Outcomes After HPV Vaccination

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Human papillomavirus (HPV) is a small, non-enveloped, double-stranded DNA virus of the *Papillomaviridae* family. This family contains hundreds of different viruses, in a wide range of hosts in both animals and humans, and at least 13 types are known to be oncogenic, i.e. responsible for cervical and other anogenital and oropharyngeal cancers. Since it was first causally implicated in the development of cervical cancer over 30 years ago, a large body of evidence has accumulated substantiating the causal role of certain high-risk subtypes of HPV [1]. HPV types 16 and 18 are known to cause about 70% of all cases of invasive cervical cancer worldwide [2], with type 16 reportedly having the greatest oncogenic potential, while low-risk HPV genotypes 6 and 11 are reported to be responsible for around 90% of cases of anogenital warts [3].

Over 600,000 new cases of anogenital and oropharyngeal cancers per year, accounting for 5% of all cancers, can be attributed to HPV infection, including virtually all cases of cervical cancer and 88% of anal cancers [4]. Indeed, cervical cancer is the first cancer to be recognized by the WHO as being 100% attributable to an infectious agent [5].

A review and synthetic analysis estimating the number of cancer cases attributed to infection in 2008 reported that among an estimated 12.7 million new cancers worldwide, around 2 million were attributable to infections, corresponding to 16.5% of cancer cases [6]. HPV was responsible for an estimated 610,000 cases worldwide (30% of all infection-attributable cancers), of which 490,000 occurred in less developed regions and the remaining 120,000 in more developed regions [6]. Cervical cancer accounted for half of all attributable cases in women. There were an

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estimated 311,365 deaths from cervical cancer worldwide in 2018, accounting for 7.5% of all female cancer deaths, and almost 6 out of 10 (59.4%) cervical cancer deaths occur in low and low-middle income regions [7].

HPV exclusively infects epithelial cells and exploits the differentiation pathway of epithelial cells to replicate itself; there is no viraemia. The virus penetrates the epithelium through microabrasions and infects the epithelial stem cells located in the basal layer of the epithelium. It does not cross the basement membrane and, as a result, escapes detection by the immune system. It also remains in the epithelium, and so, natural infection does not confer long-term protection against reinfection. The virus infects the basal layer stem cells and uses host cells to replicate viral DNA and express virally encoded proteins, delaying cell cycle arrest and normal differentiation [8]. This in turn allows further viral replication. Virus-encoded structural proteins L1 and L2 are expressed in the most superficial layers of the epithelium, assembled in the cell nucleus, and ultimately, new infectious virions are released with the cells as they are shed from the epithelial surface [4, 8].

Since persistent (>5 years) HPV infection with one of the high-risk genotypes has been proven to be a prerequisite for the development of HPV-related cancers [8, 9], prophylactic vaccines have been developed in recent years to prevent the future development of cancer or its precursors. The vaccines are prepared from purified L1 structural proteins and work by forming HPV type-specific virus-like particles (VLPs) that block interaction with the basal layer receptor, thus reducing the number of cells that are infected after challenge with the virus, which in turn contributes to preventing clinical disease. The vaccines contain no live biological products or viral DNA and, thus, do not cause active infection. Currently, three different vaccines are commercially available (Table 5.1), covering up to nine different HPV types. Although other HPV types are not currently included in marketed vaccines, there is such a wide array that the cost of including them in vaccines largely outweighs the potential benefit to be gained, thus making it unrealistic in the current context to expand vaccination to these types. Indeed, the 9-valent vaccine currently on the market covers up to 90% of the cancer-causing HPV types, and in a randomized trial, efficacy in terms of the rate of high-grade cervical, vulvar, or vaginal disease related to the five additional oncogenic types included in the 9-valent vaccine was 96.7% (95% confidence interval, 80.9–99.8) [10]. In addition, antibody

Table 5.1 Human papillomavirus vaccines available as of May 2018

	Bivalent	Quadrivalent	Nine-valent
Trade name	Cervarix®	Gardasil®	Gardasil-9®
Manufacturer	GlaxoSmithKline	Merck Sharp & Dohme	Merck Sharp & Dohme
HPV genotypes	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Adjuvant	AS04: 500 μg aluminium hydroxide, 50 μg 3-deacylated monophosphoryl lipid A (MPL)	225 μg amorphous aluminium hydroxyl-phosphate sulphate	500 μg amorphous aluminium hydroxyl-phosphate sulphate

responses to HPV-6, HPV-11, HPV-16, and HPV-18 were noninferior to those generated by the quadrivalent vaccine [10].

