Introduction
Cervical cancer prevention greatly evolved once the cause of the disease was identified: about 15 human papillomavirus (HPV) types (so-called high-risk genotypes) are the necessary cause of cervical cancer, and this applies for both squamous cell and adenocarcinoma.1,2 HPV types 16 and 18 are responsible for about 70% of cervical cancers worldwide. The epidemiological data complemented experimental data already available by the end of the 1980s, e.g. that (1) transcripts of specific HPV viral genes E6 and E7 were expressed in virtually all cervical cancers; (2) these genes were able to immortalize human anogenital epithelial cells upon transfection and to malignantly transform rodent cells; (3) these genes were essential for the maintenance of the malignant phenotype of cervical cancer cells.3 For all this papillomavirus research which ultimately led to the development of highly efficacious prophylactic HPV vaccines,

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was awarded the Nobel Prize for Medicine in 2008.4

Many approaches to develop a vaccine that protects against HPV infections have been attempted in the late 70’s and the 80’s but results were disappointing.5 The finding first in animals and subsequently in humans that through genetic engineering technology the L1 papillomavirus capsid proteins self-assemble into empty capsids or virus-like particles (VLPs) that are morphologically and antigenically almost identical to native virions brought the breakthrough in HPV vaccine development.6 A proof of concept study showed a 100% efficacy of such a subunit vaccine against incident HPV infection with the HPV16 genotype contained in the vaccine.7 This led to further commercial development of two HPV L1 VLP subunit vaccines licensed since 2006 and 2007. Both highly efficacious vaccines have the potential of substantially reducing HPV-related morbidity and mortality.

Characteristics of the vaccines
The quadrivalent vaccine (Gardasil®), first licensed in 2006 and contains VLP antigens for HPV6, 11, 16 and 18. The vaccine is produced by recombinant technology using yeast substrate and protects against cervical neoplasia caused by HPV16 and 18. It also protects against anogenital warts caused by HPV6 and 11, which cause about 90% of anogenital warts worldwide. The quadrivalent vaccine has aluminium hydroxyphosphate sulphate as adjuvant. The bivalent vaccine (Cervarix®), first licensed in 2007, contains VLP antigens for HPV16 and 18. The vaccine was developed using a recombinant
baculovirus expression system and a cell line derived from Trichoplusia ni cells. The bivalent vaccine protects against cervical neoplasia caused by HPV16 and 18. The adjuvant used is ASO4 which includes 3-O-desacyl-4’monophosphoryl lipid A and aluminium salt.

Both vaccines are given as intramuscular injections in three doses within six months (0, 2 and 6 months for the quadrivalent vaccine; 0, 1 and 6 months for the bivalent vaccine). Currently there is no recommendation for a booster dose. Both vaccines are liquid, and need to be stored between 2 and 8 degrees Celsius.

