



Review

Adolescents and vaccines in the western world



Nicola Principi*, Susanna Esposito

Pediatric High Intensity Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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ABSTRACT

Recent data have shown that the immune protection evoked by vaccines given in the first years of life progressively weakens, and that this is associated with a higher than expected incidence of vaccine-preventable diseases in adolescents and young adults. Furthermore, the greater circulation of pathogens among adolescents and young adults leads to a high risk of infection in unvaccinated or not fully vaccinated younger children. These findings, together with the availability of vaccines specifically developed to prevent infections that typically occur during adolescence, have induced a number of experts to suggest radical changes in the immunisation schedules usually recommended by health authorities. The most important of these relate pertussis, meningococcal and human papillomavirus vaccines but, although they are based on unexceptionable scientific premises, the suggestions have been only slowly and partially received in most countries, even in those in which vaccination programmes are usually adequately implemented and monitored. Adolescence is a particular period of life characterised by changes in intellectual, moral, physical, emotional and psychological development. All of these can have a considerable impact on compliance with immunisation schedules because the approach to any preventive method no longer entirely depends on parents' and pediatricians' judgements as in the first years of life but is the consequence of a more complex process involving the adolescents' thoughts and opinions, their relationships with their parents, friends and physicians, and the information they receive from the mass media. Every effort should be made to overcome the barriers to adolescent immunisation, including those arising from the adolescents themselves.

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* Corresponding author at: Pediatric High Intensity Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy. Tel.: +39 02 5502203; fax: +39 02 50320206.

E-mail address: nicola.principi@unimi.it (N. Principi).

1. Introduction

Without adequate prevention, the incidence of various infectious diseases peaks in the first years of life, which is why infants and young children received priority immunisation for decades [1]. Moreover, because it was long thought that vaccines administered to healthy children in the first years of life could confer long-lasting protection, booster doses of the same vaccines in later life were recommended only in selected cases, mainly in at-risk subjects with a chronic severe underlying disease [2]. Before the end of the last century, only the combined tetanus-diphtheria vaccine with a lower diphtheria toxoid antigen content (Td) was recommended for healthy adolescents [3], but a number of recent studies have clearly indicated that administering some vaccines exclusively to younger children can cause epidemiological and clinical problems. The immune protection evoked by vaccines given in the first years of life progressively weakens, and this is associated with a higher than expected incidence of vaccine-preventable diseases in adolescents and young adults [4,5]. Furthermore, the greater circulation of pathogens among adolescents and young adults is the cause of a high risk of infection in unvaccinated or not fully vaccinated younger children [4,5]. These findings, together with the availability of vaccines specifically developed to prevent infections that typically occur during adolescence [6], have induced a number of experts to suggest radical changes in the immunisation schedules usually recommended by national health authorities. The most important of these relate pertussis, meningococcal and human papillomavirus vaccines [4–6] but, although they are based on unexceptionable scientific premises, the suggestions have been only slowly and partially received in most countries, even in those in which vaccination programmes are usually adequately implemented and monitored. This is what occurred when the second dose of the combined measles, mumps and rubella (MMR) vaccine was recommended in children and adolescents. Also in that case, compliance by health care workers, parents and adolescents, already suboptimal for the first dose, was very low leading, particularly in European countries, to several repeated outbreaks of measles [7–9]. The number of cases reported to the European Center for Disease Prevention and Control by the 29 participating countries increased 4-fold, from 7817 in 2008 to 30,567 in 2011 with five countries (France, Italy, Romania, Spain, and Germany) accounting for >90% of all measles cases reported in 2011 [7–9].

The USA is the only country in which particular attention has been given to improving immunisation schedules, and recommendations for adolescent immunisation have been regularly prepared and annually updated since 2005 [10]. These recommendations highlight the importance of catch-up strategies for adolescents who did not regularly complete their childhood immunizations as well as the need of influenza and pneumococcal vaccination in adolescents belonging to high-risk groups because of underlying chronic disease. However, even in the USA, adolescent immunisation coverage is still not completely satisfactory, probably because the barriers to it are more complex than those relating to recommended vaccines in younger children.

Adolescence is a particular period of life characterised by changes in intellectual, moral, physical, emotional and psychological development. All of these can have a considerable impact on compliance with immunisation schedules because the approach to any preventive method no longer entirely depends on parents' and pediatricians' judgements as in the first years of life but is the consequence of a more complex process involving the adolescents' thoughts and opinions, their relationships with their parents, friends and physicians, and the information they receive from the mass media [11–13].

