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Focusing on new research presented on Human Papillomavirus and Cervical Cancer

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Introduction

The 19th International Federation of Gynecology and Obstetrics (FIGO) World Congress was held from the 4th to the 9th October 2009 in Cape Town, South Africa. The overall focus of this year's congress was on the challenges of maternal health in developing countries. The event provided a venue for presentation of important data regarding human papillomavirus (HPV), its prevention, and its relationship with cervical cancer. The following is a summary of some of the most compelling of these new data.

Cervical Cancer: A Worldwide Health Priority

NEW DATA ON DISTRIBUTION OF CERVICAL CANCERS AND HPV TYPES

The prevalence of invasive cervical cancer (ICC) worldwide is estimated to be approximately 2.3 million.¹ In the developing world, ICC is the most common cancer among women. In a presentation at FIGO 2009, one of the foremost international experts on global distribution of HPV types, Dr. Xavier Bosch, suggested that the burden of cervical cancer will increase 42% by 2020, largely due to increasing rates of cases in the developing world.²

Dr. Bosch presented data compiled from 1998 to 2002 through the International Agency for Research on Cancer (IARC). The data include samples from more than 10,000 cases of cervical cancer from 60 countries, representing 225 registries.

Currently, squamous cell carcinoma makes up 89.6% of all cervical cancers but, in the high-resource countries where screening systems allow for identification and treatment of ectocervical precursor lesions (usually squamous), there is a rise in the rate of adenocarcinomas.³ In fact, in Finland, adenocarcinoma accounts for 28% of cervical cancers. This is in stark contrast to the 1.5% of cervical cancers attributable to adenocarcinoma in Algeria, a country where screening is not readily available. Furthermore, Algeria neither tracks nor differentiates adenocarcinoma from squamous cell carcinoma.

Extrapolating the 2002 data to 2008, Dr. Bosch's group showed that there is a higher rate of adenocarcinoma in younger women (25- to 49-year-olds) compared to the next oldest generation (50- to 74-year-olds).² This

is likely based on differences in age of initiating sexual activity and number of partners, and demonstrated the presence of the high virulence of the HPV types seen in adenocarcinomas.²

Other groups have also reported that adenocarcinoma presents at an earlier average age than squamous cell carcinoma. At FIGO 2009, Dr. Silvia de Sanjose presented data from her group that included 10,365 cases in 36 countries. In this population it was found that, on average, adenocarcinoma presents at 48.4 years of age compared to squamous cell carcinoma, which presented at 51 years.³

HPV types. Tissue analysis from the IARC samples collected from 1998 to 2002 shows that the most common HPV types causing adenocarcinoma are HPV-18 (37.9%), HPV-16 (35.5%) and HPV-45 (5.6%). All other individual types account for 2% or less of adenocarcinoma cases. In terms of single infections, HPV-16, HPV-18 and HPV-45 make up approximately 90% of adenocarcinoma cases.²

De Sanjose *et al* have also analyzed the proportion of cases of cervical cancer attributable to HPV, and identified the HPV types most commonly implicated by histology. As shown in Table 1, they found that 84.8% of cervical cancers overall were HPV-positive.⁴ Of these, HPV-16 was implicated in 56.6% of cases, HPV-18 in 9.6% and HPV-45 in 5.3%, while HPV-33 and HPV-31 were each implicated in 3.5% of cases. Specifically for squamous cell carcinoma, they found that 86.9% of cases were HPV-positive, with HPV-16 implicated in 57.7% of cases, HPV-18 in 7.8%, HPV-45 in 4.9%, and HPV-33 and HPV-31 in 3.7% of cases each. Finally, for adenocarcinoma, they found that 61.9% of cases were HPV-positive, with HPV-16 implicated in 45.9% of cases, HPV-18 in 30.5%, and HPV-45 in 10.6%.

Importantly, it should be noted because of the difficulty in screening for adenocarcinoma of the cervix, these malignancies are usually detected at a more advanced stage than squamous cell cases, and they are associated with a poorer prognosis.⁵

VACCINES FOR HPV

The mechanism of action of vaccines against HPV was summarized at FIGO 2009 during a presentation by

Prof. Peter Stern (Head of the Immunology Group, Paterson Institute for Cancer Research, University of Manchester, Manchester, United Kingdom).⁶

One of the problems of any HPV infection is that it does not cause a viremia. The HPV virus infects basal-layer epithelial cells and hijacks the cellular processes as the epithelial cell begins differentiation. During the life cycle of the epithelial cell, the virus causes minimal cellular damage; thus, in 50% of women, the body does not see the viral antigen and there is no detectable antibody response. In the other 50% of women, the antigen is presented to the woman's immune system via the antigen presenting cells (APC), and antibodies are created by B-cells. Unfortunately, the level of antibodies created to natural infection are low and not reliably protective.

