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Sound efficacy of prophylactic HPV vaccination
Basics and implications

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Prophylactic human papillomavirus vaccine efficacy is almost too good to be true. The benefits of herd immunity will, however, not be gained without high vaccine coverage. Here the authors of two recent papers on HPV16/18 vaccine efficacy elaborate on the basics and implications of this approach for infection and cancer prevention.

In the US and Nordic countries 14 high-risk (hr) human papillomavirus (HPV) types cause 5 and 10 percent of cancers in males and females, respectively. Half of these cancers are caused by HPV type 16.[1] Hr-HPVs are acquired by sexual contact, and one third of young adults are hr-HPV DNA positive, i.e., transmitting HPV.[2] Ninety percent of cervical hr-HPV infections heal in 1.5 y but if persistent can develop into cervical cancer (CC). The world age-standardized incidence of CC was 14.5/100,000 in 2008, and in a number of countries is increasing together with the incidence of hr-HPV associated oropharyngeal and other anogenital cancers. Developing countries can never tackle hr-HPV disease burden by screening/treatment. Primary prevention by vaccination is the only hope.

Thirty years ago zurHausen's group discovered HPV16 in cervical cancer,[3] 20 years ago HPV16 virus-like particles (VLPs) were developed,[4] and 10 years ago first results on the immunogenicity and efficacy of the HPV16 VLP vaccine were published proving the principle.[5] Recently, we showed in a four-year clinical Phase III trial that HPV16/18 vaccine prevents 93.2% of all CIN3$^+$ lesions in baseline naive adolescents.[6] The lower 95% confidence limit of 80% indicates that this highly efficacious vaccine provides better protection against CC than the best Pap-screening programs. Partial cross-protection against HPV31/33/35/45/51 and associated sequelae is the key to the overall efficacy.[6,7]

The basis for the cross-protection may be comparable conformational structure close to the major neutralizing VLP epitopes that are recognized by HPV16.V5 and HPV18.J4 antibodies in the FG and HI loops of the corresponding viral pentamers.[8] Due to this conformational correspondence, the cross-reactive sites may reside or be recognizable in the vicinity of amino acids 261–280 and 397–416[8,9] (**Fig. 1**). These, so far hypothetical, epitopes might correspond to their monoclonal antibody recognized counterparts in HPV16 L1 and HPV31/33/35 L1, and in HPV18 L1 and HPV45 L1 as suggested by the cross-reactivity of HPV16.J4 and HPV18.Q2 antibodies.[8,9] Mechanisms of cross-protection against HPV51 remain elusive.

Possibly due to the AS04 adjuvant, HPV-16/18 vaccine induced antibodies are detectable > 8 y post vaccination. Very long-term stability of the cross-neutralizing human antibodies, and whether boostering is needed at all remain to be seen.

HPV vaccination coverage is at best 80% but usually much lower. A form of denialism, clustering of non-attendance to vaccination and screening, threatens to jeopardize public health programs aiming to control HPV disease burden. It might also give rise (by creating ecological niche) to type-replacement following implementation of HPV vaccination. With up to 22 percent HPV16/18 vaccination coverage we did, however, not find signs of HPV type-replacement within 4 years follow-up (Palmroth J, Merikukka M, Paavonen J, Apter D, Eriksson T, Natunen K, et al. Occurrence of vaccine and non-vaccine HPV types in adolescent Finnish females four years post vaccination, unpublished data, submitted February 2012). On the contrary, the incidence of clade A9 infections was decreased in HPV16/18 vaccinated as compared with hepatitis A vaccinated women. The full impact of herd immunity on hr-HPV epidemiology will, however, be assessed in an ongoing community-randomized trial in which 12–15 y old girls and boys received the HPV16/18 vaccine (11 communities), girls only received the HPV16/18 vaccine (11 communities), or girls and boys received hepatitis B vaccine (11 communities).[10] The yet-to-be-verified most efficient vaccination strategy will hopefully guide decision makers.

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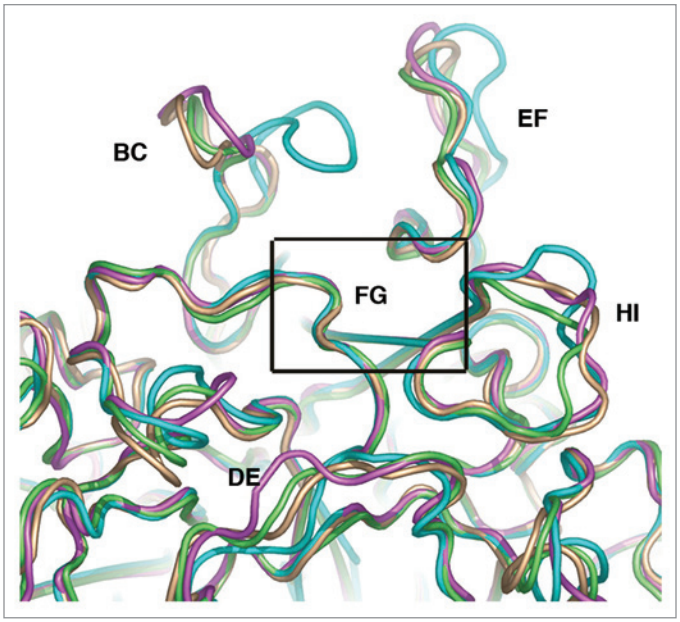

Figure 1. Superposition of human papillomavirus (HPV) type 11 (green), HPV16 (brown), HPV18 (cyan) and HPV35 (violet) L1 pentamers[8] showing structurally similar regions, with type-common epitopes detectable by monoclonal HPV16.J4 and HPV18.Q2 antibodies[9] (see text). This research was originally published in Journal of Biological Chemistry by Bishop B, Dasgupta J, Klein M, et al. Crystal structures of four types of human papillomavirus L1 capsid proteins. J BiolChem 2007; 282:31803–11. © The American Society for Biochemistry and Molecular Biology.

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