

## Immunization in Adolescents: Past, Present and Future

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**Abstract:** In the past, immunization programs worldwide mainly focused on the delivery of infant and early childhood vaccines. An increasing awareness of the importance of investing in adolescents' health has led to the introduction of new vaccines targeted specifically to adolescents over the last ten years: this has improved the adolescent's opportunities to protect from certain diseases for which they are at an increased risk. Safe and effective vaccines against human papilloma virus, *Neisseria meningitides* and *Bordetella pertussis* are recommended in many parts of the world; nevertheless, vaccination coverage in this age group is relatively low compared to coverage in infants. Barriers to adolescent immunization are believed to be complex and multifactorial but overcoming these barriers will be of primary importance for the future.

**Keywords:** Adolescents, immunization, vaccine, vaccine acceptance.

### INTRODUCTION

Until the 1990s, infants and children received priority in immunization: in fact the majority of the vaccines were administered during infancy and a series of public health initiatives were directed to immunize infants and young children; on the other hand no vaccines were specifically available and recommended for adolescents [1]. Thus in 1997 the American Academy of Pediatrics defined the adolescents as "the orphans of immunization practices" [2].

Over the last ten years, adolescents have received increasing attention and the importance of continued immunizations in this age group is now recognized. A historically unprecedented number of new vaccines and recommendations for adolescents have been made by CDC's Advisory Committee on Immunization Practices (ACIP) in the last few years. The recommendations are based on the evidence that teenagers have an increased risk of infection of some vaccine preventable diseases (pertussis, meningococcal disease and papilloma virus related diseases) and they represent a reservoir for infection to spread to other age groups, such as infants and the elderly. Moreover, due to the success of the routine childhood immunization, the age of distribution of some diseases has shifted from infants and young children to older age groups exposing adolescents to an increased risk of disease [3].

The adolescent vaccination schedule comprises 3 types of immunization opportunities: booster vaccinations [e.g. the combined tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap)], catch-up on missed vaccinations but also new primary immunization with recently approved vaccine specifically targeted to adolescents such as meningococcal conjugate vaccine and the bivalent and quadrivalent

human papillomavirus (HPV) vaccine, currently available in many countries. During adolescence booster doses are required for many vaccines routinely given during infancy and early childhood because immunity wanes over time and they increase the duration of protection through late adolescence and adulthood while "catch-up" vaccinations provides an additional opportunity for initiation or completion of infant and early childhood immunization.

From a public health point of view immunization of adolescents is essential not only for protecting the individual but also for protecting the community as a whole because achieving and maintaining high immunization rates in the general population is critical for disease prevention. Furthermore high vaccination coverage rate in adolescents is a prerequisite for long-term protection in adult life.

Despite these considerations and the evident example given by the success of infant and childhood vaccination programs in terms of prevention of many infectious diseases such as polio, measles, rubella, and smallpox, adolescent immunization rates have remained low. Few large studies on vaccination coverage in adolescents have been conducted, because, in comparison with younger age groups, it is harder to reach them and to obtain reliable data. In the USA vaccination coverage among adolescents increased substantially from 1997 to 2003 [4] and, in particular, from 2006 [5] to 2009 [6] but the Healthy People 2010 goals (vaccination coverage > 90%) [7] for preteens and teens aged 13-15 are not being met for many of the vaccines for which goals were set. Measured against the Healthy People 2010 targets of 90% coverage, vaccination coverage for adolescents aged 13-15 years was 89.0% for  $\geq 2$  doses of measles-mumps-rubella, 91.2% for  $\geq 3$  doses of Hepatitis B, 74.7% for  $\geq 1$  dose of diphtheria-tetanus-pertussis and 90.5% for  $\geq 1$  dose of varicella.

Few and partial data about the adolescent vaccination coverage in European countries are available: nevertheless

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studies shown that, as in the United States, immunization rates in this age group are not satisfactory [8, 9].

### **ADOLESCENT IMMUNIZATION: A BIG CHALLENGE**

The barriers to adolescent immunization are believed to be complex and multifactorial. Different factors contribute to low adolescent immunization rates despite the establishment of age-specific recommendations in many countries: adolescents, parents and health care providers play an essential role in the acceptance of immunization.

