Chapter 14: HPV vaccine introduction in industrialized countries

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Abstract

Introduction of a vaccine requires the achievement of three initial milestones. These are licensure by a national control authority that determines the vaccine is safe and effective, development of recommendations for use by expert advisory bodies on immunization, and obtaining funding for vaccination. Once these milestones have been achieved, a successful vaccination program requires that a number of interlinked programmatic components be brought together in a coordinated fashion. These include vaccine purchase and supply, vaccination service delivery, high coverage rates, surveillance of the vaccination program, immunization finance policies and practices, and political will. Human papillomavirus (HPV) vaccination provides unique challenges in all of these areas because of the many gaps in our knowledge.

Keywords: HPV; Vaccines; Vaccine introduction

1. Introduction

This chapter focuses on the vaccine delivery systems available in industrialized countries, reviews the lessons learnt from the integration of other recent vaccines in immunization programmes, addresses issues specifically relating to the introduction of HPV vaccines and raises a substantial number of questions regarding HPV vaccination that need to be addressed as additional scientific data become available. As with all vaccines, it is likely that the introduction of HPV vaccination will evolve through multiple stages and that there will be large differences between countries in how vaccination is implemented. Therefore, in this chapter we will compare how HPV vaccines are likely to be introduced in industrialized countries, using countries in the European Union and North America as examples. These examples were selected because they have widely varying approaches to vaccination.

2. Elements required for introduction of a vaccine

In most industrialized countries there are three elements to the introduction of a new vaccine. The first is licensure. Almost all countries have a national control authority that must license vaccines after determining that they are safe and effective. In the US, vaccines are licensed by the Center for Biologics Evaluation and Research at the Food and Drug Administration, and in Canada by the Biologics and Genetic Therapies Directorate of Health Canada. Previously, individual countries in Europe licensed vaccines according to local regulations. Now, new medicinal products, including vaccines, introduced in the 25 EU countries are licensed through a centralized procedure at the European Agency for the Evaluation of Medicinal Products (EMEA), located in London, UK.

The second element is the development of recommendations for use. Most countries have expert advisory bodies on immunization that advise the national immunization program on which vaccines should be incorporated and on vaccination schedules. In the US, recommendations for use of childhood vaccines are made by two groups: The Centers for Disease
Control and Prevention (CDC) and the American Academy of Paediatrics (AAP). The CDC recommendations are developed by the Advisory Committee on Immunization Practices (ACIP), which is a federal advisory panel that is organized and overseen by the CDC and advises the Director of the CDC and the Secretary of the Department of Health and Human Services on how vaccines should be used and whether federal funds should be used to pay for them. The second group is the AAP, which publishes recommendations for paediatricians on vaccination schedules and doses. For the last decade these two groups, together with the American Academy of Family Practitioners (AAFP), have collaborated to publish a single, harmonized, childhood vaccination schedule. Since 2002 the CDC has also produced an adult immunization schedule for individuals 19 years and older. This adult schedule has been formally accepted by the AAFP and the American College of Obstetricians and Gynecologists (ACOG).

Most countries in the EU have a national advisory committee on immunization that makes recommendations to the responsible ministry. The impact of these recommendations varies depending on how centralized the country’s immunization programme is and the balance between public- and private-sector vaccination. In an increasing number of countries, such as Belgium, Italy and Spain, individual regions within the country are responsible for providing preventive health services and overseeing public health. Thus, recommendations of the national advisory committee are often applied at the local level. The types of vaccine and the vaccination schedule are determined by the national committees, but local health authorities control procurement issues. In France, for example, immunization policies are decided and implemented at the national level, but may be adapted at the regional level according to epidemiological situations.

In Germany, individual physicians have responsibility for vaccinations; there is no other organizing body or system.

