health-care infrastructures and scarce health-care resources. The success of the whole program relies heavily on capacity building for relevant health-care professionals such as cytologists, gynecologists, pathologists and even program managers. In low-resource settings, creating this infrastructure can be prohibitively difficult. Visual tests such as visual inspection with acetic acid (VIA) or Lugol’s iodine (VILI), with sensitivity for cervical cancer precursors comparable to that of cytology, have been suggested for use with simple equipment and relatively easy training, and at lower cost. However, a limitation for their use is that they are unreliable in postmenopausal women because of changes in the transformation zone of the cervix. In addition, they are inherently subjective and differences in training of personnel and in the light sources used also generate variability in test performance.

Although HPV DNA testing performs well when compared with other screening tests, the technical, financial, and logistic requirements are far beyond the capacity of many developing countries.

The current commercial HPV DNA testing kits are generally expensive and involve demanding technologies and sophisticated procedures that potentially restrict their use to well-equipped regional hospitals. Moreover, as cervical specimens are conventionally collected by health-care providers, screening coverage is apparently subject to the lack of health-care professionals in places where infrastructure is not readily available. How to obtain appropriate cervical specimens thus becomes an obstacle to using HPV DNA testing in low-resource settings.

What are the advantages of self-sampling HPV DNA testing over other screening options?

Our experience to date in low-resource settings suggest that certain restrictions and potential challenges have limited the applicability of current cytology, VIA/VILI and physician-sampled HPV DNA testing.

Self-sampling HPV DNA has certain advantages compared to these screening methods. Thus, it does not require a speculum examination, health-care providers or a visit to a clinic; women can self-collect specimen at home or any place of convenience. They do not need to travel far to a health facility or wait to see a health-care provider. Samples from self-collection can be delivered by post to a regional hospital or laboratory for testing. It is therefore a less expensive and non-invasive sample-collection procedure. It also respects individual privacy, thus meaning that women who might otherwise be reluctant to participate may be encouraged to undergo cervical cancer screening. This appears especially important for ethnic groups with particular beliefs and people with particular religious faith. All these potential advantages support the possible application of self-sampling in low-resource settings.

What is the significance of your findings for China and other developing countries?

Self-sampling HPV DNA testing may potentially increase the participation of women in cervical cancer screening programs. Self-collected samples can be more easily obtained than in the conventional approach.
led by health-care providers in settings with limited resources or in difficult-to-reach populations. With marked unbalanced development, China has a large poverty-stricken population in rural areas where primary health-care services are basically inaccessible. The currently available free government-sponsored cervical cancer screening program proposed by the All-China Women’s Federation, which was launched in 2009, has to date only covered around 10 million rural women aged between 35 and 59 years. At the current rate, it would take about another 40 years to screen all 142 million women in this age range by Pap smear or VIA once. China cannot wait to pay the high price for such an avoidable delay. If properly managed, self-sampling HPV DNA testing could serve to expand the coverage of screening and participation by rural women without sacrificing overall effectiveness. If screening programs were to be rolled out on a larger scale in the near future, this technique could replace or at least complement conventional Pap smear or VIA to meet the urgent needs of women in China’s vast rural areas. This also offers substantial implications for screening programs in developing countries or low-resource areas where cultural and program barriers may limit the acceptance of standardized gynecological procedures among women.

**How do you envisage the utility of self-sampling HPV DNA testing in developing countries or low-resource settings in the future?**

Self-sampling HPV DNA testing may provide the most viable primary screening option to maximize the coverage and effectiveness of screening programs in low-resource settings. In these settings, although not specific enough to be a stand-alone test, it may serve as a primary screening test that can be followed by the more specific tests such as cytology or HPV genotyping reserved for women who have tested positive by self-HPV testing and require further close monitoring. Since progression from persistent HPV infection to invasive cancer is estimated to take up to 10-15 years, this test can be performed every five or even ten years as a primary screening method in low-resource settings. Infrastructure support, such as a regional hospital or laboratory network for HPV DNA testing, and a customized postal service for sample delivery, needs to be in place to support the screening initiatives. We anticipate that targeting women aged 30 years or older with self-sampling HPV DNA testing even only once in their lifetime may achieve great public-health benefits in developing countries like China.