#### **The Role of Adolescents**

Adolescence is a crucial time during which individuals establish behavioral patterns that have profound effects on adult health. Many adolescents consider themselves to be adults, capable of choosing their own paths and making their own choices and they are actively involved in healthcare decisions. Therefore one of the big barriers to immunization is the adolescent vaccine acceptance. Needle-phobia, multiple dose vaccines, misperceptions regarding the safety of vaccines, a lack of knowledge about the importance of immunizations and their health benefits, unawareness of being at risk for infectious diseases and peer-pressure are determinant factors for the vaccine acceptance and vary by age [10-12]. In addition the role of Internet, in particular blogs, regarding the diffusion of misperceptions about the safety of vaccines has been recently underlined [13]. In fact Internet is a primary source of information for adolescents and the presence of internet sites presenting inaccurate information about vaccine safety could be a further important barrier for the implementation of immunizations in this age group [14].

Another factor that should be considered is the relationship between the adolescent and the use of preventive care services. Even though during the past 20 years the number of clinical preventive care services recommended for adolescents by national organizations has increased considerably, it is well known that the use of preventive health care service is low and declines from childhood to adolescence. Only 9% of all adolescents' health care visits are for preventive care with the lowest rate recorded in older adolescents aged 15-19 years compared to younger adolescents aged 11-14 years [15]. The utilization level of preventive care visits correlates with the socioeconomic status and the possibility of reimbursement [16, 17]. In a more recent study one-third of adolescents had no preventive care visits from 13 to 17 years old, and another 40% only had a single visit [18]. This lack of access to healthcare services has led to missed opportunities for vaccination for this age group and to low vaccination coverage rate. In this context the feasibility of delivering vaccines to adolescents in settings outside of physician's office such as school and home should also be considered [19].

#### **The Role of Parents**

Adolescence is a time period when adolescent-parent dynamics change: teenagers usually develop a new sense of autonomy from their mother and father and begin to make decisions that impact them for the rest of their lives [20]. Nevertheless parental involvement is clearly an important

influence in decision-making: parental attitudes and beliefs are a major factor in adolescent vaccine compliance [21]. Moreover parents provide concrete support such as transportation, insurance coverage and authorization for vaccinations to take place [22].

Parental attitudes towards vaccination are not homogeneous and are influenced by different factors [23-25]. Parents' perceptions of potential morbidity and mortality for vaccine preventable diseases, perceptions of vaccine efficacy and safety and the overall attitude towards vaccination, influenced by past experience with children's immunizations, were associated with vaccine acceptance [26, 27]. On the other hand, lower propensity for vaccination seems to be related to underestimation of infection and lack of knowledge regarding new vaccines, in particular HPV vaccine [28, 29].

A recent study showed that, although parents believe that vaccines are a good way to protect their children and adolescents from disease, these same parents express concern regarding the potential adverse effects and especially seem to question the safety of novel vaccines. This concern can lead to a high rate of vaccine refusal: in fact overall 11.5% of the parents of children aged  $\leq 17$  had refused at least 1 recommended vaccine in particular HPV (56%), followed by varicella, meningococcal conjugate and measles-mumps-rubella vaccine [30].

An additional factor that needs to be considered is the influence of ethnic and socioeconomic milieu in parental vaccine acceptance. Several previous studies, looking at the question of acceptability of the vaccines among parents in various populations, in particularly HPV vaccine, showed different results. Some authors reported that Hispanic and black individuals have a higher rate of negative attitudes towards immunization than white individuals [31-33], while other studies showed that the Caucasians are less likely to support the uptake of the vaccines than parents of other races and minor ethnicities [34-36]. No correlation between race and parental vaccine acceptance was found in other studies [37-39]. Nevertheless it is reasonable to suppose that different socio-cultural attitudes towards vaccination and a different perception of risk of catching a disease are often seen in different populations and might influence vaccination choices; however the reasons why differences exist between racial ethnic groups remain largely unknown [40].

