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Managing Inequities in Protection Against HPV-related Disease Through Gender-neutral Vaccination

Prague - When routine vaccination against the human papillomavirus (HPV) was first approved in 2006, it was focused on preventing cervical cancer in women. However, a range of cancers is now known to be associated with HPV in men and women, including head and neck cancer and anal cancer, as well as vulvar and vaginal cancer in women and penile cancer in men. Overall 5.2% of all cancers are now known to be HPV-attributable. Two vaccines are licensed worldwide to protect against HPV in females. Both are very effective against diseases caused by HPV types 16 and 18, which cause most cervical cancers. Only one, the quadrivalent vaccine, has been shown to protect against precancers of the vulva, vagina and anus. The quadrivalent vaccine also protects against HPV types 6 and 11 which cause >90% of genital warts in females and males. As reflected here at EUROGIN 2012, over recent years, awareness of the significant burden of HPV-related diseases in men has increased. The quadrivalent vaccine has been approved for males in 73 countries. In countries such as Australia, vaccination of males is scheduled to be added to an already successful national vaccination program against HPV-related disease in females.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

“We are beginning to get a fuller understanding of the burden of disease related to human papillomavirus (HPV) in men and also the epidemiology of these infections from large international cohort studies such as the ongoing HPV Infection in Men (HIM) study,” declared Anna R. Giuliano, PhD, Director, Center for Infection Research in Cancer, Moffitt Cancer Center, Tampa, Florida. “In females, HPV incidence is highest at younger ages and decreases steadily with advancing age; we see no difference in rates of genital HPV acquisition by age in males.” The global burden of HPV disease is still high among men and women, Dr. Giuliano stressed. Genital warts (condyloma) are the most common clinical manifestation of HPV infection. From the placebo arms of HPV vaccine trials, the incidence among women and men aged 16-26 years has been calculated as 8.7 and 15.8 per 1000 person-years, respectively. Although benign, genital warts are associated with emotional distress and physical pain; the treatment itself is painful and recurrence common. It has been reported that they significantly increase the risk of developing an HPV-related cancer by approximately sevenfold in men and threefold in women (Blomberg et al. *J Infect Dis* 2012;205:1544-53).

Burden of Noncervical HPV-related Cancers

Among the noncervical HPV-related cancers, the incidence of anal cancer is low in the general population but increasing in both genders. In women, anal HPV infection may now be as or more common than cervical HPV infection, suggested Dr. Joel M. Palefsky, University of California, San Francisco. The prevalence of anal cancer in men differs by sexual orientation and is lowest in men who have sex with women. Men who have sex with men (MSM) have a 30-fold increased risk of anal cancer compared with the general population. Penile cancer is rare (<0.5% of all cancers in men) but in some countries such as Denmark and The Netherlands, the incidence

appears to be increasing, Dr. Giuliano told delegates. Around 40-50% of penile tumours are caused by HPV and the rate of HPV infection is highly dependent on histologic type of penile cancer.

The prevalence of oral HPV infection in the general population (5-7%) is significantly lower than either anal or external genital HPV infections (50-60%), but it is significantly higher in males than females. Oral HPV infection appears to increase with age in men, noted Dr. Maura L. Gillison, Ohio State University, Columbus. The differences in incidence, prevalence and infection duration when comparing males to females is attributed to differences in sex (e.g. oral) as well as differences in the epithelial site (e.g. cervix and anal vs. keratinized penile skin) of infection, Dr. Giuliano explained. She called for more research to fully understand the interaction of sex differences and tissue-specific viral infections.

Rationale for Male HPV Vaccination

For cervical cancer prevention, the benefits of including males in a vaccination program (gender-neutral vaccination) may depend on the coverage obtained among females, Dr. Giuliano pointed out. Vaccinating males enhances herd immunity to reduce disease burden in women, she noted. Similar trends are apparent in terms of cost-effectiveness. However, extending vaccination programs to males would also include MSM, who gain no benefit from a female-only vaccination policy. It has been calculated that an HPV gender-neutral vaccination program would result in an additional 64% reduction of remaining HPV-related cancer burden in men and an additional 40% reduction in women (Bresse et al. *Value Health* 2011;14:A464-A465). Dr. Giuliano also questioned whether women should assume all the responsibility of vaccination. “Is it ethical that men should not be able to directly benefit from HPV vaccination?” she mused.