References:
TWO DOSES OF HPV VACCINE TO PRE-ADOLESCENTS – THE RECOMMENDATION OF THE QUEBEC ADVISORY IMMUNIZATION COMMITTEE

Although the history of HPV vaccines is relatively short, enormous progress has been made in terms of both our understanding of, and clinical experience with, these vaccines.

Pre-licensure clinical trials were conducted mainly in females aged 16-26 years. The choice of this study population was based on several criteria, including pertinence, equity and feasibility. Although different antigen dosing were tested in these trials, the vaccination schedules evaluated were almost exclusively 0, 1-2 and 6 months. This schedule has proven to be optimal when protection is required as soon as possible after initial vaccination and when two doses of vaccine are needed to ensure optimal priming. Notably, this is the case for many infant vaccine-preventable diseases.

Unlike early childhood infections, the risk of HPV infection is related to the debut of sexual activities. Such a pattern of infection allows the best timing and vaccine administration schedule to be chosen.

The main goals of HPV immunization programs are as follows:
1. to ensure maximal protection during the period of highest risk
2. to ensure the most robust immune response possible in order to protect for a longer period of time
3. to offer the vaccine to an age group and within an immunization program that will allow for optimal vaccine uptake, thus ensuring maximal impact on disease burden.

Pre-adolescents and adolescents best fill the above criteria, and are therefore of high priority for HPV vaccination.

Despite the above, no randomized placebo-controlled clinical efficacy trial was conducted in 9-15 year-olds. Thus, the approval of clinical use of HPV vaccines for those under the age of 16 was based exclusively on bridging immunogenicity studies.

In 2007, the Comité sur l’immunisation du Québec (CIQ) recommended an extended schedule (0, 6, 60 months) for immunization against HPV, starting in grade 4. The committee further stated that the third dose should be administered “if judged necessary.” The objective of an extended schedule was to ensure adequate protection of the highest possible number of women through the most effective use of available resources.

Since introduction of the HPV immunization program in Quebec in 2008, similar programs have been introduced in Mexico and British Columbia with the subsequent option of considering the need for a third dose. In 2012, Switzerland introduced a two-dose vaccination schedule. During the same period, studies on the impact of alternative vaccination schedules focusing on both immunogenicity and effectiveness were published or presented at scientific conferences.

In 2012-2013, the CIQ mandated an HPV task force to revise the existing data on alternative vaccination schedules for HPV vaccines. The objective was to assess available data that would inform recommendations regarding the pertinence of the third dose of HPV vaccine 60 months after primary vaccination at the age of 9-10 years according to a 0-6 months schedule. The recommendation was needed before girls immunized during the first year of the public program (2008) arrived in Grade 9 (Fall 2013). The theoretical framework put forward by Erickson et al., was used when summarizing the key data available.

* Deceased at time of publication of this paper.
Immunogenicity data for available HPV vaccines show that the immune response measured in pre-adolescents (9-13 years) who received two doses six months apart is not inferior (in fact it is generally superior) to that obtained in individuals aged 16 years or more vaccinated with three doses of vaccine – a group for which excellent efficacy data has been observed for at least 10 years.

In girls aged 9-13 years, antibody levels one month after the administration of two doses (0, 6 months) or three doses (0, 2, 6 months) are comparable for all four HPV vaccine types. Thirty-six months later, levels are still comparable for types 16 and 11. For types 18 and 6, however, observed antibody levels are lower in girls who received two doses than in girls of the same age group (9-13 years) who received three doses according to a 0-2-6 month schedule. However, their antibody levels remain higher than those of women aged 16-23 who received three doses. Preliminary Quebec data on girls aged 9-10 years indicate that the first dose of quadrivalent vaccine produces detectable antibodies in 93-100% of girls, depending on the HPV type. The data also indicate that the second dose increases antibody levels considerably. Indeed, a 56–109-fold increase of geometric mean titers (GMTs) was observed one month post-second dose when compared to pre-second dose GMTs. Such an increase indicates an anamnestic response. The data also indicate that GMTs are only slightly higher one month post-third dose than one month post-second dose (Figure 1).

