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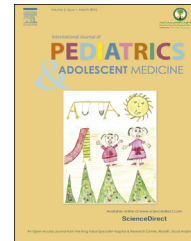


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INVITED REVIEW

Adolescent immunization – Protecting youth and preparing them for a healthy future



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Abstract Adolescence is a period of profound biological, physical, intellectual and neuro-cognitive growth and development, during which new social roles and responsibilities are acquired. Vaccination has the potential to avert acute and chronic illness during this period and to decrease the risk of illness, disability, and cancer in adult life. Here, the vaccines recommended for adolescents are reviewed, and the essential role of health care providers in providing education to adolescents about immunization is highlighted. Each health care encounter is an opportunity to ensure that the adolescent has the benefit of all available vaccines.

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1. Introduction

The adolescent years, during which children make the transition into adulthood, are characterized by profound biological, physical, intellectual and neuro-cognitive growth and development and the acquisition of new social roles and responsibilities. In many ways, adolescent health is a product of child and maternal health, and it lays the framework for adult well-being [1,2]. Immunization is one of the 10 public health achievements of the 20th century [3], and it plays an integral role in the prevention of

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acute and chronic infectious diseases, including cancer. Health care providers play an essential role in ensuring that adolescents have the opportunity to be immunized and in helping adolescents understand that immunization prevents morbidity and mortality for them and their families throughout their lives. In this narrative review, the vaccines that are recommended for adolescents are described. It is recognized that the specific vaccines that are recommended for adolescents vary across countries based on local disease epidemiology and available economic resources for implementing vaccine programs.

2. Background – adolescence as a life stage

The importance of adolescent health to societal prosperity was highlighted by the 2014 World Health Organization (WHO) report *Health for the world's adolescents. A second chance for the second decade*: "Promoting healthy practices during adolescence, and taking steps to better protect young people from health risks are critical for the prevention of health problems in adulthood, and for countries' future health and social infrastructure" [4]. Indeed, the sheer numbers of adolescents, estimated at 1.2 billion, merits the attention of health care planners.

As a "social construct", the concept of adolescence as a distinct life stage was developed relatively recently [2,5]. Non-governmental societies focused on adolescent health were developed in the last century [6,7]. Definitions of the adolescent age span vary; adolescence has been proposed to begin as early as 10 years of age and to extend to as late as 24 years of age [2]. The recognition that brain maturation continues to as late as 25 years of age [5] supports a more extended duration for the adolescent stage of life. The WHO considers the adolescent age span to be from 10 to 19 years of age [4].

For the immunization provider, adolescent patients should be evaluated in terms of whether they have received all recommended childhood vaccines, whether new vaccines have been introduced that they should receive, and which vaccines may require a boosting dose. Each encounter between a health care provider and an adolescent is an opportunity to discuss vaccine-preventable diseases and, more broadly, preventive health. These "teachable moments" can deepen adolescents' understanding of their health and help them recognize their role as active agents in maintaining their own health and the health of their community.

3. Are recommended childhood vaccines up-to-date?

Immunization in childhood has dramatically reduced the worldwide burden of diphtheria, pertussis, tetanus, polio, *Streptococcus pneumoniae*, tuberculosis, meningococcal disease, *Haemophilus influenzae* type B (Hib), hepatitis B and A, rotavirus, human papilloma virus (HPV) measles, mumps, rubella and varicella [3]. In certain regions and in certain populations, vaccines are also recommended to protect against Japanese encephalitis, yellow fever, tick-borne encephalitis, cholera, typhoid, rabies or hepatitis A [8]. The WHO position papers on recommended

immunization provide detailed guidance for immunization providers on childhood, adolescent and adult vaccines at the country and individual level [9].

The vaccine records of adolescents should be reviewed at every visit to prevent missed opportunities for immunization. If the adolescent is un-immunized or under-immunized or vaccine doses have been delayed, the appropriate vaccine, dose, route, and catch-up schedule can be determined from the product monograph, the country department of health or useful resources such as the WHO [8]. If a reliable history of previous immunization does not exist, most experts recommend assuming that the person is unimmunized and providing all necessary vaccines [10]. In general, fewer doses are needed to immunize an older child, and a vaccine series does not need to be restarted in an older child, regardless of the interval between doses.