The effect of socioeconomic status and education in vaccine acceptance is still under debate: findings suggest mixed effects of socioeconomic status, with lower education associated with higher acceptability, while higher income is associated with higher acceptability [41].

Finally, the dramatic decline observed in vaccine preventable diseases compared to the pre-vaccine era has led to parents' lack of experience with the morbidity and mortality associated with these diseases [42]. This fact has led to a decrease in the perceived importance of vaccination as a valuable preventive health intervention and could hinder the diffusion of vaccines in the future.

#### **The Role of Health Care Providers**

Physicians have a role of primary importance in promoting a healthy lifestyle for adolescents and both pediatricians and family physicians play a critical role in vaccine counsel-

ing. A good communication between the healthcare provider, parents and patients is essential for vaccine compliance and the physician's ability to establish a confidential relationship with the adolescent could be an important factor for promoting immunization.

Healthcare providers are one of the main information sources about vaccines for parents and since their recommendations are considered to be a strong predictor of vaccine acceptance, providing clear information about vaccine efficacy and security both to parents and adolescents is essential [43, 44]. In order to do so, physicians should have an appropriate knowledge of vaccines: in particular a good knowledge of those specifically targeted to adolescents is of primary importance and may be the most decisive factor recommending particular vaccines [45].

Healthcare provider attitudes towards adolescents' vaccination are quite different: even though most physicians recommend appropriate vaccinations to their adolescent patients and include immunization activities in preventive health visits, they experience barriers to adolescent immunization, particularly as adolescents grow up [11]. A recent study of healthcare barriers in delivering HPV vaccine showed that personal beliefs towards vaccination in general (and specifically to HPV vaccine) and the importance of adhering to the official recommendations are associated with higher rate of vaccination. Nevertheless high financial costs and encountering patients (more often patients' parents) who have negative perceptions of vaccine are the strongest barriers to immunization reported by providers [46]. Thus, overcoming these barriers in addition to a continuous physician education on vaccines and the creation of an alliance among adolescent and health care professionals is crucial for increasing adolescents' immunization rates.

#### **NEW VACCINES FOR ADOLESCENTS: WHEN, WHY AND WHAT?**

The term *adolescence* is commonly used to define the period of life between childhood and adulthood. Even though adolescence is a recognizable phase of life, its onset and its end are not always easy to define. The exact age range of adolescents has been largely debated over the years because adolescence varies considerably across cultures and within individuals. This poses problems for practitioners when adolescent patients require care in facilities with restrictive age limits. Despite the large variation in adolescence definition in term of cut-off age range, actually the American Academy of Pediatrics and the American Medical Association have defined adolescence as a time period between the age of 11 and 21 [47].

In 1996 specific recommendations for the immunization of adolescents were developed in the USA to improve vaccination coverage among adolescents [48]. Over the years an extensive review of all aspects of vaccines (e.g., effectiveness, safety, cost) and an update of adolescent recommendations were made by ACIP. A milestone in adolescent immunization was the licensing in 2005 of three vaccines [quadrivalent meningococcal conjugate (MCV4), HPV and the Tdap] specifically targeted for this age group: in fact their introduction has opened new preventive possibilities for adolescents.

The CDC in collaboration with the American Academy of Pediatrics update periodically the adolescent immunization schedule considering additional data on efficacy, safety and cost-effectiveness of vaccines but also trends in disease epidemiology. We summarize below the three main vaccines for adolescents against diphtheria-tetanus-pertussis, HPV and Neisseria meningitidis.

#### **DIPHTHERIA-TETANUS-PERTUSSIS VACCINE**

Over the past several decades, the introduction of the routine childhood vaccination programs against diphtheria, tetanus and pertussis has reduced the morbidity and mortality associated with these diseases [49, 50]. Although cases of diphtheria and tetanus are very rare in countries with successful vaccination programs, in the past two decades resurgence of pertussis has been reported in many areas of the world [51]. This increase in incidence of pertussis reflects different factors (waning in vaccine-induced immunity to pertussis in the 4–12 years after vaccination and a decrease of natural boosting of immunity) and has been associated with a shift in age groups afflicted with pertussis [52, 53]. In fact before the introduction of the vaccine, pertussis mostly affected school-age children, but it has now shifted to very young infants not completely vaccinated and to adolescents and adults [54, 55]. In Europe the incidence of reported pertussis cases was higher among infants, (22 cases per 100,000) and among those aged 10-14 (20 cases per 100,000 inhabitants): these data indicate that adolescents are at an increasing risk of disease [56].

