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Invited Editorial

Human papillomavirus vaccines: A great leap forward

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In September 2006, the European Medicines Agency (EMA) approved the use of the Gardasil 4 vaccine against human papillomavirus (HPV) strains 6, 11, 16 and 18. A year later, the bivalent vaccine Cervarix against HPV strains 16 and 18 was approved by the EMA. In the UK, the National Health Service (NHS) implemented a national immunisation programme for girls with Cervarix in September 2008, then switched to the use of Gardasil 4 in 2012, in order to reduce the incidence of cervical cancer due to persistent infections with HPV 16 and 18 as, in the UK, those two HPV strains are responsible for approximately 80% of all cervical cancers [1]. Routine vaccination was offered to girls in year 8 at school, that is, aged 12–13 years. So-called catch-up programmes were offered to women up to the age of 25 years.

In the last couple of years, several studies have been published that have established the efficacy and effectiveness of the HPV vaccine against HPV infection and high-grade cervical lesions, namely cervical intraepithelial neoplasia (CIN 2) and CIN 3. A decade after the introduction of the HPV vaccine in England, HPV 16, 18, 31, 33 and 45 infections had substantially decreased, as seen in women screened for chlamydia [2]. Since a span of 5–20 years has been shown between the acquisition of a persistent HPV infection and the emergence of cervical cancer [3], one would expect the effects of the vaccine on the incidence of cervical cancer in England to be evident now, 13 years after the introduction of the vaccination programme.

Studies looking at the incidence of cervical cancer since the introduction of HPV vaccination, however, have been scarce, even though a reduction in the risk of invasive cervical cancer is the ultimate intent of the vaccination. In 2018, a study reported in the *American Journal of Preventive Medicine* observed a significant decrease in the incidence of cervical cancer among young women after the introduction of the HPV vaccine [4]. Just last year, a retrospective Swedish population study looked at the relationship between the quadrivalent HPV vaccination and subsequent risk of invasive cervical cancer in girls and women who were 10–30 years of age (from 2006 to 2017). At the population level, a substantially reduced risk of invasive cervical cancer could be observed, the reduction being greater in women who had received the vaccine at a younger age (88% lower for women vaccinated before the age of 17 years than for women who had never been vaccinated against HPV) [5].

Now, finally, Falcaro et al. have published the data on the effects of the national HPV vaccination programme with Cervarix in England on cervical cancer and CIN 3 incidence, in *The Lancet* in December 2021 [6]. In this observational register-based study, the relative risk of cervical cancer in three vaccinated cohorts was compared with that in earlier cohorts, who had not received the vaccination. The three vaccinated cohorts were divided according to the age at which the women got their vaccine (16–18 years, 14–16 years or 12–13 years). Data extracted in January 2021 were assessed for diagnoses of cervical cancer and CIN 3 from January 1, 2006 to June 30, 2019 in women aged 20–64 years resident in England. In accordance with the other two studies mentioned above, this study showed a substantial reduction in cervical cancer and CIN 3 in young women after the introduction of the HPV immunisation programme, especially in women who had received the vaccine at the early age of 12–13 years. In this group, a relative reduction in cervical cancer of 87% and a 97% reduction in CIN 3 could be observed, compared with the reference unvaccinated cohort. In the age range of 16–18 years at the administration of the vaccine, those numbers were 34% and 39%, respectively, and for the age of 14–16 years 62% and 75%, respectively. Overall, the authors estimated that by the end of the study period, 448 fewer than expected cervical cancers and 17,235 fewer than expected CIN 3 precursor lesions had arisen.

This study strengthens the recommendation to administer the HPV vaccine at an early age, in order to achieve the most pronounced benefit, ideally before first sexual intercourse has taken place, as we know that the vaccine does not work in treating a preexisting HPV infection. The magnitude of the reduction among the women receiving the vaccine at the age of 12–13 years, however, seems to be also explained by the fact that the prevalence of HPV high-risk strains 16 and 18 (covered by the Cervarix vaccine) among women who were diagnosed with cervical cancer under the age of 30 in the UK was particularly high and that, potentially, the unvaccinated women profited from a certain amount of herd protection. Cross-immunity against other strains of HPV is also an ongoing subject of discussion and research.

At the moment, in Great Britain, HPV screening is not recommended

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to women under the age of 25. Starting at the age of 25, women are screened for HPV every 3 years up to the age of 49 years and then every five years between the ages of 50 and 64 years. The study presented here showed that the HPV vaccine given to girls in year 8 at school has almost eliminated cervical cancer and cervical precancer up to the age of 25 (during the course of the study, the screening recommendations had changed, as, previously, women were screened from the age of 20 years onwards).

It will be interesting to see in future studies how the introduction of the Gardasil 9 vaccine in June 2015, covering five further strains of high-risk HPV (HPV hr 31, 33, 45, 52 and 58), will impact the incidence of high-grade cervical lesions and invasive cervical cancer. The NHS is planning to switch to the use of that vaccine early in 2022. Additionally, future studies will show the effect of the decision of the NHS also to administer the HPV vaccine to year-8 boys from September 2019 onwards. If those studies were to include information on smoking status, sexual history or other lifestyle or behavioural factors, that had not been included in the current study, all the better.

Until these studies have been designed, completed and published, we know what to do: vaccinate, vaccinate, vaccinate!

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