

Should all women be vaccinated against HPV?

Czy wszystkie kobiety należy szczepić przeciwko HPV?

Heinz-J. Schmitt¹, Andreas M. Kaufmann², Achim Schneider²

¹ Infectious Diseases Service, Department of Pediatrics, Johannes Gutenberg-Universität, Mainz, Germany

² Gynecology mit Hochschulambulanz, Charite Campus Benjamin Franklin, Berlin, Germany

INTRODUCTION

There is good news for women: three large recent double blind randomized trials [1-3] as well as several previous smaller trials prove that cervical cancer can to a large part be prevented by vaccination. Worldwide there are 500,000 new cases of cervical cancer every year and 50% of women affected will eventually die. Human papillomaviruses (HPV) are a necessary cause for cervical cancers [4]. It was probably irritating news to most physicians working in clinical care to learn from their colleagues in virology that cervical cancer results from a sexually transmitted infection. Human papillomaviruses have not yet been cultured, but based on molecular typing they can be divided into genotypes. It is important to understand that the 120 genotypes to date identified are not always "serotypes". Based on their ability to induce ano-genital cancers, roughly 20 of the 40 HPV genotypes infecting ano-genital epithelia are called "high-risk HPV-types", whereas the remaining genotypes ("low-risk HPV-types") are associated with the occurrence of ano-genital warts or other non-cancerous diseases. In observational studies approximately 50% of cervical cancers are associated with HPV 16 and an additional 20% with HPV 18. Thus, if this picture of cervical cancer aetiology was true, and HPV-vaccines were 100% effective, 70% of cervical cancers could be prevented.

Far more than 50% of all females will become infected with HPV during their lifetime. More than 80% of those infections will clear spontaneously with time. Some infections will become "persistent" for >2 years; from there, a small proportion will progress to cervical intraepithelial neoplasia (CIN-1), to a higher grade pre-cancerous lesion (CIN-2, CIN-3) or eventually to cervical cancer. Remission rates for those pre-cancerous CIN-lesions vary from 55% (CIN-1), 40% (CIN-2) to only 10% (CIN-3) [5]. Human papillomaviruses vaccines work by the induction of antibodies that neutralize infecting HPVs on the ano-genital mucosal surface. Following natural infection with HPV, only 50% of women will develop

antibodies to HPV infection; such antibodies will persist at low concentrations and mostly only for up to one year. Such antibodies produced after natural infection seem not to confer durable protection against reinfection [6]. In contrast, HPV vaccines have been shown to be 100 to 1000 times more immunogenic.

Recent trials

In 2 large randomized double-blind studies with an HPV 6, 11, 16, 18 (GardasilTM) vaccine commended here – FUTURE I and FUTURE II – vaccine efficacy in preventing external ano-genital lesions and vaginal lesions (CIN-2, CIN-3, carcinoma in situ) associated with vaccine-types HPV infection was respectively 100% (95% CI: 94–100) and 98% (95% CI: 86–100) during 3 years of follow up (per protocol analysis including women without HPV infection [in polymerase chain reaction – PCR – and serologic testing] before the vaccination and one month after the last dose of vaccine, who received all doses of vaccine according to the protocol) [1,2]. Instead in interim analysis of a large double blind, placebo-controlled clinical trial with another bivalent vaccine against HPV 16, 18 (CervarixTM) [3] documented vaccine efficacy in preventing CIN-1 and CIN-2 associated with HPV 16 or 18 infection was respectively 89% and 100% during 15 months follow up (a modified intention-to-treat analysis including women without HPV 16 or 18 infection [in PCR and serologic testing] before vaccination, who received at least one dose of the vaccine) [3]. Both vaccines can also to some extent induce cross protection to related highly oncogenic HPV types 31 and 45. Thus, beyond any doubt there is now "proof-of-concept" that cervical cancer can be prevented by vaccination. Vaccines were generally well tolerated; they were safe and highly immunogenic.