The third element is funding. In almost all countries funding for vaccination comes from both the public and the private sector, albeit to highly varying degrees. Funding for childhood immunization in Europe varies considerably between countries [1]. In the UK, all infant and childhood vaccinations are free—they are purchased by the government and provided by general practitioners. In France, private paediatricians administer most infant and childhood vaccinations and most of the cost incurred is reimbursed by the government. In Germany, nearly 90% of the population is covered by compulsory health insurance and approximately 10% by private health insurance. All of the German health insurance companies pay for recommended vaccines. In Scandinavian countries, vaccinations are free and are most often offered by primary care nurses. Adult vaccination in many EU countries is predominately available through the private sector and the vaccinee has to pay the full cost of vaccination. In some countries, health insurance reimburses part of the vaccine cost in adults, typically after the vaccine has been on the market for some years.

Public-sector funding for childhood vaccination in the US is derived from two major sources: the vaccines for children (VFC) program and the federal 317 grant program [2]. The VFC program provides free vaccines to participating providers so that they can vaccinate children 18 years and younger who are poor, uninsured or are Native Americans or Native Alaskans. The 317 program provides federal funding to states and local governments for vaccines given to children who receive their vaccines in state and local health department clinics. Approximately 56% of routine childhood vaccines are currently purchased with public funds in the US [2]; the other 44% of vaccines are provided through the private sector. Many of the more traditional insurance programs in the US do not cover preventative services such as vaccines, or cover them only after an individual or family has met their annual deductible, a defined sum of money that must be paid by the individual for healthcare. As in many EU countries, in the US, the federal government plays a much more restricted role in providing vaccines to individuals over the age of 18 years.

3. Target populations for HPV vaccination

The optimal target populations for the HPV vaccines have not yet been clearly defined and are likely to vary from country to country because of differences in available vaccination platforms, epidemiology and age at first intercourse/exposure to HPV. The current HPV vaccines are “prophylactic” vaccines rather than “therapeutic” vaccines. They have been shown to prevent HPV infections in young females 15–25 years of age who are DNA and serologically negative for the specific HPv types targeted by the vaccines. Currently, we have data from immunological bridging studies demonstrating good immune responses to the vaccines in boys and girls between 9 and 14 years of age and in 25–55-year-old females. It is important to emphasize that we do not yet know whether vaccination will provide any benefit in individuals already exposed to the HPV types being vaccinated for or what the effectiveness of the vaccines will be in women over the age of 25 years and in males.

3.1. Optimal age to initiate HPV vaccination

Childhood vaccination programs have become the cornerstone of vaccination programs globally. Vaccines against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B virus (HBV), invasive Haemophilus influenzae type b (Hib) and pneumococcal or meningococcal disease are given in infancy or early in the second year of life (measles, mumps, rubella, varicella) since early childhood is the time of highest morbidity and complications from these diseases. Although only 5% of HBV infections are contracted during childhood, more than 90% of infected infants become chronic carriers of HBV [3]. Thus, even with little morbidity of hepatitis B in children, universal childhood vaccination against HBV is the
most effective strategy for reducing morbidity and mortality from HBV in the general population. Given their long tradition, childhood vaccination programs are well-structured, well-established and accepted measures of prevention all over the world. However, childhood HPV vaccination is not currently feasible since we lack information on immunological responses to the HPV vaccines in this population or evidence that childhood vaccination will provide protection against HPV infections and HPV-associated diseases in later life.

Since HPV vaccines are prophylactic vaccines, the most appropriate target population for HPV vaccination will therefore depend on the age at which individuals first become exposed to HPV. HPV infections are both extremely common and readily transmitted between sexually active adolescents and young adults. Prevalence surveys of adolescent or college-aged women typically report that at any single point in time approximately 20–25% of sexually active young women are HPV-DNA-positive (Table 1) [4–7]. After 2–3 years of follow-up, the cumulative detection of HPV in sexually active young women is 59–82%. One study of Seattle college students found that over 20% became HPV-DNA-positive within 12 months of initiating sexual contact and this increased to 50% by 36 months (Fig. 1) [7]. In all four studies described in Table 1, HPV-16 and HPV-18 were among the most common HPV types found.