The main aim of this review is to analyse why pertussis, meningococcal and HPV vaccines should be administered to

adolescents, and what problems condition the use of these vaccines in this age group. Problems related to the use of MMR vaccine in adolescents are not discussed in details in this paper because the risk of inadequate vaccination coverage of adolescents against measles and rubella is well known by health authorities worldwide and in many countries specific catch-up programmes to increase immunisation coverage against these diseases in adolescents have been implemented [14–16]. The analysis is based on data made available in industrialised countries and studies published in indexed journals over the last 10 years.

2. Reasons for administering vaccines to adolescents

2.1. Pertussis vaccines

Pertussis is endemic throughout the world, with peaks occurring every 3–5 years and frequent outbreaks. In the pre-vaccine era, the disease mainly affected children aged <5 years, had an incidence of several hundred cases per 100,000 inhabitants, and caused a number of deaths [17]. The inclusion of whole cell inactivated (wP) vaccine in the immunisation schedule of infants and young children greatly reduced the incidence of pertussis worldwide, which reached its lowest levels in the 1970s [18]. However, a slight but significant increase has been reported in the USA and Australia since the 1980s (and in Europe since a few years later) [19–21], and this trend has not changed since the wP vaccine was replaced by the less reactogenic acellular pertussis (aP) vaccine in most countries.

It was initially thought that this was not due to any real change in pertussis epidemiology, but to the development of new definitions of the disease, greater physician awareness of its clinical importance and, above all, the fact that the more widespread use of molecular methods to identify the pathogen improved their ability to diagnose pertussis even in atypical cases presentation [19–21]. Subsequently, it was thought that the increase in the number of pertussis diagnoses could also be attributed to the emergence of genetically modified *Bordetella pertussis* strains that reduced the efficacy of vaccines [22]. However, an analysis of the age distribution of pertussis cases clearly showed that the change in epidemiology was mainly due to the waning of the immune protection conferred by the vaccines [19–21].

Pertussis vaccines are immunogenic and effective in the short-term and, because they are given to most children in the first years of life, the incidence of early pertussis has significantly decreased. However, it has long been known that, like the protection following natural pertussis infection, the humoral and cellular immunity evoked by vaccines tends to wane after some years, and this has recently been repeatedly confirmed by immunological and clinical studies [23–26]. In 2001, Esposito et al. studied 38 children aged 5–6 years who had received the combined tetanus, diphtheria, acellular pertussis and hepatitis B (Tdap-HBV) vaccine when they were 3, 5 and 11 months old, and 21 subjects of similar age and gender who developed pertussis in the first year of life [27]. They evaluated the titres of immunoglobulin G (IgG) antibodies against the *Bordetella pertussis* antigens included in the vaccine (pertussis toxin, filamentous hemagglutinin, pertactin), peripheral blood mononuclear cell-specific proliferation in the presence of these pertussis antigens, and the cells' secretion of the cytokines gamma interferon, interleukin [IL]-2, IL-4, and IL-5. Five years after vaccination or infection, only a small proportion of the children had significant serum concentrations of specific IgG antibodies against all three *Bordetella pertussis* antigens, and a minority had persistent T cell responses, showing that the immune responses induced by primary pertussis vaccination was not greatly qualitatively or quantitatively different from those observed in children with

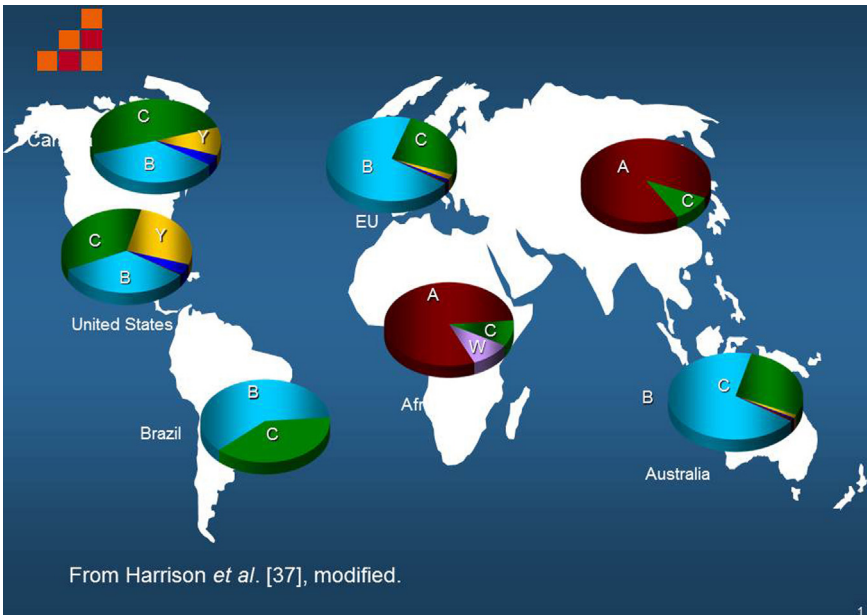


Fig. 1. Global distribution of *Neisseria meningitidis* serogroups.