HPV vaccines administered to girls aged 9-10 are well tolerated. However, a two-dose schedule would likely generate fewer adverse events than a three-dose schedule.

An evaluation of the cost-effectiveness ratio of different two- and three-dose immunization strategies, including the immunization of boys, was also carried out. According to mathematical modeling predictions by Marc Brisson and colleagues, immunizing girls with a two-dose schedule is a highly cost-effective strategy. According to the same mathematical model, immunizing both girls and boys using two or three doses is highly unlikely to be a cost-effective alternative to vaccinating girls only, at the current vaccine price. However, introducing a publicly funded program to immunize all boys could be justified on the basis of political considerations or the principle of ensuring equity, particularly for men who have sex with men (MSM).

The high vaccination coverage (75-80%) achieved in Quebec in routine and catch-up programs where the vaccine is offered free of charge to girls up to the age of 18 is contributing to create a herd immunity. If a minority of vaccinated individuals were to lose their immunity over time, they would remain protected indirectly. Cervical cancer screening activities also provide an additional safety net, at least in terms of preventing this specific health problem.

After evaluating the available scientific data and consulting with experts, the members of the CIQ have recommended by consensus not to provide a booster dose to grade 9 girls who received two doses of vaccine in grade 4.

This recommendation is conditional upon the implementation of effective mechanisms to monitor the epidemiology of HPV, and to detect any sign that might question the reasons for this decision in a timely fashion.
The DH made a strong recommendation to the NHS/PCTs (as stated by JCVI) that the HPV programme should be delivered in schools.

Funding for the programme was based on costs of school delivery, and uptake data are collected monthly and annually based on school year (from September to August). In 2010/11 all but two PCTs delivered the programme in schools (DH, 2012).

The JCVI recommendation stressed that the aim of the programme was to provide protection against cervical cancer, and hence the vaccine to be used would be primarily determined by cost effectiveness, which was highly dependent on the negotiated cost of the vaccines (JCVI, 2008). Following a competitive tendering process at the DH the vaccine purchased nationally for use in the programme was Cervarix® (Glaxo Smith Kline), which protects against HPV types 16 and 18.

This vaccine was supplied “free” to PCT Providers throughout 2008/09, 2009/10, 2010/11 and 2011/12. The competitive tendering process was repeated in 2008/9 2009/10 2010/11 2011/12.

**Figure 1.** Percentage uptake of all 3 doses of HPV vaccine by year among 12-13 year old school girls within Dudley, West Midlands and England, 2008/09-2011/12.

Source: Inform, DH
2011 (DH, 2011) and the Department of Health (DH) will be providing the human papillomavirus (HPV) vaccine Gardasil® (Sanofi Pasteur MSD) for the national HPV immunisation programme (2012/13) for girls in school year 8 (aged 12 to 13 years) from September 2012. This vaccine protects against HPV types 6, 11, 16 and 18.

LOCAL PROGRAMME DELIVERY

Dudley Primary Care Trust was based in the West Midlands, England and served a population of approximately 305,000. There was an Immunisation Co-ordinator post in the Public Health Directorate. The post holder had responsibility for ensuring all the national immunisation programmes were available for the Dudley PCT responsible population. This included planning for, monitoring delivery of, and submitting uptake data for all the programmes, including HPV immunisation.

Planning for the HPV immunisation programme started at local level in 2007. Close collaboration with the School Health Advisors (SHAs), also known as “School Nurses” and Commissioning colleagues consisted of monthly meetings to discuss delivery options, plan contractual content and engage other stakeholders. These Working Group meetings continued, although less frequently, through the first and second years of the programme. Occasional meetings were held each year to review processes and discuss any changes or problems.