HPV can be transmitted through non-penetrative sexual contact as well as sexual intercourse. Therefore, to provide maximum protection the vaccines will need to be administered prior to the onset of any sexual activity. Global data are only available on the average reported age of first sexual intercourse, which varies considerably between countries and for males and females. The average reported age of first intercourse in selected EU countries and the US is shown in Table 2 [8]. For women, the average age at first sexual intercourse ranges from 15 in the Czech Republic to 20+ in Italy. For men, the earliest average age of first intercourse is 16 in Portugal and Iceland. However, in order to determine what levels of protection will be afforded by the HPV vaccines if targeted to a specific age group, data on the percentage of children of a given age that have ever had sex are also needed. This also varies considerably. In Portugal only 25% of 18-year-old women have been sexually active, whereas in Iceland 72% have been (Table 2). Survey data from various locales in the US obtained by the CDC demonstrate dramatic differences according to the sex and race of respondents as well as the geographic location (Table 3) [9]. Only 12.1% of boys and 5.0% of girls 11–12-years-old in middle school in Wyoming self-report having had sexual intercourse. For comparison, 29.8% of boys and 11.9% of girls of the same age living in Mississippi report having had sex. It is likely that similarly wide variations in age at first intercourse exist in other industrialized countries. Therefore, in order to assure that recipients receive maximum protection, we would need to target young adolescents (9–13 years of age) for vaccination.

Table 1
Prevalence and cumulative detection rates of HPV in young women (adapted from refs. [4–7])

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>No.</th>
<th>Mean age (years)</th>
<th>Follow-up (months)</th>
<th>Percent HPV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enrolment (%)</td>
</tr>
<tr>
<td>Woodman et al.</td>
<td>2001</td>
<td>UK</td>
<td>2011</td>
<td>18</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>2003</td>
<td>Canada</td>
<td>621</td>
<td>23</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Winer et al.</td>
<td>2003</td>
<td>US</td>
<td>553</td>
<td>19</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>2005</td>
<td>US</td>
<td>60</td>
<td>15</td>
<td>26</td>
<td>28</td>
</tr>
</tbody>
</table>

^a NA, not available.
Table 3
Young adolescents in the US reporting having had sexual intercourse (adapted from ref. [9])

<table>
<thead>
<tr>
<th>School gradea</th>
<th>Percentage (95% CI) self-reporting sexual intercourse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wyoming</td>
</tr>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Sixth grade</td>
<td>5.0 (3.8)</td>
</tr>
<tr>
<td>Seventh grade</td>
<td>11.0 (3.9)</td>
</tr>
<tr>
<td>Eighth grade</td>
<td>12.5 (3.4)</td>
</tr>
</tbody>
</table>

a Sixth grade is typically 11- and 12-year-old, seventh grade is 12- and 13-year-old, and eighth grade is 13- and 14-year-old.

The pivotal phase-III clinical trials of the two HPV vaccines were restricted to women 15–25 years of age. It was not feasible to demonstrate efficacy in younger populations because it would have taken years before most of the trial participants became sexually active. Therefore, “bridging” immunogenicity studies have been conducted in younger girls and boys 9–14 years of age which demonstrate that the HPV vaccines produce at least as robust an immune response in the younger population as in 15–25-year-olds.

3.2. Vaccination of sexually active women

Vaccination of sexually active women, of any age, is controversial. The controversy stems from competing views of the role of vaccination in public health. One view contends that since HPV vaccination is likely to be relatively expensive and will be most effective when administered to young adolescent girls (9–13 years of age) prior to sexual debut, it should be restricted to this target population. The other view contends that since many sexually active adolescents and women will benefit from vaccination, depriving these women of the potential benefits of vaccination would be inequitable.