From Harrison et al. [37], modified.

natural infection, and that protection had rapidly declined in both groups [27].

The speed at which the protection wanes depends on various factors, including the vaccination schedule and the type of vaccine. AP vaccine seems to provide shorter-lasting protection than WP vaccine: Clark et al. found that children who had received the entire series of aP vaccinations at the correct time were protected for a few years but became more likely to develop pertussis at 7–10 years of age, whereas those previously vaccinated with WP vaccine were only at risk during adolescence [28].

When protection wanes, the incidence of pertussis increases. This not only explains why the highest incidence rates are currently observed in older children and adolescents worldwide, but also why adolescents have become the main cause of the spread of the infection in the community and the persistently high incidence of disease in children aged <1 year, who are at the greatest risk of severe disease and death because they are still unvaccinated or not fully vaccinated [19,20]. Although there were considerable differences between countries, a total of 15,446 cases of pertussis were notified to the European Center for Disease Prevention and Control (ECDC) in 2010 [29]. As in previous years, the highest incidence was among children aged 5–14 years, with a confirmed case rate of slightly more than 11 cases per 100,000 inhabitants, although younger children were the second most affected group. The USA Centers for Disease Control and Prevention (CDC) analysed the incidence of pertussis by age group between 1990 and 2012, and found that the highest rate of reported cases involved infants aged <1 year, although a significant proportion involved children aged 7–10 years and there was a progressive increase among adolescents aged 13–14 years [30].

The immunisation of adolescents against pertussis can lead to a number of advantages, including a significant reduction in the total number of new cases among vaccinated subjects. A retrospective analysis of pertussis cases reported in the USA between 1990 and 2009 showed that the introduction of Tdap for adolescents in 2005 was associated with a considerable decrease in the number of cases involving subjects aged 11–18 years [31]. Another advantage is that the reduction in circulating pertussis bacteria in the community due to the vaccination of adolescents can allow better control of the potentially severe pertussis of unvaccinated or not fully

Table 1
Adolescent and adult pertussis vaccine recommendations in Europe.

Country	Pertussis-containing vaccine
Austria	Tdap 13 years; Tdap 18–20 years; Tdap every 10 years until 60 years, then every 5 years
Belgium	Tdap 14–16 years, cocoon
Finland	Tdap 14–15 years
France	DTaP-IPV 11–13 years or, if missed, catch-up Tdap-IPV 16–18 years; Tdap-IPV once in adulthood, HCW, cocoon
Germany	Tdap or Tdap-IPV 9–17 years; Tdap once in adulthood, HCW, cocoon
Greece	Tdap 11–12 years, if missed Tdap once in adulthood
Ireland	Tdap 11–14 years
Italy	Tdap 11–12 years
Luxembourg	Tdap-IPV 15–16 years, then every 10 years
Norway	Tdap in adults every 10 years until 60 years
Sweden	Tdap 14–16 years
Switzerland	Tdap 11–15 years; Tdap 25–29 years, cocoon

From Vaccine European New Integrated Collaboration Effort [28] modified.
HCW: healthcare worker; Tdap: tetanus, diphtheria, acellular pertussis vaccine with reduced content of tetanus and diphtheria antigens; IPV: inactivated polio vaccine.

vaccinated infants. In Western Australia, where Tdap was administered to all high school students during the 2008–2009 epidemic, there was a decrease in pertussis case reports involving adolescents and infants aged <6 months [32]. Finally, the vaccination of adolescents seems to be significantly cost effective: it has been calculated that the vaccination of everyone aged 10–19 years in the USA in 2005 may prevent 0.4–1.8 million cases of pertussis and lead to 10-year savings of \$ 0.3–1.6 billion [33].

However, despite these premises, the inclusion of aP in the adolescent immunisation schedule is not universal, and there are differences in the age suggested for the booster dose. It is usually given combined with Td, but when 23 of the 27 EU countries recommended diphtheria and tetanus vaccination for adolescents in their national immunisation programmes in 2011, only 12 (Austria, Belgium, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Slovakia, Spain and Sweden) recommended Tdap (Table 1) [34]. Nevertheless, the number of countries recommending Tdap to adolescents is increasing, although not all of the EU countries have decided to introduce a booster dose of pertussis vaccine [35]. In terms of timing, a booster is recommended at the age of 11–12

years in the USA and Australia, 9–17 years in Germany, 11–18 years in Italy, 11–13 years in France, and 14–16 years in Canada [36].