Based on the available trial data, no direct comparison between the two vaccines is possible. However, it is evident from studies with both vaccines available to date, that women currently infected with a vaccine type-HPV have little, if any, benefit from vaccination against this particular type. Furthermore, closer to reality an intention-to-treat analysis in FUTURE II trial including all women enrolled into study (aged 17.8–22.2 years) – also those infected before vaccination or during its execution or those who had not received all quadrivalent vaccine doses or violated protocol, vaccine efficacy in

Correspondence to:

Professor for Paediatric Infectious Diseases, Vaccine Development and Epidemiology Heinz-J. Schmitt, MD, Zentrum Präventive Pädiatrie der Johannes Gutenberg-Universität, 55101 Mainz, Langenbeckstrasse 1, Germany, e-mail: joe.schmitt@novartis.com

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preventing high-grade cervical lesions (CIN-2, CIN-3 and carcinoma in situ) was as low as 44% (95% CI: 26–58). Vaccine efficacy was only 17% (95% CI: 1–31) if all CIN lesions were included, also those not due to one of the vaccine-type HPVs – which is the most clinically relevant endpoint for women considering vaccination. As it was the case with other vaccines, data from the large phase III trials mentioned here are “proof-of-concept”: There is high efficacy under ideal circumstances. Effectiveness in real life will be lower, since doses are missed, given in a wrong time frame and – as it is the case with HPV – since efficacy is low or perhaps even zero in those currently infected with the respective vaccine type.

Whom to vaccinate: the individual perspective

For each individual, the occurrence of a CIN will invariably lead to anxiety, to additional medical visits and perhaps even to invasive medical interventions. These parameters are not part of clinical phase III trials, yet they must be considered when deciding on the use of a vaccine. There is no doubt that HPV-transmission is not restricted to young ages but occurs throughout the lives of sexually active women [7]. The second peak in cervical HPV prevalence in the fourth or fifth decade is proof of this [8]. The risk of persisting infection and malignant changes may even increase with age [9]. In our opinion, from an individual point of view physicians should offer vaccination against HPV to all sexually active women: the goal is to prevent new acquisition of HPV 16 and 18 (Castellsagué et al., unpublished data). While efficacy studies are available through age 26 years only, and while exact numbers on the benefit of HPV vaccination beyond that age cannot be given, immunogenicity of an HPV vaccine in women up to 55 years has already been documented [11]. It is thus reasonable to assume that vaccination after age 26 years of age will in some cases result in protection. Even if a woman is infected with one high-risk HPV-type, vaccination may protect her from infection with the second type. While the exact “amount of a benefit” can not be quantified today, it is the duty of physicians to explain this to their patients and advice whether or not to vaccinate against HPV on the individuals life style and choice.

Whom to vaccinate: the societal perspective

Most countries have vaccination programs and vaccines that are paid for from public funds. Health is clearly a matter of the individual, but public interest in health arises if a disease:

- 1) is transmitted from human to human
- 2) is of relevance in minors
- 3) induces high morbidity or
- 4) results in high costs.

With HPV-vaccines, all four criteria are given. Despite an (admittedly very ineffective) cervical cancer screening free of charge, there are 6,000 new cases of cervical carcinoma result-

ing in 1700 deaths every year in Germany (population approximately 85 million; birth cohort of 700,000). It is furthermore estimated that there are annually 500,000 cases of CIN-1 and CIN-2 and 60,000–75,000 CIN-3 lesions. The life-time-risk of a 10-year-old girl in Germany to develop cervical carcinoma was calculated to be 1.1% and the risk to die from this disease is 1 in 400. Thus, HPV vaccination has the potential to prevent more deaths than all other recently recommended vaccines in Germany like those against *Haemophilus influenzae* b (risk to die: 1:5,000), pneumococci (1:5,000–1:10,000) or *Neisseria meningitidis* C (1:40,000). Also, HPV vaccination is likely to be cost-effective.

According to recent data, 12% of girls in Germany have had sexual experience(s) by the age of 14 years [11]. Since HPV-vaccine-efficacy is best documented for young women without previous HPV 16 or 18 infection, and since the state has a particular interest and responsibility for minors, HPV vaccination was recently publicly recommended in Germany for all girls age 12 to 17 by the Ständige Impfkommision am Robert-Koch-Institut (standing committee on vaccination; STIKO). In addition, the STIKO calls upon all physicians in Germany to individually counsel their patients on HPV vaccination. However, beyond the age groups specified, health insurances do not pay the roughly € 500 for HPV vaccine and vaccination in Germany.

Should women be tested before HPV-vaccination?