Importantly, because of the difficulty in screening for adenocarcinoma of the cervix, these malignancies are usually detected at a more advanced stage than squamous cell cases, and they are associated with a poorer prognosis.

The vaccine is created using the L1 protein (virus-like particle [VLP]), which induces neutralizing antibodies for the HPV-16 and HPV-18 oncogenic types, and an adjuvant to boost the immune response. The purpose of vaccine is to stimulate high antibody levels both in the serum and the cervical mucosa that bathes the epithelial cells.

Prof. Stern also showed that, although the vaccines were developed to primarily target HPV-16 and HPV-18, the development of neutralizing antibodies to HPV-16 and HPV-18 (as seen in the PATRICIA [PApilloma TRIal against Cancer In young Adults] study⁷) may also prevent other oncogenic types related to HPV-16 and HPV-18 on the phylogenetic tree.⁶ For example, types 31, 33 and 35 are very similar to type 16, while type 45 is similar to type 18. With HPV-45 implicated in a substantial proportion of cases of adenocarcinoma, the cross-protection demonstrated by the bivalent vaccine is a highly desirable characteristic.

Table 1. **Single HPV Worldwide Type Distribution (%) in Cervical Cancer by Histology Type: ICO Survey⁴**

	<i>Cervical Cancer</i>		<i>Squamous Cell Carcinoma</i>		<i>Adenocarcinoma</i>	
	10,365		9,292		748	
	8,792 HPV+		8,077 HPV+		463 HPV+	
	16	56.6	16	57.7	16	45.9
	18	9.6	18	7.8	18	30.5
	45	5.3	45	4.9	45	10.6
	33	3.5	33	3.7	31	0.6
	31	3.5	31	3.7	51	0.6
	Total	78.5		77.8		88.2
Percentage of multiple infections <i>i.e.</i> , detection of = 2 HPV types		6.3		6.3		7.8

In a presentation at FIGO 2009, Dr. Suzanne Garland stated that under a conservative assumption (50% coverage of HPV-45), a vaccine with cross-protection against HPV-45 is likely to reduce cervical cancer rates by an additional 2-3% overall (and adenocarcinoma rates by a further 5%).⁵

Two HPV vaccines are currently on the market – a bivalent vaccine (HPV-16/18: Cervarix™) and a quadrivalent vaccine (HPV-6/11/16/18: Gardasil®).

New data with the bivalent vaccine. Data from the PATRICIA Phase III efficacy trial were presented by Drs. Suzanne Garland and Anne Szarewski,^{5,8} with particular focus on cross-protection. The primary results were published earlier in 2009.⁷ In this trial, 18,644 women aged 15-25 with normal or low-grade cytology at enrolment were randomized 1:1 to receive the bivalent HPV vaccine or hepatitis A vaccine at 0, 1 and 6 months, with a mean follow-up of 39.4 months.

At FIGO 2009, Dr. Garland presented the results of this study with respect to efficacy of the vaccine against HPV-45 specifically, and vaccine cross-protection. She reported that the efficacy of preventing persistent infection with HPV-45 was 72.1% at six months and 55.8% at 12 months (Figure 1).⁵ The vaccine also prevented 100% of HPV-45-related lesions of cervical intraepithelial neoplasia 2+ (CIN2+) or worse.

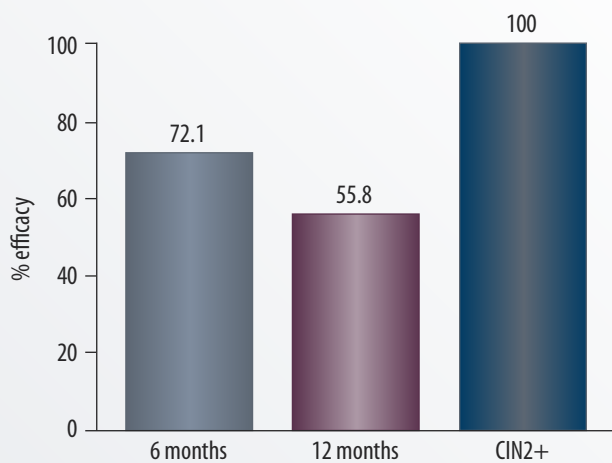
To further examine the effect of cross-protection, Dr. Szarewski presented the effect of vaccination in the