2.2. Meningococcal vaccines

The epidemiology of meningococcal disease (MD) varies widely depending on geographical area and age, and it can occur as sporadic cases, outbreaks or large epidemics. Moreover, there may be geographical differences in the prevalence of the serogroups causing disease and variations can occur relatively rapidly (Fig. 1) [37]. Serogroup A has long been the most important cause in Africa, although there have also been reports of disease caused by serogroup C, serogroup W and, more recently, serogroup X. Most of the cases in the Americas are caused by serogroups C and B, although serogroup Y causes a substantial proportion of infections in some countries, and serogroup W is also becoming increasingly problematic. The majority of cases in Europe are due to serogroup B strains, particularly in countries that have introduced serogroup C meningococcal conjugate (Men C) vaccine. Serogroup B also predominates in Australia (because of the vaccine-induced control of serogroup C disease) and New Zealand, where there was a serogroup B epidemic. Most of the cases in Asia are caused by serogroup A and C strains.

However, age distribution is consistent across countries: the highest incidence is during the first years of life, after which there is a sharp decline, followed by a substantial increase during adolescence and early adulthood (Fig. 2) [37,38]. The highest rates of MD in Europe in 2010 were among the children aged <5 years (5.95 per 100,000 inhabitants), followed by those aged 15–24 years (1.22 per 100,000), whereas MD was uncommon in older age groups [38]. The most recent data reported by the CDC (2011) indicate that, although the incidence of MD was highest among children aged <1 year, a considerable number of cases were diagnosed in adolescents and young adults [39]. These findings confirmed what was previously reported by CDC for the period 2000–2009, during which about 15% of all of the cases diagnosed in the USA involved children aged <1 year and subjects aged 18–24 years, and about 7% involved those aged 14–17 years [40].

The immature immune system of younger children can explain why they frequently develop MD, whereas the most important reason for the susceptibility of adolescents is their lifestyle. They are among the subjects with the highest contact rates, frequently live in crowded situations, share drinking glasses, and have a high number of kissing partners. This increases the risk of becoming *Neisseria meningitidis* carriers, a condition that is considered a prerequisite for the development of MD [41]. It is interesting to note that the impact of adolescent lifestyles is only slightly affected by the administration of vaccines in the first years of life because the protection evoked by the primary series of conjugate vaccines at 2, 3, and 4 months rapidly declines, even with a booster dose some months later. Data concerning subjects in the UK aged 13–18 years who had received the Men C vaccine at the age of 1–6 years indicate that they were without any protective antibody [42]. As it is known that protection against meningococci is mainly based on specific antibody concentrations (because, although present, the memory response is not fast enough to assure bacteria elimination), this suggests that all adolescents should receive a meningococcal vaccine dose regardless of their previous immunisation status [42]. Furthermore, by reducing the number of carriers and the circulation of pathogens, the immunisation of adolescents cannot only protect them directly, but indirectly also the rest of the community, particularly younger infants who are at highest risk of severe disease.

The national differences in the recommendations concerning the prevention of MD in adolescents mainly involve the composition of the suggested vaccine, which is chosen on the basis of

the circulation of the meningococcal serogroups in the area. In the USA, the Advisory Committee on Immunisation Practices (ACIP) recommends two doses of the meningococcal conjugate vaccine containing the conjugate capsular polysaccharide of serogroups A, C, Y and W135 (Men ACYW) for adolescents aged 11–18 years, with a first dose being given at 11 or 12 years, and a booster dose at 16 years [43]. HIV-infected adolescents should receive three doses: two doses 2 months apart at 11 or 12 years, plus a booster at 16 years [43]. If the first dose (or series) is given between the ages of 13 and 15 years, the booster should be given between the ages of 16 and 18 years; if the first dose (or series) is given after an adolescent's sixteenth birthday, a booster is not recommended.

The recommendations in Europe vary widely from country to country, although the number of countries that have decided to implement adolescent meningococcal vaccination programmes is increasing. Good examples of the differences in countries with effective healthcare systems are the UK, France and Italy. Starting from the academic year 2013–2014, the UK will recommend a single dose of Men C at 3 months of age and a booster at 13–15 years [44]. France recommends that all subjects aged 1–24 years receive one dose of Men C, and the tetravalent Men ACYW vaccine is only suggested for children and adolescents at high risk of developing severe MD [45]. In Italy the recent National Immunisation Plan 2012–2014 indicates the need to ensure the coverage of 95% of children and adolescents, and suggests the administration of a single dose of Men C to all children in the second year of life and all adolescents between the ages of 11 and 18 years; however, this last dose is suggested only for those not receiving an infant dose [46].