A number of points need to be considered when deciding whether vaccination will benefit a sexually active woman, of any age. The first is whether or not the woman has previously been exposed to any, or all, of the HPV types being vaccinated for. The phase-III trial of the quadrivalent vaccine enrolled over 20,000 women with a mean age of 20 years, 94% were non-virgins, the mean age at first sexual intercourse was 17 years and the mean number of lifetime sexual partners was two [10]. According to serological and HPV-DNA molecular testing, 71% of the enrollees appeared not to have experienced exposure to HPV-6, -11, -16 or 18, and very few women were DNA or serologically positive for all four of the HPV types being vaccinated for. Therefore, it can be reasoned that the vast majority of sexually active young women between 15 and 23 years of age would receive some benefit from “catch-up” immunization. It is important to stress that age is not necessarily a surrogate of sexual exposure. A 16-year-old with 10 lifetime sexual partners is more likely to have been exposed to HPV than a 23-year-old with one lifetime sexual partner. It also needs to be stressed that it is difficult to determine whether an individual has been previously exposed to HPV. HPV genotyping assays are likely to become commercially available in the near future and pre-vaccination testing using the HPV genotyping assays could potentially identify women already infected with the HPV types being vaccinated for. However, HPV genotyping assays will not accurately determine whether a woman has been previously exposed, they only determine whether or not the woman is actively shedding a given type of HPV on the day the test is administered. HPV serological assays are also not sensitive enough to provide an accurate assessment of whether or not a woman has been previously infected with HPV. Therefore, it is unlikely that pre-vaccination HPV testing of sexually active women will be recommended.

Other critical considerations are whether it is safe to vaccinate women already infected with the HPV type(s) included in the vaccine and whether women previously infected with HPV but who are now HPV-DNA-negative will receive benefit. The phase-II and phase-III trials have clearly demonstrated no increase in adverse events if women already infected with the types of HPV included in the vaccine are vaccinated (see Chapter 13). With respect to potential benefits of vaccination in sexually active women, it is important to note a couple of points. First, the HPV vaccines have not yet been evaluated in women over the age of 25 years, so we have no data to support their use in this population. Second, we do not know whether vaccination of women who have previously been infected with a type of HPV included in the vaccine but who are now HPV-DNA-negative will provide benefit. Theoretically, vaccination could protect these women from re-exposure to the same type of HPV or prevent reactivation of the HPV infection at some point in later life. Large clinical trials of HPV vaccination in older women (24–45 years of age for the quadrivalent vaccine and 26 years and older for the bivalent vaccine) are being conducted. Hopefully, these will answer these questions.

Cervical cancer is quite uncommon in women under the age of 30 years and therefore targeting only young adolescent girls means that it will take 15–20 years before any impact of vaccination on cervical cancer rates is observed (Fig. 2). Full effects of vaccination on cancer rates might not be observed for 30–50 years. In addition, in many industrialized countries cervical cancer screening has not begun until a woman reaches 25 or 30 years of age and reductions in cytological abnormalities would not occur until 10–20 years after a vaccination program was initiated if only young adolescents were targeted.

Because of all these considerations it is likely that sexually active adolescents and women will be considered candidates for “catch-up” immunization in many industrialized countries, albeit largely in the private sector. As older women begin to undergo vaccination it will be important that the healthcare community makes certain that vaccinated women continue to participate in cervical cancer screening programs.
3.3. Vaccination of men

If the HPV vaccines are proven to be efficacious in males, there is likely to be considerable interest in industrialized countries in vaccinating young adolescent males with the quadrivalent vaccine in order to reduce their risk for anogenital warts. Although the burden of disease associated with HPV-16 and -18 is considerably less in men than women, when compared to other conditions for which we commonly vaccinate, the number of cases of HPV-16- and -18-associated penile, anal and oropharyngeal cancers in males is not insignificant. Moreover, it is possible that vaccinating males will provide sufficient herd immunity to have an important impact on the burden of disease in the community (see Chapter 21). Rubella is one example where vaccination of males is widely accepted because vaccinating boys and girls against rubella is the only means to significantly reduce the burden of disease (congenital rubella) in the population.

It is currently unclear what role male vaccination with the HPV vaccines will eventually have. As with women over the age of 25 years, currently there are no data available on the efficacy of the HPV vaccines in males. Because of differences in mucosal immune responses between males and females, it cannot simply be assumed that if the HPV vaccines work in females they will work in males. Imiquimod, an immunomodulator utilized to treat genital warts, is less effective and takes longer to clear warts in males than in females [10]. Moreover, a herpes simplex virus (HSV) prophylactic vaccine that is 73% effective in preventing symptomatic genital HSV-2 disease in women has proven to have no efficacy in men [11]. In addition, although we will be able to determine the impact of vaccination on the development of persistent HPV-16 and -18 infections in males, it will be much more difficult to assess the impact on HPV-16- and -18-associated diseases since these are much less common in males than in females. Efficacy of the vaccine on HPV-16- and -18-associated diseases in males is likely to be inferred from the quadrivalent vaccine’s efficacy for genital warts.

