

IUSTI–E Scientific Advisory Council

Topic Report 2016 **Human Papilloma Virus**

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Advances in the field 2015-6

HPV vaccination

The most interesting and revolutionizing area in clinical HPV research in recent years is the development of vaccines, which have become an important tool for primary prevention of genital HPV infection as well as of anogenital cancer. Vaccination with the quadrivalent vaccine (Gardasil^R, HPV 6, 11, 16, 18) has been including in the school based vaccine programs in many countries, given to girls before sexual debut, usually at the age of 11-12 years. Previously 3 doses have been given, but studies have shown that 2 doses given at 0 and 6 months are sufficient (1). As a further improvement, a 9-valent vaccine (Gardasil-9^R: HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) has been developed. This new vaccine is FDA-approved, and is also available in Europe now. Gardasil-9^R will probably replace the old quadrivalent vaccine, and is supposed to prevent 90% of cervical cancer, 80% of CIN II and III, and 90-95% of HPV-related anal cancer. The coverage in the school-based program varies a lot between countries: Japan 30%, Finland and Australia 60-70%, England and Sweden 80% and Scotland 90% (2).

Genital warts have been used as an early marker for vaccine efficacy. Already 4 years after commencing a national HPV vaccination program in Australia there was a drop of 90% in genital warts in young women. A significant drop of 39% was also seen in young heterosexual males due to herd immunity. Interestingly, no effect at all was seen in older women or men (> 30 years) or at all, among MSM (3). In a more recent review of such data a further reduction was noted (4). Such decrease of genital warts has also been seen in other countries. The lack of effect in MSM is also an argument for inclusion of males in the vaccination programs, which only has taken place in Australia, Austria and in some parts of Canada.

In some countries fear for vaccine side effects has been widely discussed in media. In Denmark cases of POTS (postural ortostatic tachycardia syndrome) have been reported. However, the EMA concludes in a recent report that this syndrome at least affects 150 young girls and women per million, and that the rates among vaccinees do not differ from the general population (5).

Consequences of genital HPV infection

Besides genital warts, other consequences of genital HPV infection are various forms of cancers. The increase of anal and oropharyngeal cancer has caused a lot of attention recently. Anal cancer was previously a malignancy that mostly affected older women, but now also affects younger people. An increase in men of 160% and in women of 78% was seen between 1973 and 2000 in the US (6). Receptive anal intercourse and HIV infection are known risk factors. Anal cancer is usually HPV 16 positive, and could possibly be prevented by screening of certain risk groups, mainly MSM, by cytology (7). Gardasil^R is accepted both in the US and in Europe as prevention for anal cancer caused by HPV 16/18.

probably a risk factor, and HPV transmission among couples has been described (9). An increase of tonsillar cancer has been reported in many countries; for example in Sweden an increase of 2.6% per year for men and 1.1% per year for women during the last 30 years has been reported (10).

Anything new regarding treatment?

Imiquimod (Aldara^R) is used for treatment of genital warts, but has also been tried for dysplastic genital lesions such as PIN and VIN (11), AIN (12), and also for vulvar Paget's disease (13). A new drug, the green tea extract (sincatechin), Veregene^R ointment is now available. It is applied three times daily for up to 16 weeks, and has been shown to have an efficacy of 57% compared to 33% in the placebo group (14). Studies using various combinations of different treatment modalities have also been conducted, but still we lack an effective treatment that also eradicates the latent virus.

5 Most Important Recent Publications

Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajdén M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA* 2013;309(17):1793-1802.

Ali H, Guy RJ, Wand H, Read TR, Regan DG, Grulich AE, et al. Decline in in-patient treatments of genital warts among young Australians following the national HPV vaccination program. *BMC Infect Dis*;13:140. Available from: doi: 1186/1471-2334-13-140. (Accessed: 18th March 2016)

Moreira ED, Block SL, Ferris D, Guiliano AR, Iversen OE, et al. Safety profile of the 9-valent HPV vaccine: A combined analysis of 7 Phase III clinical trials. *Pediatrics* 2016;138(2):Available from: e2015438710. doi: 10.1542/peds.2015-4387. E-pub July 15

Isidean SD, Mayrand MH, Ramanakumar AV, Gilbert L, Reid SL, Rodrigues I, et al. Human papillomavirus testing versus cytology in primary cervical cancer screening: End-of-study and extended follow-up results from the Canadian cervical cancer screening trial. *Int J Cancer* 2016 Aug 18. doi: 10.1002/ijc.30385 (Epub ahead of print)

Elfström KM, Lazzarato F, Franceschi S, Dillner J, Baussano I. Human papillomavirus vaccination of boys and extended catch-up vaccination: Effects on the resilience of programs. *J Infect Dis* 2016;213(2):199-205

Potential Speakers

Charles Lacey

Margaret Stanley

Joakim Dillner

Stina Syrjänen

Joel Palefsky

Questions to be answered by future Research

- Factors affecting HPV infection clearance
- Factors relating to HPV infection persistence
- Immune targets to enhance HPV infection clearance
- Effect of HPV vaccination on pre-existing HPV infection
- Is there any meaning for vaccination to people already exposed to HPV?
- Cross protection for HPV-types not included in the vaccines
- Amount of virus required for transmission?

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