2.3. HPV vaccination

The inclusion of HPV vaccine among those strongly recommended for adolescents arises from the knowledge that: (1) HPV infection is the most common sexually transmitted infection in humans; (2) HPV is closely associated with the development of genital and oropharyngeal warts and various anogenital and oropharyngeal cancers, of which cervical cancer is the most frequent; and (3) most infections are acquired very early during adolescence, at the time of the first sexual intercourse [47]. The fact that some specific types of HPV are more frequently associated with the development of HPV-related disease has led to the development of two vaccines: the first contains types 16 and 18 (HPV2, the most important for cancer in women), and the second the same two plus types 6 and 11 (HPV4), which play an important role in causing warts. According to a recently published review, both are safe and efficacious against persistent (6-month) cervical infections and the associated pre-cancerous lesions due to types 16 and 18 in 90–100% of cases [48]. The efficacy of the bivalent and quadrivalent vaccines against the immediate precursor of cervical cancer (intraepithelial neoplasia grade 3) among adolescent HPV-negative females, regardless of HPV type, is respectively 93.2% and 43.0%. Furthermore, the quadrivalent vaccine has been found to be efficacious (>75%) against any of the more severe precursors of vulval, vaginal and anal cancers, and highly efficacious against genital warts [48].

Regarding the time of administration, all of the experts agree that HPV vaccines should be administered to adolescents before they start to engage in sexual activity [49]. This is due to the fact that HPV vaccines are inactive against the types of HPV previously acquired by a vaccine recipient and because antibody responses are highest between the ages of nine and 15 years. However, there are national differences in the recommendations concerning the age of immunisation and the subjects to whom HPV vaccine should be administered. The most recent recommendation in the USA considers that adolescents of both sexes should be vaccinated at the age of

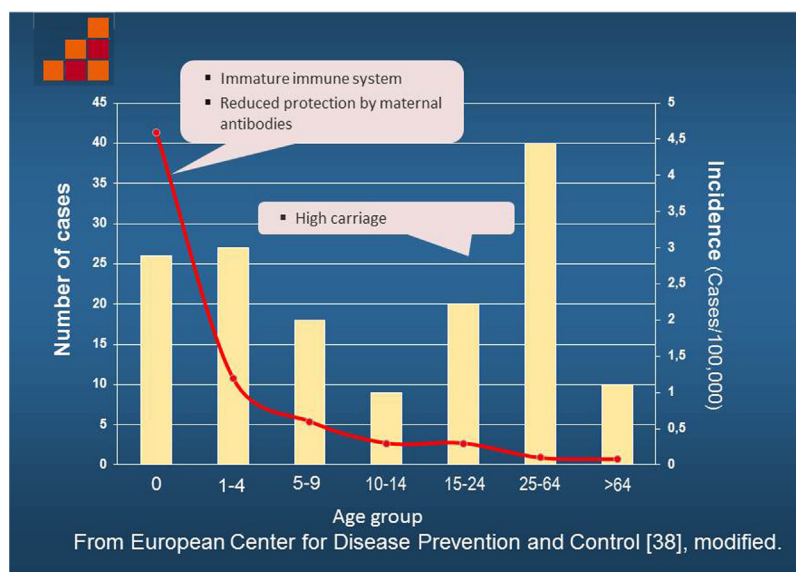


Fig. 2. Bimodal occurrence of meningococcal disease. The figure shows data collected in Italy during the year 2010.

From European Center for Disease Prevention and Control [38], modified.

11–12 years, although vaccination can be started beginning at the age of 9 years and the subjects not receiving the vaccine at the recommended age should be vaccinated between the ages of 13 and 18 years. Either HPV2 or HPV4 may be used for females, but only HPV4 for males. American experts strongly support the vaccination of males because they think that it provides a direct benefit for the vaccinated subjects, including the prevention of genital warts and anal cancer, and an indirect benefit for females through herd immunity [49].

In Europe, HPV vaccine is only recommended for girls. The number of countries introducing the vaccine increased from three in 2007 to 22 at the beginning of 2012, but there are still some that do not recommend it [35]. All of the national programmes target young adolescent girls, but there are differences in specific target age groups and catch-up recommendations. The existence of different healthcare systems and infrastructures have also led to different implementation strategies, with some countries delivering vaccine in schools and others through health centres or primary care providers (Fig. 3). The highest coverage is usually obtained by means of school-based vaccination programmes.