During the planning stage the Immunisation Co-ordinator discussed the proposed programme with the Dudley Head Teachers’ Forum, General Practice representatives and School Health teams. These discussions produced some excellent suggestions for improving the delivery and measurement of performance, and ensured all providers felt engaged, as stakeholders, in the programme.

In Dudley the SHAs work in five teams across the borough and each secondary school has a dedicated school nurse. The teams also have secretarial/administrative support, which is a vital component of the programme success.

The secondary schools in Dudley primarily provide education up to the age of 15-16 years only. Pupils aged 16-17 and 17-18 years access further education via “Sixth Form Colleges”. The SHAs were not contracted to provide health services to these colleges. As a result, Dudley PCT decided to commission primary care General Practitioners (family doctors) to offer the immunisation programme to these older girls, under the arrangements of the “catch-up” programme. Although the catch-up programme and uptake among these groups will not be discussed in any detail here, it is worth noting that uptake in these older girls was not as high as among the routine cohort (12-13 year olds) (DH, 2012).
A national HPV immunisation communications programme in 2008 was highly professional and wide reaching. Nationally produced communication materials were used at local level and some local advertising used the national text to ensure consistency of message.

ELEMENTS FOR SUCCESS

- A dedicated working group for planning that was maintained during the first year of the programme.
- A detailed Contract Specification for the expected programme delivery from the SHAs which included requirements to follow-up every eligible girl until she was immunised or refused immunisation, and to submit data on every girl eligible and the outcome for that girl with regard to HPV immunisation.
- Dedicated funding provided by the DH to support the extra resources required for this new school-based programme.
- Nationally funded and supplied vaccines, with easy ordering and delivery systems.
- Early engagement of the secondary school head teachers, adopting their suggestions for smooth delivery of the vaccines during the school day.
- Education sessions covering HPV disease, vaccine, and Dudley delivery model open to all providers but particularly targeted at primary care general practice staff and school health staff.

RESULTS

Dudley performed exceptionally well compared to the national average uptake during the first four years of the programme (Figure 1) and obtained one of the highest uptakes for three doses in England in 2008/09 (DH, 2010). The attrition between the first and third doses of the vaccine was remarkably low (Figure 2). During the second year of the programme (2009/10) a young girl died within hours of receiving her HPV vaccine in a neighbouring area (The Guardian, 2009). The news announcement was released the morning that Dudley was due to commence the school programme. Unexpectedly this resulted in loss of confidence in the vaccine and many schools and parents withdraw from the programme. Within days the cause of this young girl’s death revealed no link with vaccine (The Guardian, 2009) but this failed to restore confidence among the cohort offered vaccination that year. Despite this, Dudley still managed a better uptake than the average for England as a whole and the West Midlands.

The third and fourth years of the programme saw a return of confidence in the vaccine and uptake was again higher in Dudley than nationally, although down a little on the first year. Reinvigoration of the marketing and public health messages at a national level are ensuring this programme remains one of the most successful HPV programmes worldwide.

References:

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To communicate recent advances in the HPV field and the novel options afforded by HPV screening technologies and HPV vaccines in appropriate formats, it is necessary that tens of thousands of health professionals acquire the information and communicate to literally millions of families worldwide. This is difficult to achieve using only conventional strategies. Distance learning has proven to be an appropriate tool for disseminating information. The ICO/FIGO/UICC/IEAE/IARC course on cervical cancer epidemiology and control has been operational since 2011, is available in five languages and has graduated over 9,600 participants. A total of 34 tutors have been qualified and are able to offer and tutor the course to their colleagues, students or working parties. The course is expanding following the natural interest of professionals willing to receive and pass information on to additional professional groups. The course is offered free of charge to participants thanks to unrestricted public and private educational grants administered by the program e-oncologia at ICO. Information and registration available at www.e-oncologia.org and courseccp@iconcologia.net
THE HPV VACCINE MARCH, RIO DE JANEIRO 2013