Oropharyngeal cancers are the most common HPV-associated cancers among men. No study to date has evaluated the efficacy of vaccines in preventing oropharyngeal HPV infections, mainly because there is no precursor lesion that can serve as a clinical end point, explained Dr. Anil Chaturvedi, US National Cancer Institute, Bethesda, Maryland. However, “there is good reason to think that a vaccine might work against oral HPV infection,” he declared.

Safety Update

According to the European Centre for Disease Prevention and Control (ECDC) in Stockholm, Sweden, the HPV vaccines currently in use for girls are safe, well tolerated and highly efficacious in the prevention of persistent infection, cervical cancer and other morbidities related to the vaccine-HPV serotypes. “This high safety profile has been recently confirmed also through systematic reviews and meta-analyses that demonstrated no significant difference in occurrence of severe adverse events between the vaccinated group and controls,” confirmed Dr. Pierluigi Lopalco, Head, Vaccine-Preventable Disease Programme, ECDC. In males, observational studies have confirmed that the safety profile of the quadrivalent vaccine is the same as that in females, Dr. Lopalco added. He announced that new ECDC guidelines on HPV vaccines will be issued in August 2012, updating the previous recommendations published in 2008. “The experts who advised on these guidelines again concluded that these vaccines present a very good safety profile,” he revealed. Their findings were largely based on a meta-analysis of 7 randomized controlled trials in over 44,000 females which concluded that the risk of serious adverse events did not differ significantly between vaccinated women and nonvaccinated controls (Lu et al. *BMC Infect Dis* 2011;11:13).

Over 97 million doses of HPV vaccine have been delivered worldwide since their introduction in 2006. Dr. Lopalco pointed out that the quadrivalent vaccine is one of the most scrutinized vaccines for safety and has demonstrated a very good safety profile. “Severe adverse events have been rare or almost nonexistent,” he said. Nonetheless, fear of adverse events remains a barrier to vaccination for the public and consequently for physicians. The majority (90%) of GPs have a favourable opinion of HPV vaccination and confidence in its safety (Piana et al. *Med Mal Infect* 2009;39:789-97). Among those who are not in favour of vaccination, however, about 37% appear

to be influenced by patients’ concerns about potential side effects (Lutringer-Magnin et al. *Vaccine* 2011;29:5322-8). “It is important that any serious adverse events are managed properly. Only in this way can we build trust in and support for vaccination programs,” stated Dr. Lopalco.

Impact of HPV Immunization in Australia

As a result of a government-funded, school-based HPV vaccination program in females in Australia, there was an “extraordinary” 97% decline in cases of genital warts in women aged <21 years who received the quadrivalent HPV vaccine between 2007 and 2010, reported Prof. Andrew Grulich, Kirby Institute, University of New South Wales, Sydney. A 73% decline in genital warts was seen in women aged 18-26 years who received the quadrivalent vaccine as part of a community program. In 2007, a 44% decline in genital warts was recorded in resident heterosexual men aged ≤26 years and a 25% decline in older men. “Genital warts are becoming a rare condition in women and heterosexual men in Australia,” Prof. Grulich declared. There has been no transfer of herd immunity to MSM, however. A male vaccination program has now been recommended for government funding by the Pharmaceutical Benefits Advisory Committee based on cost-effectiveness. Following government approval, which usually follows such recommendations, vaccination of boys aged 11-13 years is expected to begin in 2013 as part of the school-based program. “Without male vaccination, HPV-related cancer will soon become a male disease,” Prof. Grulich stressed.

Summary

“Analyses like those from Australia show that if we do not vaccinate boys now, there will be more HPV-associated cancer in men in 20-30 years than there are in women,” declared Prof. Margaret A. Stanley, University of Cambridge, UK. She noted that one argument against vaccinating men is the assumption that high coverage of women will achieve herd immunity. “Herd immunity is exactly what it says: it is for the herd,” she told delegates. “If you are an individual who is not immunized and you move outside the herd, you are not protected. That is really the issue. You cannot look at a national immunization program as being in a ring-fenced area. We all move and therefore the herd has to have both individual as well as complete immunity. So I believe that everyone should be vaccinated against HPV infections.” □

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