4. Adolescent vaccines

The immunity induced by a full series of a childhood vaccines may be considered lifelong (e.g. measles vaccine) or may be known to wane over time (e.g. tetanus toxoid vaccine). Inactivated vaccines, such as tetanus, diphtheria and pertussis, are more likely to require boosting doses, whereas live vaccines, such as measles, mumps, rubella and varicella, are more likely to produce a longer duration of protection. A boosting dose in adolescence provides protection through the adolescent and early adult years. Other vaccines may be given for the first time in adolescence to protect against a disease that is more common or is not encountered until the second decade of life (e.g. human papilloma virus, HPV vaccine).

The vaccine provider should be able to explain the disease that will be prevented by the vaccine and provide non-judgmental answers to questions that the adolescent may have.

4.1. Tetanus – diphtheria – pertussis vaccine (Tdap)

The recommendation for a combined tetanus toxoid (T) and diphtheria toxoid (D) vaccine every 10 years is longstanding [11]. The addition of an acellular pertussis component to the adolescent Td dose occurred approximately 10 years ago, when major outbreaks in this age group were recognized in North America and elsewhere [12,13].

Tetanus (lockjaw) is a neurologic illness caused by spores of *Clostridia tetani*, an organism that is ubiquitous in the environment. Tetanus is characterized by muscle spasms that can prevent respiration, leading to death, and it most commonly occurs in newborns born in conditions that are not adequately aseptic and when open wounds are exposed to soil, feces or environmental contamination. Diphtheria is a respiratory illness caused by exotoxin-producing strains of *Corynebacterium diphtheriae*. Pharyngitis can progress to upper airway obstruction and respiratory failure, while the systemic spread of diphtheria toxin can cause myocarditis and damage to other organs, including organs of the central nervous system and the kidneys. Pertussis (whooping cough), a respiratory illness caused by the bacteria

Bordetella pertussis, exacts its highest morbidity and mortality in infants in the first year of life, as they are susceptible to respiratory failure. The typical paroxysms of cough followed by an inspiratory stridor (whoop) may not occur in young infants. In adolescents, pertussis can present as a cough illness persisting for many weeks that interrupts their sleep and affects their ability to attend school and participate in extracurricular activities. Adolescents and adults are thought to be the infectious source of infant pertussis infection; thus, the vaccination of adolescents and adults may reduce the transmission of pertussis in addition to providing personal protection [13,14]. Although several countries (e.g., Canada, the United States, Germany, and France) [15] have introduced an adolescent Tdap vaccine program, the WHO does not recommend Tdap for routine use with the purpose of preventing infant pertussis because of insufficient evidence of its effectiveness in this regard [15].

The Tdap (tetanus-diphtheria- acellular pertussis) vaccine consists of diphtheria and tetanus toxoids combined with antigenic components of pertussis. The quantity of pertussis antigen in the adolescent Tdap vaccine is lower than in pediatric formulations. Whole cell pertussis vaccines are not used in adolescents [15]. Tdap is administered as a single intramuscular injection in the deltoid muscle.

The preferred age at which the adolescent Tdap booster is given is 11–12 years, but the timing of vaccination also depends on local epidemiology and program implementation considerations. Older adolescents who received Td but not Tdap are encouraged to receive a single dose of Tdap to provide protection against pertussis if their childhood pertussis vaccines were completed [12,13]. Tdap can be given at the same visit as other vaccines at a separate anatomic site and using a new needle and syringe.

Immunogenicity studies of Tdap vaccines compared to Td showed that they meet the pre-specified criteria for protection against diphtheria, tetanus and pertussis antigens [13]. The most common adverse event following Tdap/Td immunization is pain at the injection site, and this occurred in approximately 75% of Tdap recipients and to a lesser extent in Td recipients (approximately 72% of recipients) [13].