3.4. Need for a booster in vaccinated individuals

The durability of the immune response engendered by the HPV vaccines is unknown and, although protection can be monitored by utilizing the detection of HPV infection in the vaccine recipients, it would be useful to develop surrogate immunologic markers of protection. Both a monovalent HPV-16 vaccine and the bivalent HPV-16 and -18 vaccine produce levels of neutralizing antibodies that are considerably higher than those encountered with natural infections and these antibody responses are quite durable, lasting for at least 42 months [12]. Therefore, it is possible that additional “booster” vaccinations may or may not be necessary, depending on the age at which vaccination takes place. It will be important that we monitor the need for “booster” vaccination as we move forward with HPV vaccination. In addition, data are needed on whether the HPV vaccines are able to trigger immune memory, so that protection could persist even after disappearance of vaccine-induced antibodies. Should boosters be required, mechanisms for providing them will have to be developed to ensure that vaccinated individuals have adequate access.

4. Successfully introducing the HPV vaccine

A useful conceptual framework for understanding the complex array of what is needed to have a successful vaccination system within any industrialized country is shown in Fig. 3. The framework consists of six interlinked components. These are: (1) vaccine purchase and supply; (2) service delivery; (3) high coverage rates; (4) surveillance of vaccine coverage, effectiveness and safety; (5) immunization finance policies and practices; and (6) political will. The end result of correctly interlinking these six components is to control and prevent an infectious disease.
4.1. Vaccine purchase and supply

Government plays an important role not only in directly financing vaccination but also in arranging contracts with manufacturers for reduced rates for vaccines provided in the public sector. In many EU countries and in North America, national or regional health authorities have been able to substantially reduce the costs for providing the recommended vaccines in the public sector through such contracts. The cost of vaccination is becoming an increasingly controversial issue in many industrialized countries [2]. The price of vaccines required for providing all recommended vaccinations up to 6 years of age in the public sector in the US was only US$10 in 1975. Controlling for inflation, it increased to US$385 in 2001, and assuming that seven additional vaccines are introduced by 2020, the cost per child could triple to US$1225 [13]. Costs would be approximately 50% higher in the private sector and these estimates do not include the costs for visiting the provider and the administrative costs of vaccination. In many countries, the other new vaccines that are being introduced will compete with the HPV vaccines for public healthcare funds. These include vaccines against Hib, Neisseria meningitidis, Streptococcus pneumoniae, Varicella zoster or rotavirus. Different from most other healthcare interventions, however, vaccination programs are most often cost-effective, at least from a societal perspective [14].

Another important role of government is to assure that adequate supplies of vaccines are available for use. In the US, there were recently unprecedented shortages of many routinely recommended vaccines that placed both children and adults at risk [2]. There have also been several recent examples in Europe where manufacturers could not deliver sufficient supplies of recommended vaccines.

4.2. Service delivery

4.2.1. Adolescents

As discussed previously, 9–13-year-old females will most likely be the primary target for vaccination, at least initially. This raises a number of issues for the vaccine community. Some EU countries have successful school-based programs that deliver HBV vaccine to adolescents [1,15]. These programs provide rapid introduction and high coverage rates for adolescent vaccination in some countries. The coverage rate for school-based adolescent HBV vaccination programmes ranges from 70 to 85% for Belgium, Croatia, the Netherlands and Slovenia [16]. A recent study assessed the feasibility of introducing universal HBV vaccination in Greater Glasgow, Scotland. Vaccination was offered to approximately 10,800 11–12-year-old pupils through a school health system. Vaccine uptake was 91.3, 89.3 and 80.2% of the school roll for at least one, two and three doses, respectively [17]. General practitioners and pediatricians will play an important complementary role in Europe. In countries or locales without school health facilities to deliver vaccines, such as Germany, France and Italy, vaccination recommendations for young adolescents are frequently not implemented [18]. Thus, HPV vaccination targeted to this age group will rely totally on general practitioners, possibly pediatricians and, in Italy, hygienists. In the past, these vaccination systems have failed to achieve any vaccination-related goals and there is no reason to believe that they will work for HPV vaccination.