3. Present vaccination coverage among adolescents

There are few data concerning the immunisation coverage of adolescents against pertussis, MD and HPV-related diseases because, even in the countries that have introduced such vaccination programmes, uptake is not always reliably monitored. The 2011 report of vaccination coverage assessment in the European Union indicates that several countries do not systematically monitor vaccination coverage among adolescents [34]. Moreover, five of the 13 countries recommending pertussis vaccination did not monitor uptake. The situation regarding HPV seems to be better because all but one of the countries that have included HPV in their national immunisation programme (Ireland) monitored vaccination coverage. Furthermore, even when a monitoring system exists, it is very difficult to compare vaccination coverage between European countries because of differences in schedules, the age of assessment, the methods of computing coverage, and the timeliness of data availability [34].

However, the available data seem to suggest that adolescent immunisation coverage is generally not satisfactory. In the USA,

Tdap and Men ACWY vaccines were recommended for adolescents in 2006, and HPV vaccine for girls in 2007. At first, relatively few adolescents actually received them, but coverage progressively increased and, in 2010, had reached 68.7% for Tdap, 48.7% for Men ACWY, and 32.0% for HPV (in girls) [50]. Coverage estimates varied by state and reporting area, but were >65% for ≥1 dose of all three vaccines in only three states (Massachusetts, Rhode Island and Washington), and there were significantly lower rates among adolescents living in the south-eastern states than among those living elsewhere [50].

Use of HPV vaccine in males was initially poor, although it seems to be increasing. Reiter et al. analysed 2010–2011 data relating to a nationally representative sample of 22,365 adolescent males aged 13–17 years (mainly collected before the recommendation for routine vaccination), and found that vaccine starts increased from 1.4% in 2010 to 8.3% in 2011 [51]. Parents who reported receiving a healthcare provider recommendation to have their sons vaccinated were much more likely to have vaccinated sons (odds ratio [OR] 19.02, 95% confidence interval [CI] 14.36–25.19). The number of starts was also higher among the sons of Hispanic parents (OR 1.83, 95% CI 1.24–2.71), and adolescents eligible for Vaccines for Children, a programme designed to provide vaccines to uninsured subjects (OR = 1.53, 95% CI 1.01–2.31).

Data regarding primary immunisation series are available for only a small number of European countries, but they indicate that HPV immunisation coverage is sub-optimal because the increase over time has been less than expected, and in most cases is still no higher than 70% [52]. In 2010, of the seven countries for which data were available, only Portugal and the UK had vaccination coverage rates of ≥80%; Denmark and Italy had rates of 50–60%; and France, Luxembourg and Norway had rates of ≤30% [52]. However, more recent data from some countries in which vaccination programmes were approved in 2007–2009 show higher coverage rates for the youngest vaccinated cohorts (girls born in 1996/1997): 84% in Portugal, 79% in Denmark, 63% in Norway, 64% in Spain, 58% in The Netherlands, and 55% in Slovenia [52].

4. Reasons for poor vaccine uptake by adolescents

A number of factors can play a role in reducing vaccination coverage among adolescents, but inductive analyses have shown that

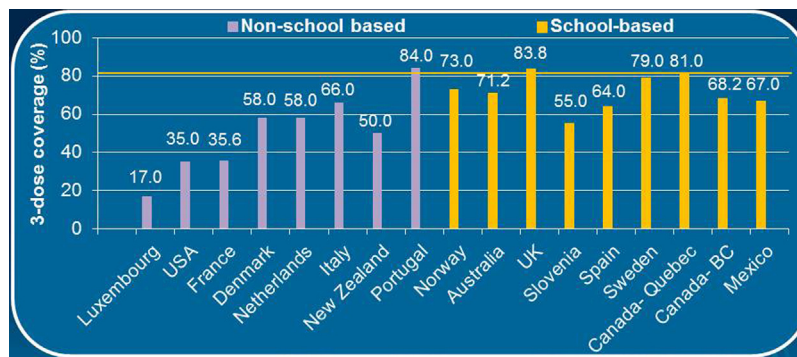


Fig. 3. Challenges for an adolescent HPV vaccination programme: achieving high coverage rates.

many are substantially the same as the barriers to the immunisation of infants and young children. However, as adolescents are personally involved in decision making, the organisation of vaccine administration and the acceptance or otherwise of vaccination are more complicated, and there is a higher risk of missed opportunities and refusals.