Efficacy

High-grade cervical intra-epithelial neoplasia (CIN2+) and adenocarcinoma in situ (AIS) are used as endpoints of vaccine efficacy in clinical trials. Phase II and III clinical trials were conducted in females aged 15-26 years for the quadrivalent vaccine, and in females of 15-25 years for the bivalent vaccine. Immunobridging studies compared vaccine immunogenicity in girls aged 9-14 years with females aged 15-26 years. In the phase III FUTURE I trial, the quadrivalent vaccine showed 100% (95% CI: 94-100) efficacy against CIN2+ and AIS and against external anogenital lesions in a per-protocol analysis. In the FUTURE II trial, efficacy was 98% (95% CI: 86-100) against CIN2+ and AIS after 3 years of follow-up in a per-protocol analysis; vaccine efficacy against HPV types was 100% (95% CI: 61-100) for HPV 18 and 97% (95% CI: 84-100) for HPV 16. In a phase Ib trial the combined incidence of HPV6/11/16/18 related persistent infection or disease (CIN1-3, condyloma) was reduced by 96% (95%CI: 84-100) five years after vaccination. In a combined analysis of phase II and III trials of the quadrivalent vaccine, an efficacy of 18% (95%CI: 7-29) was observed in preventing CIN2+ and AIS due to any HPV genotype in an intention to treat analysis. A phase Ib trial with the bivalent vaccine at 6.4 years of follow-up showed protection against HPV16 and 18 endpoints as follows: 100% (95% CI: 86-100) against 6-month persistent infection, 100% (95% CI: 75-100) against 12-month persistent infection, 100% (95% CI: 73-100) against CIN1+, and 100% (95% CI: 51-100) against CIN2+. Vaccine efficacy against CIN2+ regardless of HPV type was 72% (95% CI: 21-92). In an interim analysis of the phase III PATRICIA trial after 14.8 months, bivalent vaccine efficacy in preventing CIN2+ lesions due to HPV16/18 was 90.4% (97.9% CI: 53.4-99.3) in an intention to treat analysis. In a per protocol analysis, 100% (97.9% CI: 74-100) vaccine efficacy against HPV16/18 related CIN2+ was observed. The quadrivalent vaccine showed a seroconversion rate of more than 99% in 9-15 year old boys. The anti-HPV geometric mean titres were 2.7-fold higher in boys as compared to adult women of 16-23 years of age. Vaccine efficacy in preventing persistent infection in males is 86% (95% CI: 75-92), and 90% (95% CI: 69-98) in protecting against external genital lesions. The bivalent vaccine showed a seroconversion rate of 100% in adolescent males (10-18 years old). The anti-HPV16/18 geometric mean titres were higher for males aged 10-18 years and 10-14 years, as compared to 15-25 year old females and 10-14 year old girls, respectively.

Duration of protection

Both vaccines are highly immunogenic and induce high levels of serum antibodies after three doses for all vaccine-related HPV types in more than 99% of females. Antibody levels after vaccination are several times higher than those produced after natural infection. They peak at month 7, gradually decline and level off after 24 months to remain stable at levels 10 to 20 times higher than after natural infection. The minimum protective level of antibodies is not known. Vaccine-induced neutralising antibodies might protect against new HPV infection, prevent current infection to become established at other sites and reduce viral load after shedding of viral particles. Vaccine-induced antibodies transudate from the serum to the cervical mucosa where they may bind to HPV particles, contributing to vaccine efficacy. After three doses of the quadrivalent vaccine, more than 99% of naïve subjects seroconverted for the four HPV types. Antibody levels were higher in 9-15 year old girls as compared to 16-23 year old women. After 24 months antibodies against HPV6, 11 and 16 were observed in 95% of vaccinated women, while antibodies against HPV18 were observed in 71.6% of vaccinated women. Efficacy against HPV18-related disease remains high (98.4%), and could be explained as vaccine-induced protection by immune memory. A fourth dose after five years induced a rapid increase in antibody levels, indicating an anamnestic response. A 100% seroconversion rate was observed with the
bivalent vaccine both in young adolescents (10-14 years old) as well as in older adolescents/young adults (15-25 years old). More than 98% of women remain seropositive for both HPV16 and 18 up to 6.4 years. Antibody levels are inversely related to age. The geometric mean titres were twice as high in the age group 10-14 years old compared to the age group 15-25 years old. The higher antibody titres in this younger age group might possibly result in longer antibody persistence. However, even in the older age group, the geometric mean titres remain at least eight times higher compared to those after natural infection. Also a high and sustained immune response was seen in women older than 26 years.

A comparison between the immunogenicity of the bivalent vaccine formulated with ASO4 and the same vaccine formulated with aluminium salt only, showed that the formulation with ASO4 induced a higher frequency of memory B cells, as well as a higher antibody response as compared to the aluminium salt formulation alone.

Cross-protection
Both vaccines have some cross-protection against other HPV types not included in the vaccines. Phylogenetically related HPV types (e.g. HPV18 and 45; HPV16 and 31) share cross-neutralising capsid epitopes possibly explaining the partial cross-protection. Cross-protection against HPV45 and HPV31 would be important as these HPV types are responsible for about 10% of all cervical cancer cases worldwide. HPV45 is especially important in adenocarcinoma, and protection against HPV18 and HPV45 could prevent adenocarcinoma which is difficult to reduce by screening.