In the US, there are few school-based vaccination programs and most vaccines are administered by providers working in the private sector, including those vaccines paid for with public funds [19]. The private sector is used to perform publicly funded childhood vaccination because studies have documented that immunization levels decrease when private providers refer uninsured children to public clinics for vaccination. Therefore, children receive vaccinations as part of routine care in the private sector. This supports the integration of vaccination and primary care and provides a “medical home” for all children where other routine preventative health measures, such as anemia testing, can take place. A young-adolescent preventative health visit targeted to 11–12-year-olds has recently been introduced in the US that is scheduled to include the new meningococcal conjugate vaccines, a new tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap adolescent preparation) [20]. This young-adolescent visit currently requires only a single visit, not the three that will be required if HPV vaccine is administered in this context. Several studies in the US have noted that a number of health clinics have not experienced a high level of compliance with their adolescent HBV immunization programme. Compliance rates for the third dose have ranged from 11 to 50% [21,22]. Moreover, since the young-adolescent visit has only recently been introduced, it is too early to determine how widely it is being utilized. In the US, adolescents (9–19 years of age) have lower rates of healthcare utilization than either younger or older individuals, and access to health-care services for adolescents is largely dependent on their ability to pay for services [23]. Twenty percent of all 10–12-year-old females in the US did not have any contact with a health-care provider in 1997 [23].

4.2.2. Sexually active women

Delivery of immunization services to sexually active individuals is much less organized in most industrialized countries than delivery to children. Many countries such as Germany, France, Italy, Spain and the US have no effective system to regularly reach adolescents and/or adults for vaccination. For example, although Germany has a recommendation for adolescents to receive tdap-IPV, HBV vaccine and varicella vaccine, coverage for these vaccines is well below 30%. Therefore, many countries will need to rapidly develop new vaccination platforms if they are to effectively reach sexually active women.

For women over the age of 19, it is likely that their primary source for the HPV vaccine will be from their obstetrician/gynaecologist or a family planning clinic that they attend for contraceptive services. Unfortunately, these often offer either no, or very few, vaccinations. One survey of US
gynaecologists reported that only 64% offer any vaccinations in their offices and only 10% offer all recommended adult vaccinations [24]. One potential way to reach large numbers of relatively young, sexually active women is through antenatal care. In industrialized countries, almost all women receive antenatal care and in some countries this might provide an attractive vehicle for providing HPV vaccination if the HPV vaccine becomes licensed for use in pregnant women.

4.3. Sustain and improve coverage rates

4.3.1. Parental and provider factors

Parental factors are often cited as the critical barrier for childhood vaccination. Surveys from both Europe and the US have documented that the most important parental factors influencing vaccination rates are poverty-related [19,25]. These include low educational status of parents, large family size, low socioeconomic status and being a minority. In some countries, vaccine costs may be an issue for lower income families [26]. Coverage rates are diminished in lower income families for those vaccines that are not reimbursed by the health-care system. Intercurrent illness, delay suggested by the physician and fear of injections or vaccine side-effects represent only a small fraction of the reasons that parents list for not vaccinating their children.

There is general consensus in the vaccine community that the provider plays the major role in determining their patients’ immunization status. Parents generally want their children to be fully immunized and look to their provider to recommend what vaccines are needed. One survey of paediatricians showed that if the provider recommended against varicella vaccination only 30% of children in their practices received vaccination [19]. If the provider gave a neutral recommendation, less than half would receive the vaccination, but if they gave a strong recommendation, over 85% would be vaccinated. Recent vaccination coverage surveys in Belgium, Germany, Italy and Spain show that there is a clear need, from the side of the parents as well as the vaccinators, to be well informed about the indications for vaccination, the official recommendations and the risks and benefits of the vaccination [26–30]. Therefore, it is critical that providers be educated as to the considerable burden of HPV-associated disease in the population and the need for vaccination.

HPV vaccination provides a number of somewhat unique challenges with respect to patient and provider acceptance (see Chapter 24). In brief, these include a lack of awareness of HPV and its links to cervical cancer and significant disease among the general population, as well as concerns with respect to the acceptability of vaccinating adolescents against a sexually transmitted infection.