In the absence of specific healthcare programmes for adolescents (as is the case in most countries), contacts between adolescents and the healthcare system are very difficult, and nothing is known about the time or type of vaccinations [53]. Adolescents usually turn to physicians only when they are ill, and so there are not many opportunities to inform them that vaccines are important and should be administered. A survey in the USA found that only 29% of females and 39% of males aged 11–21 years did not have any healthcare contact during 2002 [54]. Moreover, if adolescents attend healthcare visits by themselves, they frequently do not have written consent for vaccinations signed by their parents so, by law, they cannot be administered a vaccine even if they express their personal consent. A physician's advice that a vaccine be administered as soon as possible in a vaccination centre is usually not followed because subjects are more interested in their current diseases than possible future medical problem [55]. Moreover, if a parent is present, it can be difficult to discuss particular questions such as those related to sexually transmitted infections and prevention with HPV vaccine [56]. Finally, the negative effect of misleading information published by the mass media can be significantly greater among adolescents, who are more easily biased than adults [57].

However, the most common barriers to adolescent vaccinations are a lack of knowledge about vaccines and vaccine-preventable diseases, the attitudes of parents and healthcare providers to vaccination, infrastructural issues and, sometimes, financial concerns. Poor knowledge has been systematically identified as the most important factor: a survey carried out in Italy during the year after HPV vaccine was included in the national immunisation schedule for females aged 11–12 years found that the parents' propensity to have their daughters vaccinated against HPV significantly correlated with their knowing that the aim of the vaccine was to prevent cervical cancer (OR=2.31, 95% CI: 1.69–3.16), and their awareness that HPV could affect their own children (OR=3.52, 95% CI: 2.89–4.29) [58]. Moreover, the adolescents who were aware that HPV infection could affect themselves were more in favour of HPV vaccination, regardless of whether they were male (OR=5.73, 95% CI: 2.85–11.5) or female (OR=2.39, 95% CI: 1.66–3.46) [52]. Finally, although more than 80% of paediatricians were prepared recommend HPV vaccine, many could not correctly answer questions regarding the general characteristics of HPV and its role in causing diseases, had no precise knowledge of the pathogenetic role of the different types of HPV, the composition of the available vaccines, and the best time at which to administer them to adolescents [59].

Similar conclusions have been reached by most authors who have investigated adolescent immunisation. Kennedy et al. studied the vaccine-related knowledge and attitudes of adolescents aged 11–18 years and their parents, and reported that only 21% of the parents and 11% of the adolescents correctly identified the three vaccines recommended for adolescents in the USA at the time of the survey [60]. Moreover, a Scottish study specifically designed to evaluate teenagers' understanding of vaccination and vaccine-preventable diseases, and their attitudes towards and experiences of immunisation found that they had little knowledge and experience of any of the diseases against which vaccinations were recommended for children in the UK except for chickenpox [61]. Measles, mumps and rubella were perceived as severe forms of chickenpox-like illness, and rubella was not associated with foetal damage. Boys commonly believed that HPV only affects girls, and both genders were confused about its relationship with cancer. The participants considered two key factors when assessing the threat of diseases: their prevalence in the UK, and whether they could cause fatal or long-term harm [61]. Meningitis was seen as a threat, but primarily to babies. They explained their limited knowledge as a result of mass immunisation making once-common diseases rare in the UK, and acknowledged the role of immunisation in reducing their prevalence. Interestingly, it was found that 70% of parents and 72% of adolescents disagreed with the statement that adolescents should be allowed to consent to vaccination without their parents knowing, and most adolescents agreed that the recommendations of their parents (87%) or healthcare provider (84%) concerning vaccines were important to them [61].

The role of parents seems to be greatly influenced by the age of adolescents. Gowda et al. conducted a quality study of adolescents, parents and providers in which attitudes towards vaccination were explored by means of focus group discussions, and found that most adolescents agreed that parents were the primary decision-makers: however, this conclusion was significantly more frequent among younger adolescents. The same study confirmed that only a small number of parents would leave decisions concerning vaccinations entirely up to their children [62]. The importance of parents in conditioning the acceptance of vaccines by adolescents was further supported by the providers' view that teenagers were less likely to receive vaccines partially because their parents do not force them to when they complain about vaccine-induced pain, or do not state decisively that they need to be vaccinated.

Parental doubts about the use of vaccines can arise for various reasons, mainly the absence of a recommendation by a healthcare provider or concerns about the efficacy, safety and cost of vaccines. Dorell et al. found that adolescent vaccination coverage estimates were significantly higher when parents reported receiving a healthcare provider's recommendation (85.2% vs 76.7% in the case of Td/Tdap, 77.3% vs 49.7% in the case of Men ACWY, and 62.2% vs 21.5% in the case of HPV) [63].