4.2. Human papilloma virus vaccines

Human papilloma virus (HPV) is a DNA virus that infects keratinocytes of human skin and mucous membranes. HPV infection can be self-limiting or become persistent. Persistent infections of the respiratory and genital tracts can regress, be subclinical, progress to papillomatous growths (warts), or develop into invasive cancers of the oropharynx, vulva, vagina, penis or anus. HPV types are characterized as high risk (e.g., serotypes 16 or 18) or low risk (e.g., types 6 and 11) depending on the strength of their association with invasive cancers. Worldwide, at least 70% of all cervical cancers, the fourth most common cancer in women, are caused by the high risk HPV types, 16 and 18. Furthermore, approximately 90% of anal squamous cell cancers are caused by these two HPV types. Vaccines are available that protect against two HPV types (16 and 18), four HPV types (16, 18, 6, 11) and nine HPV types (16, 18, 6,

11, 31, 33, 45, 52, 58). The 9-valent vaccine has the potential to prevent 90% of HPV-associated anogenital cancers [16]. HPV infection can be acquired through sexual contact (intercourse or other intimate contact) with an infected person or, in the case of newborn infection, through transmission from mother to infant during delivery [17,18].

HPV vaccine are composed of virus-like particles (VLPs) produced by recombinant DNA technology using a baculovirus expression system. The VLPs consist of purified HPV capsid proteins (HPV L1) from each HPV type. The capsid proteins self-assemble to form VLPs. HPV vaccines do not contain any infectious material, antibiotics or preservatives. HPV vaccines contain aluminum hydroxide as an adjuvant. The bivalent vaccine also contains monophosphoryl lipid A as an adjuvant [17].

To prevent HPV infection, the bivalent or quadrivalent vaccine series must be administered before sexual exposure. Most countries with HPV vaccine programs provide the vaccine to adolescent girls beginning in middle school years (9–13 years of age). Some jurisdictions offer the vaccine to adolescent males in addition to adolescent girls. HPV vaccines are administered by intramuscular injection in the deltoid muscle.

For HPV vaccines, 2 and 3 dose schedules have been recommended. The WHO recommends a 2-dose schedule (0 and 6 months) or a 3-dose schedule (0, 2, 6 months) for girls and boys aged 9–13 years receiving the quadrivalent vaccine and a 2-dose schedule for girls aged 9–14 years receiving the bivalent vaccine [17]. In some countries, 2-dose HPV vaccines schedules are not used or have not received regulatory approval. A three-dose schedule is recommended for girls and boys 14 years of age and older receiving the quadrivalent vaccine series and for girls ≥ 15 years of age receiving the bivalent HPV vaccine. The 9-valent vaccine is given at 0, 2 and 6 months [16]. When older adolescents are given the HPV vaccine series, the three-dose schedule should be used. HPV vaccines can be given at the same visit as other vaccines at a separate anatomic site and using a new needle and syringe.

HPV vaccines were initially approved based on the demonstration of their protection against histologically proven carcinoma-in-situ in young adult women and men. In females that received HPV vaccines, antibody responses were similar or higher in adolescent girls than in women, and this “immunologic bridging” data serves indicates that HPV vaccines protect against infection [17]. The WHO Global Advisory Committee for Vaccine Safety reviewed HPV vaccine safety and concluded that HPV vaccines have excellent safety profiles [17]. The most common adverse event following immunization is pain at the injection site, which occurs in up to 80% of recipients, and pain preventing normal activity occurs in approximately 6% of recipients [17]. These responses are temporary and resolve spontaneously.

4.3. Hepatitis B vaccine

Hepatitis B (HBV) is a DNA virus that can cause asymptomatic infection or florid acute hepatitis. If a hepatitis B infection becomes chronic, the person has increased risks of liver cirrhosis and hepatocellular liver cancer. A

chronically infected person also serves as an ongoing reservoir for transmission. HBV infection can be transmitted perinatally, through exposure to blood or certain body fluids, through the mucosa and non-intact skin, and through percutaneous exposure [19,20].