4.3.2. School requirements for vaccination

School laws requiring that students have specific immunizations before entry into day-care or school are widespread in the US. These laws are passed at the state level and there is some variation between states as to which vaccines are required as well as in dosages and schedules of a given vaccine. This approach has been highly effective in increasing coverage rates and preventing disease. During the 1978 measles epidemic in the US, the incidence of measles in children was 2.7 per 100,000 in the six states that strictly enforced requirements for vaccination against measles compared to 35.2 per 100,000 in the other states [31]. Similarly, in 1986 there was a major resurgence of mumps in the US. However, this occurred almost exclusively in states that lacked school requirements for mumps vaccination [32]. There are no school requirements comparable to those found in the US in Europe.

4.4. Political will

A critical component of introducing and sustaining a given vaccination program is developing political support for the program. Policy makers often argue that there are inadequate data as to whether the burden of a targeted disease is sufficient to warrant the introduction of a new vaccine. Although there is a significant burden of HPV-associated disease in industrialized countries, policy makers will still need to be convinced to allocate a substantial amount of money to HPV vaccination programs, especially since they will still be bearing the cost of cervical cancer screening programs, probably for more than 20–30 years (see Chapter 21). Results of health economic evaluation comparing several preventative alternatives will most likely be very helpful in informing policy makers of the need for HPV vaccination programs (see Chapter 21).

4.5. Other components

The other components required for a successful vaccination system include surveillance of vaccine coverage, effectiveness and safety as well as immunization finance policies and practices. These are covered in depth in the other sections of this monograph (see Chapters 22 and 26).

5. Lessons learned from the introduction of other vaccines

To assure that we do not repeat the same mistakes with the HPV vaccines that delayed the effective introduction of vaccination programs for rubella, HBV, and N. meningitidis in industrialized countries, it is important to examine how these other vaccines were introduced.

5.1. Rubella

Vaccines for rubella were first licensed in the US in 1969 and shortly thereafter in Europe. The goal of rubella vaccination is to prevent congenital rubella syndrome (CRS). In the US, childhood rubella vaccination was rapidly introduced with the intent to allow herd immunity to protect older pregnant women. By 1978, rates of rubella infections
in children under the age of 15 years were dramatically lower, but vaccination had not reduced the rubella rates in older individuals [33]. As a result, vaccination was expanded to include adolescents and adults. This produced a marked reduction in the number of cases of CRS. In the 1970s, the UK adopted a policy of vaccinating only schoolgirls against rubella. With adoption of this policy, the number of cases of CRS dropped approximately 75%, but rubella infections in pregnant women and CRS continued to be a problem. Subsequently, Britain included rubella vaccination as part of the measles, mumps, rubella vaccination (MMR), which was recommended for all infants, and the number of cases of CRS and pregnancy terminations on account of infection with rubella dropped markedly [34]. It has also been shown that if coverage rates of vaccination for rubella are too low in children, primary infection shifts from children to older age groups, which leads to more infection risk in pregnant women and more CRS [35].

5.2. HBV

Safe and effective HBV vaccines became commercially available in 1982. The initial HBV vaccination strategy in industrialized countries was to selectively vaccinate “at risk” individuals, including men who have sex with men (MSM), healthcare workers (HCWs), sex workers and some categories of patients. However, many “at risk” individuals proved difficult to target or were often already infected prior to being identified. More importantly, many HBV-infected individuals have no identifiable risk factors, therefore the incidence of acute HBV initially showed no reduction in many countries after vaccine licensure [3]. In the US, the incidence of acute HBV actually increased between 1982 and 1985 (Fig. 4). In 1986 a steep decline in incidence began which was attributable to reductions among MSM and HCW. In 1992, infant vaccination was recommended and this was followed by a recommendation to vaccinate all children in 1995, and all persons 0–18 years of age in 1998. This resulted in a continued decline in acute HBV. In 1992 the World Health Organization called for all countries to add, by 1997, HBV vaccination to their national universal immunization programs at birth, in infancy or in adolescence, according to the endemicity [36]. Substantial progress has been made in implementing this recommendation and the incidence of HBV has now declined in all EU countries, as well as globally. By the end of 2005, 168 countries worldwide had incorporated HBV vaccination into their national immunization programme.

