How can we achieve HPV control in Europe?

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The upcoming year 2016 will be marked by two significant events: the ninevalent HPV vaccine will be available in Europe and The Netherlands will be the first country to implement primary HPV screening for the precursors of cervical cancer.

Europe has a substantial burden of HPV-related disease. More than 44,000 new cases of HPV-related anogenital cancers affect men and women in Europe annually [1]. In addition, more than 15,000 new cases of mainly HPV-16-related oropharyngeal cancer affect predominantly males. The estimation of genital precancer is in the order of 300,000 or more annual cases. Genital warts are a substantial limitation in the sexual well-being; probably more than 800,000 new cases are diagnosed in European females and males every year [2].

In 2006, a quadrivalent HPV 6/11/16/18 vaccine (Gardasil[®], Sanofi Pasteur MSD) became available, in 2007 a bivalent HPV 16/18 vaccine was licensed in Europe (Cervarix[®], GSK) [3].

These vaccines effectively prevent infections and disease caused by the two most potent oncogenic HPV types. The quadrivalent vaccine also prevents highly efficacious infections with HPV 6/11, causing approximately 90% of genital warts. Both vaccines have an excellent safety profile [4]. HPV 16 and 18 cause 70% of HPV-related cervical cancer but only 50% of cervical precancer. A vaccine covering HPV 16/18/31/33/45/52/58 potentially prevents 85–90% of cervical precancer, 90% of invasive cervical cancer and a substantial proportion of other HPV-related cancers [1,5].

In a Phase III study including young women aged 16–26, the ninevalent vaccine has been shown to prevent 97% of infections and lesions related to HPV 31/33/45/52/58 with a noninferior immunogenicity for HPV 6/11/16/18 [6]. In June 2015, this vaccine was licensed by EMA for females and males from the age of nine [7]. The immunogenicity has been even superior in boys and girls compared with young women [8]. It can be given concomitantly with other vaccines [9]. With this new vaccine, almost 40,000

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“For every vaccination program, coverage is key.”

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new cancers are potentially preventable annually in the long run, an additional 6000 cases in comparison to the first-generation vaccines [1].

So far only three European countries have achieved a sufficient coverage rate in the target population of adolescents. Denmark, Portugal and the UK have achieved 80% or more coverage in females, a prerequisite for the building of herd protection. Denmark has provided excellent data on the reduction of genital warts and cervical precancer [10]. In countries with a lower coverage gender-neutral vaccination is an even more important option. The quadrivalent vaccine has been demonstrated to be highly effective in preventing genital warts and anal disease in males [11,12]. A female-only program even with a good coverage leaves men having sex with men unprotected [13]. Austria was the first country worldwide to recommend HPV vaccination for both sexes as early as 2007, and in 2014 the first European country to provide a fully funded gender-neutral HPV vaccination program. This program focuses on the age group of 9–10-year-old children, with a catch-up to the age of 15 and is considered to be cost effective [14]. The young age for vaccination gives the opportunity to apply a two-dose schedule which is easier to apply and cost saving [15]. For every vaccination program, coverage is key. Vaccinating at a young age, preferably in a school-based program is most effective, however it remains to be evaluated up to which age such a catch-up program remains to be cost effective. Both first-generation vaccines have demonstrated clinical efficacy up to the age of 45 [16], and even after treatment for HPV-related disease, vaccinated persons have less subsequent disease [17].

Today, we are aware that HPV causes a broad spectrum of disease in both sexes, the prevention of cervical cancer remains a key issue. In eastern Europe, a high incidence is observed, but also in other parts of Europe women are still at risk of dying from this disease. Large trials have demonstrated that HPV testing is not only more sensitive in the detection of cervical precancer, it has also been shown that HPV testing is also superior in preventing invasive cervical cancer in comparison to cytology, a negative test almost excludes invasive disease for more than 5 years [18]. With HPV tests identifying the most important oncogenic types HPV 16 and 18, women at risk can be better stratified and undergo adequate treatment [19].

Other oncogenic HPV types cause cancer later in life, hence in women with non-HPV 16/18 infections conizations can be delayed and preterm deliveries avoided.

In an HPV vaccinated population, the positive predictive value of cytology screening is even lower. This favors primary HPV screening followed by triage cytology. The Netherlands introduces primary HPV testing in 2016, reducing the number of screening rounds to five. For noncompliant women who account for about 30% of the population and who have a higher risk of cervical cancer, the opportunity of HPV self-testing is offered. It has been demonstrated that this strategy has the potential to further decrease the number of cervical cancers [20]. HPV testing in the urine has shown promising results and may be an option for women reluctant to pelvic examination and even self-manipulation [21].

The future perspective is a sensible and cost effective combination of vaccination and screening. With a ninevalent HPV vaccine most of cervical and other HPV-related cancers can be avoided. A gender-neutral vaccination program at an early age with a broad catch-up for adolescents and even adults is currently the most effective way to prevent HPV-related infections and disease, in infants two doses of any HPV vaccine are probably sufficient and even one dose might be a future option [22]. In a nonvaccinated population, HPV testing is superior to the conventional PAP screening; in a vaccinated population it will become mandatory. A transition from the annual PAP smear, which is still practiced in countries like Germany to just a few lifetime HPV tests, has already started and screening algorithms will be adopted. The value of adult vaccination remains to be evaluated in upcoming large-scale trials [23].

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