EDITORIAL


Long-term follow-up of human papillomavirus vaccine efficacy

Matti Lehtinen* “Vigilare necesse est…” Amended from Plutarch’s remark to Pompeius Maximus

Oncogenic, high-risk human papillomaviruses (HPV) have, in less than four decades, become the showcase of translational science. Harald zur Hausen first suggested the concept of oncogenic high-risk HPV in 1975, before confirming HPV's link to cervical cancer in 1983; work which led to him being awarded the 2008 Nobel Prize for physiology and medicine [1,2]. Then, between 1996 and 2001 HPV were proven to cause increased risk for later development of carcinomas of the uterine cervix, other anogenital sites and the oropharynx [3–5], before being shown to be preventable between 2002 and 2012. In clinical trials, efficacy of the two licensed vaccines against genital infections with the two most important high-risk HPV types, 16/18, and their neoplastic sequelae – most notably cervical intraepithelial neoplasia grades 2/3 (CIN2/3) – have been between 97 and 100% with tight, albeit overlapping 95% CIs (for a recent review of this topic, see the 2012 work by Lehtinen et al. [6]). Overall, vaccine efficacy (VE) against CIN3 also appears to be almost too good to be true (>93%), but numbers of incident clinical trials or cancer-registry follow up-based end point cases are still limited. So far, observations of VE against the most stringent cervical adenocarcinoma in situ, as well as CIN3 end points, are based on small numbers [6,7]. These, and other still missing HPV-associated cancer end points, need to be verified in the future. It is especially important to verify and exploit wide-spread cross-protectivity of the currently licensed vaccine(s) against a number of oncogenic HPV types and their sequelae [8].

A substantial lag period existed in gathering convincing evidence on the impact of hepatitis B virus vaccination programs, implemented in 1984 in Taiwan and Alaska on hepatocellular carcinoma, since it was 25 years before a 90–100% reduction in the hepatocellular carcinoma incidence was achieved [9,10]. In the case of HPV, an even longer lag period in completing this kind of a chain of evidence via national HPV vaccination programs was imminent. This is because the age-peaks of high-risk HPV infections and cervical cancer are between 18 and 22 and at approximately 45 years of age, respectively [11]. Thus, from vaccination of early adolescents it would take 30 years to start to see the impact of HPV vaccination on cervical cancer incidence, and long-term follow up of sizeable population-based clinical trial cohorts, enrolled approximately 10 years ago in Costa Rica, Finland and the Scandinavian countries, is pivotal [12,13].

The major flaw in the originally US FDA-approved CIN2 surrogate end point is that it has proven to be irreproducible and unstable [14,15], which makes inferences on the probable HPV VE against overall invasive cervical cancer (ICC) vague. It is, however, not only about getting convincing evidence on the VE against ICC, but evidence on the VE against other HPV-associated cancers as well.

Keywords: cancer • human papillomavirus • long-term follow-up • registry • vaccine efficacy

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VE data against anal, vaginal, vulvar or penile intraepithelial neoplasias (AIN, VAIN, VIN and PIN) [6,16,17], have the same caveats as the CIN2 efficacy data. At present, it cannot be concluded if an HPV vaccine is equally efficacious against CIN, AIN, VAIN, VIN or PIN lesions that would have regressed as it is against the lesions that would have progressed to cancer. Prolonging active clinical follow up of the study subjects does not help here since it is ethically imperative to treat the defined lesions before they develop into invasive cancer (end points).

Sizeable population-based cohorts of adolescent females and males recruited in Phase II–IV trials are the key into the earliest possible VE estimation concerning the most stringent ICC and other HPV-associated cancer end points. In Finland alone there are 3400 and 12,400 originally 16–17 and 12–15 year-old girls, respectively, who participated in clinical trials with one of the two prophylactic HPV vaccines launched in 2002–2007 [12]. As population-based controls, there are 8100 hepatitis B-virus vaccinated, originally 12–15 year-old girls, and 3300 placebo or hepatitis A-vaccinated, originally 16–17 year-old girls. Cross-vaccination was offered at the clinical trial exit to all of these, Phase II/III trial controls, approximately 50% of whom took it. In addition, there are, 15,700 originally 18–19 year-old unvaccinated girls. To avoid performance bias and interference from differential cytological screening of the altogether >40,000 consented young females from 25 years of age onwards, the trial has been organized in a similar manner [18].

The informed consent and unique personal identifier-based linkage of the (registries of) HPV- or placebo-vaccinated and unvaccinated individuals with the country-wide, population-based Finnish Cancer Registry, provides data on the incidences of all HPV-associated cancers in the above-mentioned different cohorts, on line or annually, when the Finish Cancer Registry files are officially updated. We have ≥80% power to provide data on vaccine efficacy against CIN3 in 2014, against ICC in 2022 and against other HPV-associated cancers in 2024 – two- to ten-times faster than in the hepatitis B virus and hepatocellular carcinoma story. Furthermore, the possibility to retrieve all diagnostic blocks of the identified CIN3 and cancer cases enables early identification of the unlikely [19], but possible, HPV-type replacement following vaccination. The flip side of this surveillance is the fact that eventually >50% of the female cohort participants will donate a serum sample at each of their pregnancy/pregnancies to the population-based Finnish Maternity Cohort during the next decades [20]. Prospects for identifying if a decrease in vaccine-induced HPV antibody level is associated with a risk of developing CIN3- or HPV-associated cancers – necessitating booster vaccination – could not be better.

Financial & competing interests disclosure
M Lehtinen has received funding from Merck & Co., Inc. and GlaxoSmithKline Biologics through his employer University of Tampere (Tampere, Finland) for his clinical vaccination studies, as well as grants from the Finnish Cancer Organizations and the Nordic Cancer Union for establishing registries of human papillomavirus-vaccinated and -unvaccinated individuals, who are participating in the various Finnish human papillomavirus-trial cohorts. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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