5.3. Meningococcal disease

A meningococcal polysaccharide vaccine (MPSV4), which prevents two of the three most common types of meningococcal disease in the US, has been available since the 1970s. In 1997, the American College Health Association recommended that all college students be informed of the dangers of meningococcal disease and offered vaccination. The CDC made a similar recommendation in 2000, and by 2004 the majority of states had passed laws requiring colleges to provide information on the risks of meningococcal disease to students and 10 states had passed laws requiring vaccination for certain students, unless a vaccination waiver was provided. However, during the 2004–2005 academic year, it is estimated that only 1.1 million of the approximately 17 million college students in the US had been vaccinated for meningococcal disease prior to going to college and only 50,000–100,000 students were vaccinated after going to college [37,38].

These three case studies in vaccination demonstrate several important lessons that apply to the introduction of HPV vaccines. From rubella we have learned that if we want to have an impact on HPV-associated diseases that typically occur in older individuals (e.g., CIN-2, 3 and invasive cervical cancer), it is critical that we target older as well as younger individuals for vaccination. Other lessons come from HBV. Our experience with HBV suggests that attempting to target high-risk individuals for vaccination would have a relatively nominal impact on the incidence of HPV-associated diseases in the population. Moreover, unlike other infections, such as HBV, where there are clearly defined “high-risk” populations for infection, with HPV it is impossible to identify “high-risk” individuals since almost all sexually active adults will be exposed to HPV at some point in their lives. Therefore, universal HPV vaccination will be critical to have a significant impact. The HBV example also clearly demonstrates that without the political will to put in place an effective delivery program directed towards 9–13-year-olds, we will not achieve high coverage rates for HPV vaccination. Ten years after the introduction of recommendations and funding for HBV vaccination in adolescents, the coverage rate in Germany is well below 30%. This lesson is confirmed by
the recent US experience with meningococcal vaccines. Recommendations are not enough—they have to be backed by policies that ensure high coverage rates.

6. Summary

In many industrialized countries, the target population for vaccination is likely to be young adolescent females 9–13 years of age. It is also likely that in many countries there will be a call for older adolescents and adults to be included as part of a “catch-up” vaccination campaign. The successful introduction of HPV vaccines will require six interlinked components, and it will clearly be a challenge to make certain that all of these components come together in the correct way. A recent survey of new vaccine candidates found that vaccines against more than 80 different pathogens are currently under development [39]. Therefore, a key question is how successfully will the HPV vaccines compete for funding and priority with other recently introduced vaccines like rotavirus or conjugated pneumococcal vaccines. Another key question is how we will implement vaccination of young adolescents. In countries with an adolescent HBV vaccination program, the experience and infrastructure gained from these programs could be used for the introduction of a young-adolescent HPV vaccination program. In countries such as the US that are currently introducing a young-adolescent preventative health visit to provide a pertussis boost and meningococcal vaccination, it may prove possible to adjust this approach to include the HPV vaccines. More data are urgently needed on the possibility of co-administration of HPV vaccines with other vaccines if this is to become a reality.

In the real world of competing healthcare priorities, political will remains a critical component to the successful introduction of any new intervention or policy. Because of the way vaccination programs are currently organized in Germany, France and Italy, it appears unlikely that a HPV vaccine will be more widely used than other vaccines, such as the measles vaccine, unless there is a significant change in the level of political support for vaccination. Developing the political will necessary for effective HPV vaccination programs is expected to be challenging. Improving public and provider awareness regarding HPV, cervical cancer and the benefits of HPV vaccination is an early and important step in gaining political support for HPV vaccination programs. There is an urgent need for sexual and reproductive health-educational programs to break down the taboos around the sexual transmission of HPV. It must become common knowledge among the general population that almost all sexually active individuals are infected with HPV at some point in their lives and that preventing infection though vaccination can prevent the development of cervical cancer. Only by this means will parents allow their children to be vaccinated against cervical cancer.

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