Most countries with hepatitis B vaccine programs have implemented universal infant vaccine programs, with the first vaccine dose given within 24 h of delivery. An infant HBV vaccine strategy reduces the risk of perinatal transmission, prevents horizontal transmission through household and community contacts, and has a significant impact on the overall burden of HBV disease because peripartum infections are more likely to become chronic than infections later in life [19]. Jurisdictions that introduced adolescent HBV vaccine programs did so to establish immunity prior to the onset of sexual contact or high risk behaviors, such as injection drug use, and have been successful in reducing the burden of disease. In countries with an infant HBV vaccine program, booster doses of the hepatitis B vaccine are not recommended [19,21] based on the observed effectiveness of the vaccine over time and the expectation that immunity does not wane or will increase to protective levels if the vaccinee is exposed to hepatitis B. In countries with infant HBV vaccine programs, the immunization provider should confirm that the adolescent received all childhood doses and should provide catch-up doses, if necessary.

HBV vaccines are produced as purified recombinant HBV antigen (HBsAg) produced in a yeast or mammalian cell line. Preparations are subsequently purified, and an aluminum adjuvant or a preservative may be used. The vaccine is available in a monovalent form or in combination with hepatitis A, polio and diphtheria-tetanus-polio or Hib or *Neisseria meningitidis* antigens. Most of these combination formulations are intended for use in early childhood. When the HBV vaccine is administered to adolescents who were not immunized in childhood, a three-dose schedule (0, 1, 6 months) of a monovalent HBV vaccine or a three-dose schedule of a combination HBV-hepatitis A vaccine is recommended. An alternate two-dose schedule of HBV-hepatitis A (0, 6–12 months) is also available. HBV vaccines are administered intramuscularly.

A complete hepatitis B vaccine series produces a protective immune responses in over 95% of vaccine recipients. The most common adverse event following hepatitis B vaccination is pain at the injection site. The WHO Global Advisory Committee on Vaccine Safety has reviewed the safety of hepatitis B vaccines and confirmed that they have excellent safety profiles [19].

4.4. Meningococcal vaccines

Invasive meningococcal disease (IMD) is caused by *N. meningitidis* bacteremia and/or meningitis and is a life-threatening event. Survivors may have long-term sequelae, including neurocognitive deficits, hearing loss, and limb loss. The disease can also manifest as arthritis, myocarditis, pericarditis or endophthalmitis. Infection begins when pathogenic *Neisseria* species penetrate the nasopharynx and enter the blood stream, through which the organisms are subsequently disseminated throughout the body.

Disease may occur sporadically in individuals or as outbreaks, and in some geographic settings, the disease is endemic. Outbreaks are more common in crowded areas and conditions of close contact, such as college student and military recruit residences and annual pilgrimages to the Haj [22].

Meningococcal vaccines are available in monovalent (C, B, A) and quadrivalent formulations (A, C, Y, and W-135). The first meningococcal vaccines were purified, lyophilized capsular polysaccharides from meningococci of the selected serogroup. These vaccines were poorly immunogenic in young children, and in pediatric practice, they have been replaced by vaccines in which the serogroup polysaccharide is conjugated to a protein, either diphtheria or tetanus toxoid. Protein conjugate vaccines are highly immunogenic in young infants [22,23].

The choice of an adolescent meningococcal protein conjugate vaccine depends on the epidemiology of the disease and meningococcal vaccination earlier in life. For example, an adolescent meningococcal vaccine booster dose is recommended in Canada (monovalent C or quadrivalent) because immunity from infant vaccination is expected to have waned by adolescence and the risk of IMD increases in adolescence [24]. In the United States, which does not have a routine infant meningococcal vaccine program, a single dose of quadrivalent meningococcal vaccine is recommended at 11 years of age, and a routine single booster dose is offered at 16 years of age [25]. In the United Kingdom, the primary meningococcal C vaccine series is given in infancy, with a single booster dose between 13 and 15 years of age [26].

Meningococcal vaccines are administered by intramuscular injection in the deltoid muscle. Meningococcal vaccines can be given at the same visit as other vaccines at a separate anatomic site and using a new needle and syringe.