Safety concerns are a frequent cause of reduced vaccination coverage, as was demonstrated when the measles/mumps/rubella vaccine was wrongly associated with the development of autism [64]. As far as vaccines for adolescents are concerned, the most important safety issues have been raised in relation to HPV vaccine. The fear of severe adverse events following vaccination was the parental reason for refusing HPV vaccine in 16.4% of the unvaccinated cases included in a National Immunisation Survey of teenagers carried out in 2010 in the USA [65]. Moreover, the pain of injectable vaccines is a potential problem for some adolescents, who can refuse both a physician visit and the vaccination [60,66]. Moreover, healthcare providers have reported that the financial burden of the HPV vaccine is a professional barrier to vaccination in about 44% of the adolescents to whom the vaccine is recommended [67]. Finally, although it has been clearly shown that the administration of HPV vaccine does not increase the risk of pregnancy, sexually transmitted infection or contraceptive counselling, parents may object to it because they fear that it could increase adolescent sexual promiscuity as a result of risk compensation or behavioural disinhibition [68].

5. Methods of increasing compliance with adolescent vaccination recommendations

All experts agree that, in order to increase adolescent vaccination coverage, it is necessary to inform adolescents and their parents that a given vaccine should be administered in a timely manner. This is crucial because not all countries monitor vaccinations and it is therefore not possible to identify who has not been vaccinated or introduce an appropriate reminder/recall system, which may be extremely important. Szilagyi et al. conducted a randomised controlled trial among low-income adolescents to evaluate the impact of a reminder/recall system based on mailed letters and telephone calls on the rates of immunisation against pertussis, meningococcus and HPV and the number of preventive care visits [69]. They found that the system was effective because, in comparison to controls, the proportion of adolescents with a preventive visit (within 12 months) was significantly higher (65%, $p < 0.01$, and 63%, $p < 0.05$ for mail and telephone, respectively, vs 59% for controls). Moreover, it was reported that mail was more effective than telephone because it was calculated that the number needed to treat for an additional fully vaccinated adolescent was 14 in the case of mailed reminders and 25 for telephone reminders [69]. The use of text messages could be even more effective, especially in countries in which wireless networks reach more than 90% of the population. Stockwell et al. send text messages as reminders and have found that adolescents whose parents received them were significantly more likely to be administered a needed vaccination [70].

In the absence of reminder/recall systems, schools could be used to inform adolescents about the need for vaccinations at a given age. Simpson et al. found that the introduction of state-wide immunisation requirements for school entry significantly increased ($p < 0.0001$) meningococcal vaccination rates among 11- and 12-year-olds in Arizona between 2007 and 2008, regardless of differences in family characteristics [71]. All demographic groups had significantly higher odds of receiving vaccinations on schedule after the change (odds ratio range 5.57–12.81; $p < 0.0001$). County demographic factors that were associated with lower odds included greater poverty, more children younger than 18 years, fewer high school graduates, and a higher proportion of Native Americans [71].

The visits arising from reminder/recall systems and schools are ideal occasions for educating adolescents and parents about the characteristics of vaccine-preventable diseases, and the importance, safety and tolerability of vaccines, and eliminating doubts

and concerns. Appropriate education can also be provided by the media used by adolescents, such as newspapers, magazines, television and the Internet. Educational programmes for parents and adolescents are usually organised by professional medical organisations, scientific societies, regional health authorities or national Ministries of Health.

Educating healthcare providers is essential particularly when new vaccines against previously unpreventable infections are recommended. The example of HPV is paradigmatic because the physicians mainly interested in recommending the vaccine (paediatricians) know little about the disease. Furthermore, healthcare providers should make the most of the new adolescent vaccine guidelines to review their knowledge of vaccines and the vaccination efforts of their practices. Scientific societies and professional medical organisations are the best points of reference, as can be seen by the example of AFIX, a programme specifically designed by the CDC to change the attitudes of healthcare personnel to the problem of low immunisation rates in their practices [72]. The programme is available on the CDC website and teaches users how to assess the immunisation coverage of public and private healthcare providers, provides diagnostic information to improve service delivery, identifies incentives to motivate providers to change their practices, and allows providers to exchange information.

Finally, as strongly recommended by the American Academy of Pediatrics (AAP) [73], healthcare providers who encounter a parent who refuses or delays one or more vaccines for an adolescent use the AAP form to document their discussions with parents about the serious risks of what could happen to an unimmunised or under-immunised child, and record the signed refusal of both parents.

6. Conclusions

The immunisation of adolescents against pertussis, meningococcal disease and HPV-related clinical problems is an important extension of the traditional immunisation schedule that has long been almost exclusively aimed at infants and younger children. This new preventive approach can have positive effects not only on the adolescents themselves, but also on the community. However, many countries are slow to update their immunisation schedules and a considerable proportion of adolescents do not receive adequate vaccine prevention. Every effort should be made to overcome the barriers to immunisation, including those arising from the adolescents themselves.

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