HPV-serology is unreliable, not routinely available in daily practice and only 50% of infected women may develop antibodies which will mostly disappear within one year. Detection of HPV by PCR is possible; however since most infections become undetectable after some time and will clear spontaneously in most cases, PCR-results are of no benefit for the patient. Detection of infections with a high-risk-HPV-type may cause unnecessary anxiety, additional medical interventions and costs without any benefit to the individual. Clearly, HPV vaccine should be given without any prior microbiological testing to young women (societal perspective: care of minors; best efficacy) and to women of all age groups if it is in their individual interest. Irrespective of HPV-testing, screening of women for cervical carcinoma must continue, since: 1) it will take at least one decade before the effect of HPV-vaccination will result in reduced mortality from cervical cancer and 2) only a fraction of cancers (<70%) are vaccine preventable.

Other lessons learned

1. With the reduction of the prevalence of cancerous lesions due to vaccination, the predictive value of a positive finding by cervical cancer screening will become lower. Clearly, new methods of cervical cancer screening must be established and validated. The ultimate goal should be to have in place a comprehensive system encompassing HPV vaccination plus

screening to optimally reduce the burden of HPV-diseases in the population at low cost. Societies need to come up with comprehensive disease management programs that encompass all possibilities of modern medicine if they want to be able to finance high-quality health care for all in the future.

2. Links between HPVs and cervical cancer were first suspected almost 30 years ago [12]. Yet worldwide public responses to this finding were almost nihil, let alone political responses. Science did not reach public health in a timely manner and science regularly fails totally when it comes to political implementation: politicians only act, if they are forced to – they never proactively plan health matters in advance. Vaccine manufacturers have apparently discussed their study designs and other HPV-related aspects with the regulatory authorities (e.g. American Food and Drug Administration) but not with other health officials. Would any politician in Europe have cared anyway? More so, states all over the world (including Germany) to date even failed to provide any baseline epidemiological data regarding HPV infection and the possible impacts of vaccination.

3. Human papillomaviruses vaccination was on the horizon ten, latest five years ago. Their market price could be estimated from the investments made by the companies involved. New vaccines will come shortly (zoster, meningococcus B), and

their development will have to be paid for as well. Vaccine prices will either rise – or there will be no new vaccines (see malaria; tuberculosis).

The benefits of vaccination are immense (Andre et al., unpublished data), but as compared to emergency care or curative interventions primary prevention always has the disadvantage that its efficacy is never perceived by those who have had the benefit: Nobody knows that without vaccination he would be paralysed by polio or would have died from measles. Health care systems worldwide must be changed in order to proactively plan how to implement new developments and how to pay for them.

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From the Editor

Synopsis: Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New Engl J Med.* 2007; 356: 1928-1943.

In this randomised controlled trial the authors asked the question if in women between the ages of 16 and 24 years administering i.m. 3 doses of quadrivalent HPV-6/11/16/18 L1 containing virus-like-particle in comparison with placebo, reduce the risk of external anogenital and vaginal lesions (genital warts, vulvar or vaginal intraepithelial neoplasia, cancer) and cervical lesions associated with HPV-6, 11, 16 or 18 infection. 5455 women were included in the analysis (age 18–22 years) and after a mean of 3 years of observation in vaccinated as compared with receiving placebo the risk of external anogenital and vaginal lesions associated with HPV-6, 11, 16 or 18 infection was lower by 73% and the risk of external anogenital and vaginal lesions associated with HPV infection of any type was lower by 34%. The effect mainly depended on lowering the risk of vulvar condyloma. The risk of cervical lesions associated with HPV-6, 11, 16 or 18 infection was also lower by 55% and associated with HPV infection of any type by 20%. The effect mainly dependent on lowering risk of cervical intraepithelial neoplasia grade 1. Vaccine recipients were more likely than placebo recipients to experience adverse events at the injection site and injection related systemic events (mainly fever).

Synopsis: The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007; 356: 1915-1927.

In this randomised controlled trial the authors asked the question if in women between the ages of 15 and 26 years administering i.m. 3 doses of quadrivalent HPV-6/11/16/18 L1 containing virus-like-particle, in comparison with placebo, reduce the of high-grade cervical lesions associated with HPV-16 or 18 infection. 12,167 women were included in the analysis (age 17.8–22.2 years) and after a mean of 3 years of observation in vaccinated as compared with receiving placebo the risk of high-grade cervical lesions associated with HPV 16 or 18 infection, but the likelihood of adverse events at the injection site was higher. In the same period of time the risk of high-grade cervical lesions associated with HPV infection of any type was lower by 17%.

Prepared by: Małgorzata Bała, MD, PhD

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