The quadrivalent vaccine showed cross-protection against 6-month persistent infection with HPV31 of 46.2% (95% CI: 15.3-66.4), 56.9% against CIN1-3/AIS, and 70.0% against CIN2-3/AIS. Cross-protection was shown for HPV33: 28.7% against 6-month persistent infection, 39.2% against CIN1-3/AIS and 24% against CIN2-3/AIS. No protection against infection or lesions associated with HPV45 was observed. A protection of 32.5% was observed against CIN2-3/AIS with 10 combined non-vaccine oncogenic HPV types.

The bivalent vaccine showed cross-protection against 6-month persistent infection with HPV45 of 59.9% (97.5% CI: 2.6-85.2), HPV31 of 36.1% (97.5% CI: 0.5-59.5), HPV33 of 36.5% (97.5% CI: -9.9-64.0) and HPV52 of 31.6% (97.5% CI: 3.5-51.9). A protection of 27.1% was observed against 12-month persistent infection with 12 combined non-vaccine oncogenic HPV types.

Safety
Both HPV vaccines are safe and well tolerated. Local reactions like pain, swelling and redness were reported. However, the duration of these local symptoms was short. Reported systemic adverse events included fever, nausea and dizziness for the quadrivalent vaccine, and fatigue, headache and myalgia for the bivalent vaccine. No differences were noted in the proportion of women developing a serious adverse event between the vaccine and control groups. Both vaccines are also well tolerated in boys.

The HPV vaccines can be co-administered with other paediatric and adolescent vaccines. This was shown for the quadrivalent vaccine with the recombinant hepatitis B vaccine and with DTP-IPV, and for the bivalent vaccine with DTP-IPV.

It is not recommended to vaccinate during pregnancy, though no teratogenic effect has been observed in women who became pregnant during the vaccination period. Studies on the safety in HIV-infected individuals are ongoing for both vaccines.

Economic analysis and public health aspects of HPV vaccination
With the licensing of HPV vaccines, a powerful new tool to prevent cervical cancer has become available. As the effect of HPV vaccination on the incidence of cervical cancer can only be measured after several decades, vaccine effectiveness cannot be measured directly. Therefore, mathematical models play an important role in our understanding of the projected impact and economic aspects of HPV vaccination. These models use data from epidemiological studies of age-specific incidence of high-risk HPV genotypes, natural history of HPV infection, and vaccine efficacy to project vaccine effectiveness.

As vaccination against HPV16 and 18 has no effect on the clearance of pre-existing HPV16/18 infections, vaccine effectiveness is the highest when initial series are completed before sexual debut. High vaccine coverage of women alone, sustained over many decades, with a long duration of vaccine-conferred protection, would have the greatest impact on type-specific cancer incidence. Long duration of protection by initial series or boosters is necessary to
prevent high-risk HPV in older women who are no longer protected. High coverage in subsequent cohorts of young females will induce herd immunity. Vaccination of boys has little additional protective effect on cervical cancer in women. In many countries, the decision making process to introduce a new vaccine requires a cost-effectiveness assessment of that vaccine as a pre-requisite for public funding. The analysis should compare the cost-effectiveness of HPV vaccination with the existing prevention programme using cytological screening to determine the incremental cost-effectiveness. There are two main types of mathematical models to project the incremental cost-effectiveness of HPV vaccination. State-transition or Markov models simulate changes in health state due to HPV infection, screening, treatment and vaccination in a population where all probabilities are fixed at the start of the simulation. This model cannot simulate transmission dynamics and herd immunity. Dynamic models reflect changes in the transmission probabilities in the population as functions of time and age, and therefore can project complex transmission dynamics, including herd immunity. Both types of models use data from different sources on cost and effectiveness of existing cytological screening programmes and different strategies of HPV vaccination. For variables that are not yet determined (e.g. duration of immune protection) assumptions are made and the sensitivity of the effect on changing assumptions is measured. Combined sensitivity analyses of key epidemiological and economic assumptions are carried out by most studies to project a broad range of possible scenarios. Most economic studies on HPV vaccination measure the health gains as cost per quality-adjusted life years (QALYs). Studies in most high-income countries conclude that HPV vaccination is cost-effective in girls between 10 and 13 years of age with a vaccine that provides protection for at least 20 years, based on the criteria of the WHO Commission on Macro Economics and Health recommendations that compares incremental cost-effectiveness ratios with per capita Gross Domestic Product. A catch-up programme for a limited period of time in older girls up to 18 years of age may also be cost-effective but at a higher cost.