Usually pertussis in adolescents has not very severe course and results in only mild symptoms; however the morbidity may be significant since paroxysmal cough, difficulty in breathing, post-tussive vomiting, whoop, and difficulty in sleeping are reported in this age group. Complications such as pneumonia, rib fracture, seizure and loss of consciousness can occur and lead to hospitalization [57]. In addition a long delay in diagnosis, typically seen in adolescents, results in an unsuspected and uninterrupted prolonged period of infectiousness and contributes to *Bordetella pertussis* transmission to unvaccinated young infants [58]. In this scenario the introduction of a booster dose of pertussis vaccine (in association to a boosted dose of tetanus toxoid and diphtheria antigens) during adolescence could prevent this cycle of transmission from older individuals to susceptible infants, reduce the incidence and prevent the morbidity of this disease. Moreover this vaccine is useful to maintain the standard of care for tetanus and diphtheria prevention: in fact waning immunity to tetanus and diphtheria was observed after primary tetanus vaccination [59].

The first acellular pertussis vaccines for adults and adolescents were licensed in 2005: this vaccine, containing a reduced-dose of acellular pertussis antigen combined with diphtheria and tetanus toxoids (Tdap), was introduced as a booster on the basis of non inferiority of the serologic response and the minor reactogenicity to the various components compared with the pediatric formulation [60].

Two different booster vaccines are currently licensed for adolescents: the three pertussis component Tdap booster vaccines and the five pertussis component ones that contain fimbriae types 2 and 3 in addition to detoxified pertussis

toxin, filamentous hemagglutinin and pertactin. These vaccines showed an excellent immunological response after one booster dose and were noninferior to the tetanus-reduce dose diphtheria vaccine. In adolescents they elicited robust immune responses to pertussis antigens and protective levels of anti-diphtheria and anti-tetanus antibody after immunization. In terms of reactogenicity Tdap is generally well tolerated: local injection-site and systemic adverse events were of mild intensity and were resolved without sequelae [61-64]. Some neurologic outcomes (Bell Palsy and encephalopathy) after Tdap have been reported to the Vaccine Adverse Events Reporting System; nevertheless a recent study found no evidence of an association between Tdap and encephalopathy, encephalitis, meningitis, paralytic syndromes, seizures, cranial nerve disorders and Guillain-Barré syndrome [65]. Moreover no evidence for an increased risk for hematologic, allergic events or new onset of chronic illnesses among adolescents vaccinated with Tdap was seen [66]. Effectiveness during outbreaks was also reported [67].

Vaccine-induced immunity to pertussis, like naturally acquired immunity against the disease, fails to induce life-long protection. A study conducted in adolescents with the acellular pertussis vaccine showed an increase in antibodies against pertussis antigens for up to 5 years [68], nevertheless pertussis antibody levels were predicted to be sustained for at least 10 years [69]. These data support the use of a booster dose once every 10 years [70].

The ability to coadminister Tdap with more than one recommended vaccine at the same time without compromising the safety, tolerability, and immunogenicity of each vaccine has the potential to increase compliance in adolescents, enhance implementation of immunization strategies and increase disease prevention [71-73]. These data support the ACIP recommendations for adolescent immunization for the use of Tdap vaccine: a single booster dose should be administered to persons aged 11-18 who have completed the recommended childhood diphtheria and tetanus toxoids and pertussis/diphtheria and tetanus toxoids and acellular pertussis vaccination series. Moreover Tdap can be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine [74]. These strategies are made to facilitate the use of Tdap to reduce the burden of disease and the risk for transmission to infants.