according-to-protocol (ATP) cohort (those who received all three doses of vaccine: n=16,162).⁸ The bivalent vaccine had a 37.4% (95% CI, 7.4-58.2% in single HPV-infected lesions) to 54% (95% CI, 34-68.4% single and multi-HPV-infected lesions) efficacy in preventing HPV types beyond 16 and 18. Dr. Szarewski indicated that it appears that the majority of this benefit is due to cross-protection from HPV-31 and HPV-45, with a small contribution from HPV-33. She stated that the cross-protection provides an additional 48% reduction in preventing CIN2 or worse lesions than was previously predicted if only lesions from HPV-16 and HPV-18 were prevented.

The long-term duration of action of the bivalent vaccine has also been investigated. At FIGO 2009, data were presented evaluating the long-term immunological effects for up to 7.3 years (range 83 to 88 months) in 433 women initially aged 15-25 years.⁹ This is the longest duration of followup reported for any licensed HPV vaccine. Blood samples were taken annually, cervical samples collected every 6 months for HPV DNA typing by polymerase chain reaction (PCR), and cytopathological examinations conducted annually. At the end of the followup period, 100% of the subjects were seropositive for HPV-16, while more than 96% were seropositive for HPV-18 (Figure 2). The antibody titres were still significantly higher than natural infection (more than 13-fold higher for HPV-16, and more

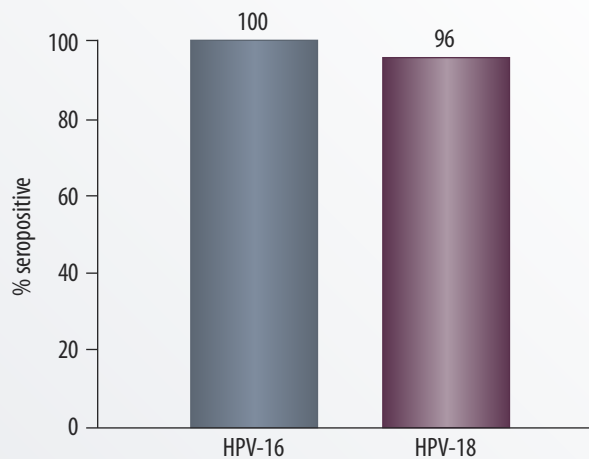
than 11-fold higher for HPV-18). In terms of the neutralizing antibodies, it was more than nine-fold higher in the case of HPV-16 and more than five-fold higher in the case of HPV-18 when compared to natural infection. For safety, in this cohort there was no new-onset autoimmune disease and no adverse pregnancy effects detected.

Figure 1. **Prevention of Persistent Infection of CIN2+ with HPV-45*: Bivalent HPV Vaccine in the PATRICIA (PApilloma TRIal against Cancer In young Adults) Trial⁵**



*Total vaccinated cohort

Figure 2. **Persistence of Bivalent Vaccine: Long-term (up to 7.3 years) Seropositivity for HPV-16 and HPV-18⁹**



Comparisons between the bivalent and quadrivalent vaccines. In separate studies in vaccine-naïve populations, the efficacy against CIN2+ lesions caused by HPV-16 and HPV-18 has been shown to be higher with the bivalent vaccine (100%) compared to the quadrivalent vaccine (58.7%).⁵ When one expands the list to include HPV-31/33/45/52 and 58, these figures drop to 68.2% for the bivalent vaccine and 32.5% for the quadrivalent vaccine.¹⁰

The two vaccines have now been compared in a direct, head-to-head study, the results of which were presented at FIGO 2009. This multicentre, blinded, randomized Phase IIIb study compared the immunogenicity and reactogenicity of the bivalent and quadrivalent vaccines among 1,106 females aged 18-45 years.¹¹ Dr. Philippe Moris presented data showing that, while both vaccines induced HPV-16/18-specific CD4+ T-cell responses, the proportion of subjects with these responses was higher following vaccination with the bivalent vaccine compared to the quadrivalent vaccine. The bivalent vaccine also induced significantly higher neutralizing antibody titres than the quadrivalent vaccine at months 7 and 12 for each antigen in each age group.¹¹ Both the enhanced immunogenic response and proven length of action suggest that it is unlikely that a booster for the bivalent vaccine would be required before 10 years, if at all.