Mauro Romero Leal Passos
Doctor, Associate Professor and Head of the STD Department, Fluminense Federal University

Rio de Janeiro, and indeed Brazil as a whole, is currently experiencing a serious STI epidemic (syphilis, congenital syphilis, chlamydia, HPV). As vaccines against HPV have been available since 2006, politicians in Rio de Janeiro have recently proposed a specific law making HPV vaccination compulsory. Press agencies, the scientific community and the general population are fully supportive of this bill. However, the government did not approve the HPV vaccine. As such, we held a Pro-Vaccine March, on May 19, on the sidewalk of Copacabana beach. This was a peaceful demonstration that aimed to convince the government of the urgent need to offer HPV vaccination for adolescents of both sexes. After the march we distributed educational materials such as a DVD of the short film: Larah's Show, “HPV What’s That Bug?”, available in You Tube.

Two weeks later, Brazil was brought to a halt by a huge wave of popular demonstrations with varying demands, ranging from better public transport to better conditions for education and health.

One month after the Pro-Vaccine March, the Federal Government announced that it will launch a comprehensive HPV information campaign and begin to administer HPV vaccine to girls aged 10 and 11 years early in 2014. The aim of this program is to achieve a coverage of 80%, for a total of 3.3 million girls. On this occasion, doctors left their comfort zone and went out onto the streets to fight for one of the basic tenets of public health, namely disease prevention.

Some people claim that the Pro-Vaccine March may have been one of the triggers that sparked the subsequent wider ranging demonstrations of dissatisfaction with Brazilian public administrations as this was something that had never occurred before in Brazil: a popular demonstration demanding a specific vaccine.

Figure 1: Health professionals and the general population, including many children, taking part in the Pro-Vaccine March on Copacabana Beach, Rio de Janeiro (19 May 2013).
KEY PUBLICATIONS

COMPREHENSIVE CONTROL OF HPV INFECTIONS AND RELATED DISEASES: THE ICO/VACCINE MONOGRAPH PROGRAM

The Institut Catala d’Oncologia (ICO) Information Centre on HPV and Cancer and Elsevier have published in 2012 and 2013 six monographs of its series on HPV and disease prevention. These monographs include an update of the general chapters describing scientific advances in the field (Vaccine, 2012 Vol. 30, Suppl. 5), a special report on the statistics of HPV and cancer prevention for the GAVI countries (Vaccine, 2012 Vol. 30, Suppl. 4), and four regional reports covering epidemiology and prevention strategies in the regions of Sub-Saharan Africa (Vaccine, 2013, Vol. 31, Suppl.5), Extended Middle East and Northern Africa (EMENA) (Vaccine, 2013, Vol. 31, Suppl.6), Central and Eastern Europe and Central Asia (Vaccine, 2013, Vol. 31, Suppl.7) and Israel (Vaccine, 2013, Vol. 31, Suppl.6).

The general monograph is structured into 19 chapters and has involved 101 key experts on the field serving as authors or editors. This monograph offers an updated review on the biology, immunology and natural history of HPV, therapy of HPV-related diseases, HPV vaccine introduction and trial results, screening strategies and evidence regarding HPV tests, modelling preventive strategies in developed countries, the biological interaction between HIV and HPV, and public health programs for HPV prevention and control in the developing world.

The regional reports offer specific details on the epidemiology and prevention strategies for each region, and provide recommendations for the control of cervical cancer and other HPV-related diseases in the region.

The monographs can be obtained through the publisher at Elsevier (G.Rodgers@elsevier.com) and are online accessible at http://www.journals.elsevier.com/vaccine. Institutions from countries included in the WHO HINARI Access to Research program (http://www.who.int/hinari/en/) can access the monographs free of charge or at a low cost under an agreement set up between WHO and major publishers.

The ICO Vaccine monograph series was initiated in 2006 and includes a grand total of 11 Monographs, over 450 authors, reviewers and editors have contributed data and interpretation. The series up to 2012 has generated over 200,000 full text downloads and over 10,000 printed copies have been distributed. The Latin American report is also available in Spanish and the Asia Pacific report is available in Chinese and Japanese. The EMENA report will be available in French and the Eastern European report will also be translated into Russian in 2013/4.

