

Human papillomavirus vaccination and screening as the new paradigm in cervical cancer prevention



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Unless one has tried hard during the last 3 years to be completely isolated from all medical news, whether from scholarly journals or from the lay media, it is impossible not to have been exposed to the contagious excitement about the advent of prophylactic vaccines against human papillomavirus (HPV) infection. Those outside of the fields of oncology and sexually transmitted infections may be surprised to see how much progress there has been in the area of cervical cancer prevention. As the culmination of more than 25 years of vigorous multidisciplinary research by molecular biologists, virologists, immunologists, clinicians and epidemiologists, there is now broad consensus for the notion that infection with oncogenic HPV genotypes is a necessary cause of cervical cancer [1,2]. This realization has paved the way for new exciting approaches for preventing cervical cancer, which is the second most common malignancy of women worldwide [3].

Since the 1960s, secondary prevention (i.e., screening) of cervical cancer with the Papanicolaou (Pap) test has been practised with different degrees of success in most of the world. Countries that have successful Pap screening programs could only attain substantial gains in reducing cervical cancer incidence and mortality by investing appreciable resources to maintain the public-health infrastructure of coverage, quality assurance and case management that is required for such programs to operate optimally. Such resources are largely beyond the means of developing countries. There is growing concern that Pap screening is largely inefficient because of its high false-negative rate, but especially in view of the strong evidence that now favors tests for the DNA of oncogenic HPVs to improve the accuracy of early detection [4]. Most importantly,

however, as covered in this Special Focus issue of *Therapy*, we now have HPV vaccination, which emerged in 2006 as a promising evidence-based technology for the primary prevention of cervical cancer [5,6]. In optimal combination, these two strategies – prophylactic HPV vaccination and HPV testing in screening – have the potential to bring unprecedented gains in reducing the burden of cervical cancer worldwide [7].

This Special Focus issue provides an eclectic and cutting-edge view of the evidence for the efficacy of HPV vaccination in preventing cervical cancer and other HPV-associated diseases, of the immune response mechanisms augmented by the HPV vaccines, and of the public-health issues related to vaccine implementation and screening technologies. The contributions are by well-known senior scientists and public-health actors in the field of HPV research. Much has been written on these themes in recent years, but we believe that *Therapy* readers will find in the articles that follow many new insights, provocative positions, and plenty of inspiration to help them appreciate the challenges that lie ahead.

Five review articles set the stage for the accrued knowledge on HPV vaccination and preventive technologies. Diane Harper provides a lucid overview of the vaccine formulations, study methods, and results from Phase II and III randomized controlled trials of both HPV vaccines, Merck's Gardasil® and GlaxoSmithkline's Cervarix® [8]. Because of the inherent differences in study designs and methods used by the two vaccine teams, it is a daunting task to summarize efficacy results for both virological and lesion end points. Harper juxtaposed the efficacy estimates to assist the reader to appreciate the importance of these differences and to provide a general picture of the strong protection conferred by both vaccines. Against this backdrop of a strong preventive effect against cervical cancer precursors, Jorma Paavonen summarizes the findings on the efficacy of vaccination in preventing vaginal and vulvar pre-cancerous lesions with the quadrivalent vaccine (Gardasil), as the bivalent Cervarix has not yet been evaluated with respect to these end points [9]. Again, there is much reason for enthusiasm as one learns that the umbrella of protection

conferred by HPV vaccination is wide enough to potentially prevent all female lower genital tract cancers associated with the vaccine-targeted HPV types. Matti Lehtinen *et al.* revisit the point of coverage from the perspective of evaluating herd immunity and cross-protection in an optimally designed community-randomized trial of HPV vaccination, which is now ongoing in Finland [10]. They argue convincingly that such studies will provide the necessary evidence to evaluate the population impact of HPV vaccination, which is likely to be positively influenced by herd immunity in contributing to decreased HPV transmission and negatively affected by HPV type replacement. The latter potential issue is a theoretical concern that has little biological plausibility, but must be verified empirically. Lynette Denny provides an overview of old and new cervical cancer prevention strategies as they apply to the high disease burden of developing countries [11]. Challenges abound, but new low-tech approaches, such as visual inspection with acetic acid in connection with a 'screen-and-treat' strategy, will stand as viable alternatives, as long as universal deployment of HPV vaccination remains an unfulfilled goal for most African and Latin American countries, the very regions in which the need for effective preventive strategies is the greatest. The aforementioned two vaccines aim at inducing a strong humoral response against the major L1 viral capsid protein, thus producing a sufficiently high concentration of neutralizing antibodies that can block the binding of infective virions to the basal epithelial cells in the genital mucosa. However, a critical caveat of prophylactic HPV vaccination is that it is ineffective against infections that have already become established, either productive or latent. Therefore, development of therapeutic HPV vaccines is a most worthwhile pursuit, as reviewed by Andreas Kaufmann and Achim Schneider [12]. There is feverish research activity to this end, with many promising candidate vaccines, but, so far, few formulations have reached the stage of Phase II trials. Ultimately, the availability of one or more efficacious therapeutic vaccines will contribute a key supplemental strategy towards the goal of eradicating cervical cancer one day.