CHALLENGES IN INTEGRATING CERVICAL CANCER PREVENTION

As part of the 2009 FIGO World Congress program, the International Federation for Cervical Pathology and Colposcopy (IFCPC) held a symposium to discuss the challenges of cervical cancer prevention across five continents.¹² Chaired by the current IFCPC president, Dr. Patrick Walker (United Kingdom), the symposium included presentations by Drs. James Bentley (Canada), Christine Bergeron (France), Silvio Tatti (Argentina), Neerja Bhatla (India) and Lynnette Denny (South Africa). Each presenter spoke about the challenges of cervical cancer in their own countries and continents.

North America. In North America, the screening rates for cervical cancer have been in excess of 60% for a long time, which has led to low disease rates. There are several differences between the American and Canadian systems with respect to cervical cancer prevention. In the United

States, screening is often done with high-tech methods, including HPV testing. In Canada, the introduction of organized, school-based HPV vaccine programs is leading to a more widespread uptake of vaccine than in the United States, where vaccination uptake is approximately 25% in school-aged females. One of the drawbacks of the current screening systems is the potential for harm from over-treatment, particularly in the adolescent age group. It is hoped that the recent approval in the United States of the bivalent vaccine (Cervarix®), which may be associated with a better cancer-protection profile than the currently used quadrivalent vaccine (Gardasil®), there may be a stimulus towards increased vaccination rates.

Europe, South America, Asia and Africa. In Europe, although cervical cancer rates are declining overall, the challenges vary greatly from country to country. In the newer states of the European Union (e.g., Slovenia), where organized screening and access to colposcopy services is inadequate, cervical cancer rates are considerably higher than in countries where organized screening is well established (e.g., the United Kingdom, Nordic countries). For example, the cervical cancer rate in Slovenia is 18.7/100,000 women, compared to 4.7/100,000 in Finland.

In South America, there is also considerable variation in standards of care. In Chile, for example, cervical cancer rates have decreased since the establishment of an organized program of cytology. However, in other areas of the continent, particularly where poverty is more prevalent, screening is not performed and cancer rates are higher. Throughout most of South America, vaccination is available but not accessible by most.

Asia accounts for the majority of annual cases of cervical cancer. Approximately half of the reported cases from Asia are from India alone. At present, there is no structured screening or vaccination program established in India, but it is hoped that HPV vaccination will become available through support from the Global Alliance for Vaccines and Immunization (GAVI).

In Africa, where there are many nations that rank among the poorest on the Human Development Index and Human Poverty Index, there is substantial room for improvement in screening and prevention. Despite limited healthcare budgets, however, there are several

nations that have screening protocols. While quality assurance issues and access to pathologists often make it impossible to utilize conventional screening methods, visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) are being used. These tests are sensitive, but not specific.

Taken as a whole, this symposium highlighted the fact that, despite the development and correct utilization of secondary prevention, cervical cancer will continue to be a concern for some time. Although there are vast discrepancies in the level of care currently being offered among countries, there was a sense of hope that appropriate vaccination will in time offer help to prevent cervical cancer for women in all countries.

CONCLUSIONS

Cervical cancer is a highly prevalent malignancy all over the world. In North America, however, although our screening practices have dramatically reduced the incidence of squamous cell cervical carcinoma, the early identification of adenocarcinoma remains elusive. HPV is implicated in 99% of cases of cervical cancer, with HPV types 16 and 18 accounting for over 70% of these cases.^{13,14} Recent evidence presented on the bivalent vaccine also shows that there is considerable cross-protection

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against other less common types (e.g., HPV-45, which is often implicated in adenocarcinoma). Initial evidence indicates that the bivalent vaccine may be superior to the quadrivalent vaccine in terms of immunogenic response and cross-protection against oncogenic HPV types.

The bivalent vaccine has also demonstrated a long duration of action. Use of HPV vaccines at a popula-

tion level should be encouraged to further dramatically lower the incidence of cervical cancer, particularly of the adenocarcinoma type. As stated by Dr. Wiebren

Tjalma at FIGO 2009, “If we play it right now, then cervical cancer will become a disease for medical history books.”¹⁰

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N.B.: The references listed below (with the exception of #1) are for the published abstracts. This review also includes data from the presentation of these papers at FIGO 2009, gathered by the on-site Canadian ambassadors.

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