## HUMAN PAPILLOMA VIRUS VACCINES

The advent of the HPV vaccine is one of the “historic milestones” in the field of adolescent immunization. Twenty years after the introduction of human hepatitis B vaccine, the second opportunity to be protected from cancer through immunization was given by the HPV vaccine. In fact HPV infection is known to cause a wide range of cancer and genital warts in both sexes: cancer of cervix, vulva, vagina, anus, penis, head, neck and bladder are known to be associated with different types of HPV [75]. Recently the role of HPV in breast and bladder has been investigated but a definitive relationship between these cancers and HPV infection has not been established [76, 77]. Adolescence is a crucial time-period in the natural history of HPV infection: in fact HPV infection is usually acquired during adolescence (up to 25 years old) and many of the risk factors for developing cervical cancer are typically found in adolescents. Cigarette

smoking, a younger age at first intercourse, high number of sexual partners and other sexual transmitted infections are associated with an increase risk of invasive cervical cancer [78]. The incidence of infections among female adolescents aged 14-19 ranges from 18.2% to 24.5% [79,80] while it is >20% in young men [81]. A meta-analysis (considering studies published between 1995 and 2009) showed that age-specific HPV distribution occurred with a first peak at a younger age (<25 years) [82]. Although, HPV infection is usually asymptomatic and clears without intervention [83, 84], persistent infection (mostly due to HPV 16 and 18) is considered to be required for developing of high grade intra-epithelial neoplasia of cervical, vaginal and vulvar tracts. In this scenario young adolescent girls are identified as the primary target group for most HPV immunization programs: in fact targeting adolescents before the onset of sexual activity and the exposure to HPV is likely to provide the greatest long term health benefits.

Two prophylactic vaccines are currently licensed in many countries. The quadrivalent vaccine contains HPV types 6,11,16,18 and was the first to be approved for use among females aged 9-26 for prevention of vaccine HPV-type-related cervical cancer, cervical cancer precursors, vaginal and vulvar cancer precursors and anogenital warts [85]. In fact HPV 16 and 18, classified as high risk types according to their oncogenic potential, are strongly associated with cervical cancer, while HPV 6 and 11 types are the most common causes of genital warts. The bivalent vaccine which contains HPV types 16 and 18 is indicated for the prevention of HPV-type-related premalignant cervical lesion and cervical cancer [86]. Both vaccines, given in a 3 shot series, have been shown to be highly immunogenic when administered to adolescent girls and young women and their efficacy against cervical, vulvar, vaginal premalignant lesions and genital warts was proved in many clinical trials [87, 88]. More research is being done to find out how long protection will last, and if a booster dose will eventually be needed: at this time there is not sufficient information and no booster doses are currently recommended [89].

HPV vaccines were safety-tested before licensing and are continually monitored for their safety. Currently the proportion of serious adverse events is below 0.1% for both vaccines and the most common reported side effects were local site reactions [90]. An increased risk of syncope was reported after the administration of quadrivalent vaccine: thus, CDC and Food and Drug Administration recommend observing the patient for a minimum of 15 minutes after vaccine administration [91].

Recently the quadrivalent vaccine has been approved for use in boys and men aged 9-26: it is the first preventive therapy against genital warts for males [92]. In fact male infection is an important concern both for the disease burden (the rate of genital HPV infection among males is similar to that in females) and for the risk of transmission to women [93]. This vaccine is immunogenic and prevents infection with HPV-6, 11, 16, and 18 and the development of related external genital lesions in this age group: the efficacy against any HPV 6/11/16/18-related external genital lesion was 90.4% [94]. As observed previously with females, the most common adverse events were injection-site reactions, fever and

headache most of which were mild to moderate in intensity [95].

In recent years the interest in using HPV vaccine in some special populations is increasing especially with respect to HIV infection. In fact the prevalence of HPV and premalignant cervical lesion is several-fold higher in HIV-infected women than in uninfected women and HPV infections tend to persist longer [96]. In particular HIV-infected adolescent girls are particularly vulnerable with a risk three-fold higher for developing high-grade squamous intraepithelial lesions [97]. In this scenario the immunization of HIV-infected girls with HPV vaccines will be a major opportunity to reduce the burden of HPV infection in this population. Although no data are available for HIV-infected adolescents, in HIV-infected children aged 7-12 the quadrivalent vaccine appears to be safe and immunogenic and no evidence for perturbation of CD4 level or HIV viral load and unexpected adverse events have been reported [98]. More studies are urgently needed to assess the vaccine efficacy in this population.

