

Assessing the effectiveness of human papillomavirus (HPV) vaccination to prevent cervical cancer: perspectives from Germany

For approximately 2 years now, cervical cancer has been "converted" from an oncological disease to an infectious disease, which is said to be preventable by and large by two vaccines licensed in many countries. However, human papillomavirus (HPV) vaccines differ from existing others, as the former target a condition which only in a minute fraction of infections will lead to serious consequences, but after a long(er) latency period. Furthermore, it should be kept in mind that in clinical trials, the quadrivalent vaccine was tested in fewer than 1200 girls 16 years and younger.¹

In Germany, as in many other countries, HPV vaccines targeting two of 15 oncogenic² HPV types are being positioned by pharmaceutical companies and universities based clinicians and scientists as a single though profoundly effective medical measure to eradicate a substantial proportion of the burden of disease indeed constituted by the occurrence of cervical cancer for the individual woman and her family. HPV vaccines primarily target individuals and in this case female minors and their parents, particular mothers. However, published data for periods beyond 2 years were not available in spring 2009 as to what fraction of cervical intraepithelial lesions (CIN) grade 2 or worse and cancer incidence, respectively, are indeed prevented in young girls not infected with any HPV type prior immunisation with a vaccine targeting HPV types 16 and 18. In spring 2006, an analysis of vaccine efficacy against CIN 2+ due to any HPV type among subgroup of girls/women (per protocol population) for all four vaccine-relevant HPV types showed an observed reduction of (only) 16.9% regarding these lesions³ (for a discussion of published efficacy data in Germany, see also Gerhardus et al⁴). Yet, data were recently published on the impact of the quadrivalent vaccine on cervical disease due to non-vaccine HPV types in a subset of girls and women aged 16 and older participating in licensing trials and followed for up to 4 years.⁵

Thus, the efficacy of the licenced vaccines to prevent cervical cancer is unknown; in other words, it is unknown whether vaccinations are indeed a "magic bullet," a term also used recently to re-evaluate menopausal hormone therapy, the benefits of which were not "magic" after all. Perhaps the magic of female nature in this case is that most infections (approximately 90%) are dealt with very effectively and permanently in immunocompetent (young) women. Therefore, girls/women with HPV infections are highly unlikely to develop invasive cervical cancer. This is crucial risk information not transported affirmatively by various parties actively promoting HPV vaccination.⁶

HPV vaccinations do not deconstruct the multifactorial nature of cervical cancer deeply affecting (sexual) life, not only for girls and women and (their) mothers but also for boys, men and fathers. HPV infection is more than an individual risk to be managed by an individual. If exogenous or endogenous factors such as high parity, smoking or long-term use of oral contraceptives interact with both the central and strong effect of HPV, cervical cancer may develop. Additional cofactors such as herpes simplex virus type 2, chlamydia trachomatis, and states of immunosuppression including infection with HIV also need consideration. It is beyond the scope

of this essay to address nutritional deficiencies, probably reflecting the socio-economic position of girls and women, not least in developing countries with by far the greatest burden of disease,⁷ and genetic susceptibility.

It was possible to reduce the impact of cervical cancer with the technology of screening utilising Pap smears worldwide. Presently, cervical cancer is the twelfth most frequent cancer in German females and accounts for approximately 6200 incident cases annually (data from the German Cancer Research Center: http://www.dkfz.de/en/krebsatlas/total/organ_e.html; updated 6 May 2009, accessed 12 August, 2009). In 1971, when the incidence of cervical cancer was much higher, an annual free-of-charge Pap smear was introduced in the former West Germany for women 20 years and older.⁸ This deviates from internationally recommended screening intervals of 3–5 years. This "statutory early detection programme" is a self-referring opportunistic screening system, without invitations and without establishment of a registration system, and not least without any known individual adherence of women. Thus, it is unknown which women attend services providing smears, and how often they do this within a given time interval. However, in Germany, a strong decline of both incidence and mortality by about 80% since the 1960s is evident.⁹

Regional study data from the state of Bavaria in Germany indicate that the highest cervical cancer screening participation was among women aged between 20 and 29, and participation rates decreased progressively with increasing age.¹⁰ Participation was lowest for women above 70 in rural areas, and in some fewer than 20% had at least one screening within 3 years. Additionally, participation rates were lower in areas with lower average household income, independent of access to gynaecological services, where by far most of the screening tests are performed.¹¹ Acceptance of services is crucial, in particular in older women and those in a disadvantaged socio-economic position. Recently, data from the European Prospective Investigation into Cancer and Nutrition (EPIC; Heidelberg cohort) were analysed to quantify personal adherence and to investigate the sociodemographic characteristics of attending women. Analyses showed that about 44% of women attended cervical cancer screening at least three times within an average of 8.3 years of observation, 74% at least twice and 93% at least once. Attendance was strongly associated with women's age, educational attainment and vocational training in this non-population-based cohort of metropolitan women with a higher-than-average social status.¹²

There are few systematic studies assessing the quality of cervical cancer screening in Germany.¹³ In one study the sensitivity of a single Pap smear for the detection of CIN2/CIN3 was 43.5% and only 20% in a further regional study.^{14 15} Thus, it is mandatory to also improve the quality of cervical cancer screening.

Where do we go from here? We do not know how available HPV vaccinations affect cervical tissues in the longer term and mortality from cervical cancer. We also do not know whether the attitude of vaccinated (and non-vaccinated) girls and women towards screening tests will change in the future. Thus, we are not able to appraise the contribution of HPV vaccines to decrease the burden of cervical cancer today in Germany. At the very least, one should consider whether the present screening systems need to be changed to a formal standardised invitation programme, particularly with regard to concepts to reach older and/or disadvantaged women in Germany. The "German system" should be restructured: written invitation and quality assurance according to existing European Guidelines. The written

invitation would cover the entire population including those groups with a low attendance. The European 3-year intervals, instead of a 1-year interval, only if combined with quality assurance of the smear evaluation, have the potential to increase the effectiveness of the programme and potentially even decrease its costs, if we assume that results, related to both attendance rates and quality, from other European countries (ie, in Finland, The Netherlands) are basically transferable. According to the IARC, the effectiveness of organised cervical screening is higher than that of opportunistic screening.¹⁶

As HPV vaccinations are available, the least we should do is to discuss a registry with a wide range of medical and socio-demographic determinants of the health of girls and women choosing or not choosing to be vaccinated, and link this complex information to cancer registry data. This long-term effort could provide some answers related to the effectiveness of HPV vaccines not available today.

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