The ICO Monograph program was initiated thanks to a grant by the Bill & Melinda Gates Fund to a consortium of institutions (PATH, IARC, WHO, Harvard University and ICO) devoted to the prevention of HPV related cancers. The essential contents and the most practical aspects of the monographs have been summarized in a distance learning project freely accessible in five languages that has completed over 9000 students worldwide (www.e-oncologia.org and courseccp@iconologia.net)

The editors wish to thank Elsevier and the rest of the sponsors that made the project sustainable. They thank also the authors and reviewers that generously contributed to this effort and to the staff at the ICO HPV Information Centre (www.hpvcentre.net) that provided the editorial workforce and the enthusiasm to conduct the project over an extended period of time.

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www.hpvtoday.com
BACKGROUND
The HPV-16/18 vaccines will decrease the positive predictive value of screening. Countries with well-established cytological screening programs therefore need to reassess them to ensure on-going and effective screening results in the vaccinated population.

THE ICELANDIC SCREENING EXPERIENCE
After the start of cytological screening in Iceland in June 1964, both the incidence and mortality rates of cervical cancer decreased significantly (Figure 1). However, the incidence increased again temporarily after 1980, mainly among younger women, and the mortality rate leveled out. Evaluation of the screening program[1,2] showed an increased rate of moderate to high-grade pre-invasive disease and a low regular attendance in the target age group of 25-69 years.

The screening program was reorganized to include a computerized call-and-recall system, together with intensified re-screening at two-year intervals and follow-up of women with abnormal screening results. Due to the increased rates of pre-invasive disease from age 20 onwards, the lower age limit was decreased from 25 to 20 years in 1988,[2] which resulted in a leveling out of these rates at age 25-29 and a decrease after age 30.[3,4] Analysis of the cumulative incidence of pre-invasive lesions at a fixed risk level showed that the number of earlier normal visits did not lead to a decision to prolong screening intervals until after age 35, thus supporting a 2-3 year screening interval before this age.[5-7]

Subsequent analysis of cervical cancer incidence rates after 1980 confirmed that the age-specific incidence remained significantly higher in women under age 35, but had decreased significantly after age 40.

The increased incidence below age 35 was due to an increased rate of squamous cell carcinoma and adenocarcinoma diagnosed at an early stage, whereas the rate of more advanced disease (stage IIA+) had decreased significantly in all age groups. The incidence of microinvasive disease (stage IA) at age 20-54 had increased at a significantly higher rate than stage IB disease, and the cumulative incidence of stage IA disease had already started to increase within three years after the last normal smear.[4,5]

Since 1980, changes to the screening program have resulted in a 90% lower mortality rate (9.5/100.000 in 1966-1970 vs. 0.9/100.000 in 2006-2010), with 48% of the invasive cases in the period 2006-2010 being diagnosed at stage IA.
IMPLICATIONS OF HPV-16/18 VACCINES

As many as 18 HPV types are classified as oncogenic, of which HPV-16/18 are found in approximately 70% of cervical cancer cases.[7] These oncogenic types are thought to act independently and to imply a statistically similar risk of developing cervical cancer.[8] Despite this, the natural history of the different HPV types and the determinants of immune response remain unclear.

In Iceland, the estimated impact of currently available HPV vaccines on the screening program is based on the results of two studies. The first of these was a population-based study concerning the distribution of 12 oncogenic HPV types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58 and -59). The study material covered 80% of CIN 2-3 cases diagnosed in Iceland in 1990 and 1999 (441 cases) and 99% of cancer cases diagnosed in the periods 1990-1994 and 1999-2003 (141 cases).[9] The second study was based on the Icelandic arm of Merck’s Phase III trial, the Future II study, which enrolled 12,167 women aged 15-26 and which included 710 women from Iceland aged 18-23.[10]

The Icelandic studies[9,10,11] indicated that HPV-16/18 vaccination at age 12 can decrease the incidence of invasive disease by 67% and the prevalence of CIN 2-3 by 53% after taking into consideration a reported 32.5% cross-protection in HPV-naive women.[12] The studies show that decisions on the age of catch-up vaccination should take into account the sexual practices in these populations.