### VACCINES AGAINST NEISSERIA MENINGITIDIS

Meningococcal meningitis and septicemia are a persistent public health concern owing to the associated morbidity and mortality. Even if people of all ages may be affected, a peak in disease incidence was reported during adolescence [99, 100]. Moreover a higher nasopharyngeal carriage rate of *N.meningitidis* was observed in teenagers (23.7%) compared to other age groups [101]. The reason for this high disease susceptibility should be found in the typical adolescent lifestyle. Studies suggested that certain behaviors influence the risk of nasopharyngeal carriage of *N. meningitidis* and invasive meningococcal disease: living in crowded situations (pub and club visits, dormitories), marijuana use, active and passive smoking, sharing of drinking glasses and high number of kissing partners are associated with an increased risk of carriage and disease [102-105]. The burden of meningococcal disease and its consequences in this age-group is high: infection in 15-24 year olds was more likely to be fatal than infection in those younger than 15 years old and poor long-term physical, psychological, educational and social outcomes were reported in adolescents survived to an invasive meningococcal disease [106]. In fact major physical sequelae, fatigue, deficits in short and long-term memory and attention, slowed psychomotor speed, depressive symptoms, less social support, reduction in quality of life and low educational attainment were reported in survivors [107, 108]. Although early diagnosis and treatment are important in reducing the morbidity and mortality associated with meningococcal disease, vaccines are required for ultimate disease control. In fact vaccination may be a key factor for avoiding infection in susceptible adolescents and thus to prevent the mortality and morbidity in this age group.

Five clinically relevant meningococcal serogroups, A, B, C,Y and W-135, are responsible for nearly all infections worldwide with different geographical distribution across countries; overall, serogroups B, C and Y cause a substantial proportion of disease across all ages [109]. These data combined with an increased frequency of travelling worldwide, underscore the need for a strong prevention strategy that incorporates all major serogroups [100, 110]. Currently there are no vaccines licensed and routinely used for serogroup B

but quadrivalent vaccines, containing serogroup A,C,Y,W-135, are currently licensed worldwide.

Polysaccharide quadrivalent vaccines have been available for several decades but have been little used due to poor immunogenicity in young children and minimal effects on nasopharyngeal carriage. On the basis of the limits of polysaccharide vaccines and epidemiological changes in the circulation of pathogenic serogroups in the United States, a quadrivalent conjugate vaccine (MCV4) was developed and approved in 2005. Recently, another tetravalent conjugate meningococcal vaccine has been licensed and made available in the USA and in the EU [111]. Both vaccines are immunogenic and have shown a high tolerability profile in adolescents [112]. An investigational quadrivalent (A,C,W-135,Y) tetanus toxoid conjugate vaccine, developed to expand available options for vaccination against invasive meningococcal diseases, showed consistently a high rise in bactericidal titres across all serogroups when administered as a single dose to adolescents and the reactogenicity profile was clinically acceptable; nevertheless more studies are needed [113-115].

New recommendations for the use of meningococcal conjugate vaccines were updated by ACIP based on new data on immunogenicity in high-risk groups, bactericidal antibody persistence after immunization, current epidemiology, vaccine effectiveness and cost-effectiveness of different strategies for vaccination of adolescents. According to the CDC, adolescents aged 11 or 12 should be routinely vaccinated and a booster dose should be administered 5 years after the first dose due to waning immunity. In fact after a booster, antibody titres are higher than after the first dose and are expected to protect adolescents through the period of increased risk up to 21 years old. In addition HIV-infected adolescents and persons aged 2 through 54 years with persistent complement component deficiency, functional or anatomic asplenia, should receive a 2-dose primary series administered 2 months apart because immune response to a single dose of meningococcal conjugate vaccine is not sufficient in persons with certain medical conditions [116].