Cost-effectiveness and vaccine characteristics
The quadrivalent vaccine containing HPV genotypes 6 and 11 protects against genital warts which usually occur during the first years after sexual debut. The bivalent vaccine does not protect against genital warts. Studies from Canada, the UK and the USA projected the price reduction required to compensate for the quality adjusted life years gained from the prevention of genital warts by the quadrivalent vaccine between 22 and 35%. Both vaccines maintained protective efficacy against CIN2+ for more than 5 years. The bivalent vaccine uses a different adjuvant system (ASO4), which has shown a stronger immune response compared to aluminium salt only. Further follow-up is needed to establish possible differences in duration of protection between the two vaccines, which would require a revision of the cost-effectiveness projections.

Booster dose
Cost-effectiveness projections were done for Canada and the US on the assumption that a booster dose at age 22 would result in life-long immunity instead of the baseline assumption of life-long immunity after the initial series. The Canadian study projected that adding a booster dose would increase the cost per QALY for the health sector from €14,000 to €24,000. This considerable increase is related to the higher cost of vaccine administration at adult age through the private sector as compared to a school-based programme. For US projections, a booster dose would increase the cost from €28,000 for initial series to €53,000 (booster dose through the private sector, plus non-medical costs such as patients’ time and transportation).

Organisation of HPV vaccination
Countries with an effective school health system such as Belgium, Canada, the United Kingdom or the United Arab Emirates foresee to integrate HPV vaccination into the existing public funded school-based immunisation programmes. These programmes foresee HPV vaccination of annual cohorts in a particular grade such as the last grade of primary school or first year of secondary school without direct or indirect costs for parents. This approach is very efficient as illustrated by 8 out of 10 European countries that reported coverage rates of over 90% for adolescent school-based hepatitis B vaccination. This high coverage will reduce the circulation of high-risk HPV genotypes contained in the vaccine and thus partially protect the unvaccinated through herd immunity which further increases the effectiveness of the programme. School-based vac-
vaccination programmes also provide opportunities for students to learn about prevention of cervical cancer and adolescent health issues in general. Alternative vaccination strategies for example through the private health sector are more expensive as illustrated by the cost per QALY gained in school-based programmes of the United Kingdom (£19,000), and Canada (£21,000) as compared to HPV vaccination through the private health sector in the US (£43,000). Moreover, marginal cost-effectiveness of vaccination is highest if HPV vaccination reaches a population that has less access to screening which is less likely when vaccination as well as screening is organised through the private sector.40 Vaccination will significantly reduce cancers and precancerous lesions caused by HPV16 and 18. There is, however, still a need for a cervical screening programme to prevent cancer from other high-risk HPV genotypes. Vaccination will make the existing approach of high-frequency screening by cytology too costly and inefficient. HPV testing has the performance characteristics that make it an ideal primary screening test in such conditions. Cytology should be reserved for triage of HPV-positive cases because it is more likely to perform with sufficient accuracy under these conditions. Cervical cancer control programmes will therefore need to be re-evaluated to determine the best screening technologies and schedules to optimise cervical cancer prevention.46

Conclusion
Currently, two prophylactic highly efficacious HPV vaccines are available. These vaccines should be administered before the start of sexual activity. The cost-effectiveness of vaccination is mainly influenced by the age at vaccination, the duration of protection and the cost of the vaccine and the organisation of the vaccination programme. Several cost-effectiveness studies demonstrated that school based immunisation programmes are most cost-effective. The cervical cancer screening programmes must continue, but will need adaptation in the post-vaccination era.

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