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In addition to the above in-depth reviews, two Perspective articles in this issue of *Therapy* expand the scope of the public-health science concerning HPV vaccines and screening. Xavier Bosch and colleagues provide a rationale for policy makers in establishing priorities for the population subgroups that should receive prophylactic HPV vaccination [13]. They argue on the basis of short-term (reduction of precancerous lesions and genital warts) and long-term (cancer) outcomes, which vary by vaccine immunogen composition. Trimble *et al.* peer into the future by examining the next generation of vaccines and promising screening technologies, while reassessing many of the issues dealt with by other contributors in this issue [14].

The News & Views section contains a medley of recent newsworthy items on the topic of HPV prevention. Rachel Skinner and Julia Brotherton review research highlights [15], and an interview with Kevin Ault, a leading author of the studies involving the quadrivalent vaccine, provides sensible answers to questions that are in the minds of most healthcare professionals [16]. In an editorial, Joseph Monsonego shows how professional societies can lead policy making into effective and rapid action by examining the role of EUROGIN in the fight against cervical cancer [17]. Finally, Nishida *et al.* delve deep into the issue of cross-type protection, by examining the biological basis for the expectation of this serendipitous bonus in the overall protection that the anti-HPV 16/18 vaccines can provide [18]. Despite the weight of evidence favoring cross-type protection, the authors caution that the ideal vaccine should be one that is able to induce strong immunity against a broad spectrum of types.

In a field where corporate interests have influenced technological progress to a substantial degree, it is important that we qualify the contributions in this issue of *Therapy*, all of which stemmed from solicited invitations by the two guest editors to prominent scientists and clinicians. Production of this thematic issue was not funded by a pharmaceutical or biotechnology company. However, readers will no doubt notice the authors' disclosure statements regarding sources of funding, some of which reveal ties with

the commercial stakeholders in the HPV and cervical cancer biotechnology sector. Lest one perceives grant funding as irrevocably linked with biased opinions, we urge readers to consider that the authors' involvement in advising the commercial stakeholders in the HPV industry should be viewed as a natural consequence of their long-standing and strong engagement with research and practice in cervical cancer prevention. Progress in the development of novel cervical cancer prevention strategies, such as HPV vaccines and screening, would not have been as properly guided if it were not for the countless prominent scientists who donated their time and expertise to advise the industrial sector on what the community expected of the candidate technologies. Prophylactic HPV vaccines and new screening

techniques are now a reality that stemmed from this dynamic partnership between industry and academic scientists and clinicians.

Financial & competing interests disclosure

Dr Franco has occasionally served on advisory boards for GlaxoSmithKline, Merck, Roche, and GenProbe. Dr Paavonen has received research grants from GlaxoSmithKline and Merck through the Helsinki University Hospital for conducting clinical trials of the vaccines, and received lecture fees or honoraria from both companies. The authors have 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.

Bibliography

- IARC Working Group: Human papillomaviruses. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (Volume 64). IARC Press, Lyon, France (1995).
- Walboomers JM, Jacobs MV, Manos MM *et al.*: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J. Pathol.* 189, 12–19 (1999).
- Ferlay J, Bray F, Pisani P, Parkin DM: GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. *IARC CancerBase No. 5. version 2.0*, IARC Press, Lyon, France (2004).
- Mayrand MH, Duarte-Franco E, Rodrigues I *et al.*: Canadian Cervical Cancer Screening Trial Study Group. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N. Engl. J. Med.* 357, 1579–1588 (2007).
- Harper DM, Franco EL, Wheeler CM *et al.*: HPV Vaccine Study group: Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomized control trial. *Lancet* 367, 1247–1255 (2006).
- Villa LL, Costa RL, Petta CA *et al.*: High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br. J. Cancer* 95, 1459–1466 (2006).
- Franco EL, Cuzick J: Cervical cancer screening following prophylactic human papillomavirus vaccination. *Vaccine* S26, A16–A23 (2008).
- Harper DM: Prophylactic human papillomavirus vaccines to prevent cervical cancer: review of the Phase II and III trials. *Therapy* 5(3), 313–324 (2008).
- Paavonen J: Efficacy of a prophylactic human papillomavirus vaccine against high-grade vulval and vaginal intraepithelial neoplasia. *Therapy* 5(3), 325–328 (2008).
- Lehtinen M, French KM, Dillner J, Paavonen J, Garnett G: Sound implementation of human papillomavirus vaccination as a community-randomized trial. *Therapy* 5(3), 289–294 (2008).
- Denny L: Prevention of cervical cancer in developing countries. *Therapy* 5(3), 329–338 (2008).
- Kaufmann AM, Schneider A: Therapeutic human papillomavirus vaccination. *Therapy* 5(3), 339–348 (2008).
- Bosch FX, de Sanjosé S, Castellsagué X: Evaluating the potential benefits of universal worldwide human papillomavirus vaccination. *Therapy* 5(3), 305–312 (2008).
- Trimble CL, Gravitt P, Roden RBS: Human papillomavirus screening and vaccines for cancer prevention: what is on the horizon? *Therapy* 5(3), 295–303 (2008).
- Skinner RS, Brotherton J: Research highlights. *Therapy* 5(3), 283–287 (2008).
- Ault K: Interview. *Therapy* 5(3), 279–281 (2008).
- Monsonego J: The need for actions to effectively prevent cervical cancer: priorities and future directions of EUROGIN. *Therapy* 5(3), 269–272 (2008).
- Nishida KJ, Pearson JM, Twiggs LB: Cross-protection from human papillomavirus 16/18 against types 45 and 31: fact or fancy? *Therapy* 5(3), 265–268 (2008).