Furthermore, the Icelandic studies show that, in women below the age of 25, the proportion of disease due to HPV types 16/18 was significantly lower, and the proportion of disease due to HPV 16/18 mixed with other HPV types (HPV 16/18+) significantly higher, than the proportions at age 25-49 (Figure 2). About 65% of women below the age of 25 developed diseases related to either non-16 or 18 HPV types or to mixed infections including 16 or 18 and other HPV TYPES.

The mean time from the last negative smear to diagnosis of cancer was found to be shortest in women under age 30, whereas for CIN 2-3 the mean time was shortest under age 25 for HPV-16/18 ONLY together with -31/35 ONLY but significantly longer for those infected with HPV-16/18 together with non-vaccine types (HPV-16/18+)."

Figure 2. Cervical cancer (141 cases) diagnosed in the periods 1990-1994 and 1999-2003 and CIN 2-3 (441 cases) diagnosed in 1990 and 1999. Distribution (%) of HPV groups within each age group.
About 60% of the women under age 30 were infected with HPV types other than 16/18 and 38% of these women had HPV-16/18 co-infection. Similarly, around 40% of both the vaccine-included and non-vaccine-included cases had gone three years, and about 65% five years, since the last normal smear. However, the HPV-16/18+ cases accumulated at a significantly slower rate during the first five years after the last normal smear (Figure 3). This could be due to a similar antagonism between HPV-16/18 and HPV-31/59 to that reported for HPV-6/11 and HPV-16.[13] Such antagonism would be highlighted by the current HPV vaccines.

**Figure 3.** Cervical cancer (82 cases) diagnosed in the periods 1990–1994 and 1999–2003 and CIN 2-3 (290 cases) diagnosed between 1990 and 1999 with an earlier normal smear before diagnosis. Cumulative frequency of different HPV groups after last normal smear.


**Concluding Remarks**

The Icelandic results show that vaccination with HPV-16/18 vaccines does not affect the previous conclusion that cytology screening should start at age 20, or soon after, with a maximum three-year screening interval, and that this interval can be extended to five years at age 40. Screening can be stopped at age 65 among adequately screened women.
Anne Marie Szarewski was a physician and medical researcher who made major contributions to women’s health. She was well known and much loved by many in the world of HPV research, and she made several important contributions to the field of prevention of HPV-related diseases. Tragically, she died suddenly and unexpectedly on the 24th of August 2013, just 8 days before her 54th birthday. She is survived by her husband Lester Venter, whom she married in 2003.

Anne learnt colposcopy from Albert Singer and epidemiology from Jack Cuzick, with whom she continued to work until her death. In 1995, they published the first study of HPV testing in cervical screening and showed that testing for the presence of HPV DNA would pick up cases of high-grade CIN that were missed by cytology testing. This early trial was followed by a larger multi-centre trial using hybrid capture II. The HART study, published in 2003, concluded that “HPV testing could be used for primary screening in women older than 30 years, with cytology used to triage HPV-positive women. HPV-positive women with normal or borderline cytology (about 6% of screened women) could be managed by repeat testing after 12 months”.

Anne was perhaps best known for the Predictors Studies in which a number of commercially available HPV tests and two collection media were compared on the same clinical samples. Initially she studied HPV testing in a triage setting, and more recently in a primary screening setting.

Anne was also one of the first to study the possibility of HPV testing on self-collected vaginal samples –an approach that is gaining increasing attention as a means of increase screening uptake in both developed countries for women who find clinician sampling embarrassing, uncomfortable or simply inconvenient, and in low-resource settings.

Anne was a principal investigator and author on key clinical trials studying the bivalent HPV vaccine. She was a strong supporter of HPV vaccination and one of the first to call for older women and boys to be vaccinated too.