Since HPV vaccination first started to be included in national vaccination policies in 2006, when the quadrivalent HPV vaccine was introduced in the USA and in Sweden, there have been a large number of publications reporting evidence of the significant positive impact of vaccination on genital warts, cervical abnormalities, and HPV prevalence. In a report from Australia, where free quadrivalent HPV vaccines were provided to girls aged 12–18 and women up to 26 years of age, free of charge, from mid-2007 to 2009, Read et al. reported the near disappearance of genital warts among young women with a decline from 18.6% to 1.9% in women under 21, accompanied by a corresponding decrease in heterosexual men aged under 21 years from 22.9% to 2.9%, even though men were not vaccinated [11]. In a meta-analysis of 20 studies undertaken in 9 high-income countries, representing more than 140 million person-years of follow-up, Drolet et al. reported that in countries with HPV vaccination coverage of at least 50% among women, infections with HPV types 16 and 18 decreased significantly between the pre- and postvaccination periods by 68% (relative risk (RR) 0.32, 95% CI 0.19–0.52) [12]. There was also a significant reduction in HPV types 31, 33, and 45 in the same age group, suggesting cross-protection, while there was also evidence of herd protection with significant reductions in anogenital warts in boys younger than 20 years of age and in women aged 20–39 years [12]. Interestingly, in countries where female vaccination coverage was lower than 50%, significant reductions in HPV type 16 and 18 infection (RR 0.50, [95% CI 0.34–0.74]) and in anogenital warts (0.86 [95% CI 0.79–0.94]) were seen in girls aged less than 20 years, but there was no evidence of cross-protection or herd effects [12].

In line with the findings in terms of HPV infections, there is a large body of evidence in support of the effectiveness of HPV vaccination against cervical abnormalities. Data from Victorian Cervical Cytology Registry in the state of Victoria, Australia, show that declines are now being observed in the rate of high-grade cervical abnormalities in the 25–29-year age group, with the first suggestion of a downturn in the long-term slow increase in rates in the 30–34-year-old age group, since the introduction of HPV vaccination among adolescent girls [13, 14]. The oldest women vaccinated as adult women as part of the catch-up programme in Australia are now 35 years old, so this suggests that new infection and disease are now being prevented in this population also, even though they may have had prevalent infection at the time of vaccination [13, 14]. Follow-up through a population-based cancer registry of two Finnish vaccination trial cohorts and unvaccinated controls demonstrated that HPV vaccination had sustained protective effectiveness against cervical intraepithelial neoplasia grade 3, irrespective of HPV type, at 10 years post-vaccination [15, 16]. This beneficial effect has recently been confirmed to extend to invasive cancer, in a report of follow-up of these same cohorts of HPV-vaccinated and HPV-unvaccinated females originally aged 14–19 years [17]. This is the first evidence that HPV vaccination provides protection against invasive cervical cancer and is a fundamental argument underpinning the need to continue and expand implementation of vaccination programmes in young women.

5.1 Future Prospects

Overall, to date, over 100,000 subjects have received HPV vaccines in randomized trials, and in routine practice, over 240 million doses of HPV vaccine have been distributed, with an estimated 60 million persons vaccinated. There have been 8 reviews by the WHO of HPV vaccine safety in over 60 countries, of which 30 are in Europe, which have introduced routine HPV vaccination, including a growing number of countries that also vaccinate males. The results are overwhelmingly in favour of vaccination programmes and their efficacy against HPV-induced infections as well as against cervical cancer and its precursors. Side effects from vaccination are minor and infrequent. In this context, it is clear that there is sufficient compelling evidence to recommend that vaccination of girls must continue and expand (i.e. to two-dose regimes). Vaccination of boys, already started in some countries, also deserves to be extended, while studies are ongoing regarding the utility of HPV vaccination in middle-aged women and high-risk groups. Finally, the WHO is considering including cervical cancer among the diseases that could be eliminated by intelligent combinations of vaccination and screening, which would indeed represent a huge step forward in terms of public health around the world, ensuring highly effective and evidence-based protection for future generations.

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