Actually little is known about the real vaccine efficacy against meningococcal disease although recent epidemiological data collected after the introduction of MCV4 showed an important reduction in incidence of meningococcal disease with an estimated effectiveness of this vaccine ranging from 80 to 85% up to 3 years after vaccination [117]. Nevertheless the peak in disease among teenagers has persisted, even after routine vaccination. Moreover the recent emergence of strains with reduced antibiotics susceptibility in many areas of the world underlines the importance of preventing meningococcal disease by vaccination [118-123]. Thus, new strategies and more efforts to increase awareness of disease susceptibility and of the importance of vaccination are urgently needed particularly in adolescent population.

### ADOLESCENT IMMUNIZATION IN DEVELOPING COUNTRIES

Although a considerable number of countries, including some low- and middle-income countries, have national recommendations to immunize adolescents, most literature about the administration of vaccines to adolescents comes from developed countries. Few data are available about ado-

lescent immunization in developing countries. Without a doubt, one of the greatest barriers to the introduction of vaccination in developing countries is cost although the lack of health care infrastructure is also determinant. Delivery costs are significant and the vaccine storage cold chain and transportation are generally problematic and expensive in these countries.

The challenge for many developing countries remains how to make available to immunization services a significant proportion of adolescents. Delivery mechanisms need to be created or strengthened to reach this population, using approaches such as school-based programs, immunization campaigns and clinic-based programs. When targeting older children and adolescents with immunization, schools have been used extensively as a delivery venue.

In many settings, school-based health interventions and immunization delivery are widely accepted and offer the advantage of easy access, convenience and time efficiency for parents [124]. However in some countries (particularly in Africa), there is not always a clear correlation between age and academic levels in school. Thus school-based programmes have to be clear as to whether target groups are defined by biological age or school year. One major concern, not just in terms of the effectiveness of these programmes, but also in terms of equity, is that such a delivery strategy will not reach the many adolescents who do not attend school [125]. Achieving widespread vaccination coverage of adolescents in developing countries in the next 10 years will require a concerted global effort, given social, logistical and financial challenges. Reaching high coverage will require addressing social and cultural perceptions about vaccination, improving health care systems for adolescents, strengthening the vaccine cold chain and improving transportation. The challenge is compounded by the need to deliver vaccines that require more than one dose over an interval of months. Innovative delivery strategies to reach adolescents are currently being investigated, building on existing immunization programs and looking for integration opportunities with other health priorities.

### WHAT IS THE FUTURE OF ADOLESCENT IMMUNIZATION?

A time when vaccines become more readily available to adolescents, more efforts should be made to increase coverage rate in this population since adolescence is the last opportunity for large-scale immunization programs. Identifying the best strategy to ensure high vaccination rates is a major challenge because a lot of factors influence attitudes towards vaccination in teenagers. Probably a multi-level strategy focused on patient-oriented interventions, provider interventions and system interventions would be the most effective ones although an “individualized strategy” based on the social, financial and cultural resources of each country may also be determinant for achieving this goal. Understanding the real shortcomings, needs and resources of each country regarding adolescent immunization could be of primary importance in order to build an effective strategy.

Making vaccine administration easier could also be an important goal for a successful adolescent immunization strategy. Other administration routes apart from intramuscular and deep-subcutaneous could increase vaccine acceptance

in this age group because they are minimally invasive. New local administration sites offer in fact some important advantages if compared with the traditional ones: reduction of adverse effect rates, in particular those associated with needle use, a better mucosal immune response through a local IgA-mediated stimulus, increasing patient compliance and cost savings. Nanotechnologies have also recently been applied to the manufacture of microscopic and minimally invasive devices for epidermal delivery of some vaccines. Microneedle devices and nanopatches are being developed for effective and pain-free administration of vaccines across the skin barrier layer [126]. Currently the role of these new technologies in adolescent immunization is not known but they may be able to positively influence attitudes toward vaccination. Nevertheless, patient-provider communication remains a vital component and the role of physicians in promoting health and immunization practices remains crucial.

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