Due to the rarity of IMD, efficacy trials of protein conjugate meningococcal vaccines have not been performed. In immunogenicity studies, these vaccines have been shown to have equal efficacy to those of meningococcal polysaccharide vaccine comparators [25]. Countries that have introduced monovalent meningococcal C vaccine programs have observed significant declines in childhood and adolescent disease [27]. The most common adverse event following immunization is pain at the injection site [22].

4.5. Influenza vaccine

The influenza virus causes annual epidemics of respiratory illnesses and, in certain risk groups (pregnant women, infants, older persons, persons with underlying cardiac or lung diseases, and immunocompromised persons) can cause hospitalization, serious morbidity and death. Influenza is transmitted person-to-person by respiratory droplets generated by coughing and sneezing and by direct contact with secretions.

There are multiple formulations of the influenza vaccine available, including inactivated subunit or split virus vaccines, oil-in-water adjuvanted vaccines, a recombinant DNA vaccine prepared in an insect virus expression system, and a live attenuated nasally administered vaccine. Vaccines may be trivalent or quadrivalent (containing two

lineages of the B strain in addition to the H1N1 and H2N2 strain). Healthy adolescents are not considered a high risk group for the annual receipt of influenza vaccine based on age [28]. Jurisdictions that offer universal annual seasonal influenza vaccine programs to their entire population (e.g. the United States and some provinces of Canada) include adolescents in their vaccine programs. Universal programs may be easier to deliver than targeted programs, which require screening of potential participants. Additionally, high vaccine coverage rates may be associated with decreased transmission in the community. The measured effectiveness of influenza vaccines varies by vaccine type and outcome measure and varies year-to-year depending on the match between circulating strains and those in the vaccine, among other factors. Please refer to review articles for further discussion of these issues [29,30].

A pregnant woman at any age and her unborn child are considered at high risk for complicated influenza-associated illness, as influenza infection can cause pre-term delivery, stillbirth and neonatal death. The WHO states that pregnant women are at the highest priority for countries considering seasonal influenza vaccine programs [28]. Pregnant women can be vaccinated with a non-live influenza vaccine at any stage of pregnancy [31].

4.6. Adolescents with immunocompromised or chronic illnesses

In addition to being fully vaccinated with all routine childhood and adolescent vaccinations, immunocompromised adolescents and adolescents with chronic illnesses may benefit from additional vaccines. Live vaccines are generally contraindicated in immunocompromised populations or are only used when certain eligibility criteria are met (e.g., varicella vaccine). Adolescents with secondary immunodeficiency due to cancer, immunosuppressive medications or biologic modifiers and those with primary immunodeficiency may require booster vaccines to protect against *H. influenzae* type B, *N. meningitidis* and *S. pneumoniae* throughout adolescence. Please consult public health or local vaccine experts when considering vaccination of immunocompromised patients [32].

Certain chronic illnesses increase the risk of developing infectious diseases that may be vaccine-preventable. Adolescents with heart, lung, neurologic or metabolic diseases should be offered annual influenza immunization. Patients on hemodialysis have an increased risk of hepatitis B infection and should undergo post-vaccination serology tests to ensure that they are immune to hepatitis B. In areas where a hepatitis A vaccine is not part of the routine vaccine schedule, some experts recommend the hepatitis A vaccine for patients with liver disease as a hepatoprotective measure.

5. Summary

Vaccination has the potential to avert acute and chronic illnesses, cancer, disability and death in adolescents during this period of growth and development and during their adult years. Vaccine recommendations for this age group vary in different parts of the world depending on local

epidemiology and programmatic considerations in regards to implementing vaccine programs. Every health care encounter is an opportunity for health care providers to provide education about immunization, and they should use these opportunities to ensure that adolescents receive the benefit of all available vaccines.

Ethical clearance

This manuscript is a review article so no Research Ethics Board submission was done.

Conflict of Interests

Dr. Langley's institution (Dalhousie University) has received funding for research from GlaxoSmithKline, Sanofi Pasteur, NovaVax, Immunovaccine, Janssen Research and Development, MedMira Laboratories Inc, Merck, Novartis, Pfizer and Pan-Provincial Vaccine Enterprise Inc.

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