Anne was something of an enigma. She professed to have no understanding of statistics but chose to work in analytic epidemiology. She thought that most mathematicians were on the autistic end of the spectrum, but spent much of her career working closely with them and enjoying their company. On social issues such as contraception, feminism and gay rights, Anne was a liberal, but in other respects she was extremely conservative. She believed that certain standards should be maintained—always being immaculately dressed—which was often at odds with the casual and sometimes scruffy dress of many academics.

To her immediate colleagues, Anne was the cake lady. Every day at 3.00 pm she would produce cakes and wander into people’s offices to offer a little cake “pick me up” and entertaining conversation. Her lively, upbeat personality, conscientious attention to detail in the increasingly bureaucratic field of medical research as well as her insistence on putting women’s needs first will be greatly missed.
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INTERNATIONAL AGENDA

Macau, China
20th - 23rd February 2014
The 19th World Congress on Controversies in Obstetrics, Gynecology and Infertility (COGI)
Venue: Venetian Macau
E-mail: cogi@congressmed.com
Web: www.congressmed.com/cogi/

Santiago de Chile, Chile
31st March - 2nd April 2014
1st South American Meeting of Human Papilloma Virus- HPV
Venue: Sheraton Santiago Hotel and Convention Center
E-mail: hpvchile2014-reg@kenes.com
Web: http://www.hpvchile2014.com/

Novara, Italy
9th - 12th April 2014
7th International conference on HPV, Polyomavirus & UV in skin cancer
Venue: Novarollo - Villaggio Azzurro.
E-mail: info@hpvpolyomanovara2014.it
Web: http://hpvpolyomanovara2014.it

Glasgow, Scotland
7th - 10th May 2014
23rd European Congress of Obstetrics and Gynecology
Venue: Scottish Exhibition and Conference Centre I SECC
E-mail: info@ebcog2014.org
Web: http://www.ebcog2014.org/component/content/category/8-programme-articles

London, United Kingdom
26th - 30th May 2014
15th World Congress of Cervical Pathology and Colposcopy - IFPC
Venue: The Queen Elizabeth II Conference Centre
E-mail: ifpc@kenes.com
Web: www.ifpc2014.com/

Zacatecas, México
23th June-7th July 2014
XVIII Congreso Internacional de Diagnóstico y Patología de Tracto Genital Inferior y Colposcopia
Venue: Hotel Don Miguel
E-mail: contacto@conejic.org.mx
Web: www.conejic.org.mx

Singapore, Malaysia
21th - 22nd July 2014
Annual International Conference on Advanced Research: Obstetrics & Gynecology
Venue: Hotel Fort Canning
E-mail: secretariat@obgynae-conf.org
Web: www.obgynae-conf.org

Seattle, Washington, USA
20th - 25th August 2014
The 29th International Papillomavirus Conference and Clinical and Public Health Workshop
Venue: Washington State Convention Center
E-mail: hpv2014@conferencesolutionsInc.com
Web: www.hpv2014.org

Lisbon, Portugal
17th - 22nd September 2015
The 30th International Papillomavirus Conference and Clinical and Public Health Workshops
Venue: Lisbon Congress Centre
E-mail: mclara.bicho@gmail.com
Web: www.sppv.org

Valencia, Spain
24th - 26th September 2014
4th International Conference on Vaccines & Vaccination
Venue: E-mail: vaccines2014@omicsonline.net
Web: www.omicsgroup.com/vaccines-vaccination-conference-2014/

Munich, Germany
8th - 11th October 2014
60. Congress of the German Society of Gynecology and Obstetrics
Venue: ICM International Congress
E-mail: dbgg2014@eurokongress.de
Web: www.dbgg2014.de

Paris, France
4th - 7th December 2014
The 20th World congress on Controversies in Obstetrics, Gynecology and Infertility (COGI)
Venue: Paris Marriott Rive Gauche Hotel & Conference Centre
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Web: www.congressmed.com/co gi/paris/

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