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Vaccination schedule for adolescents. Consensus of the AEV, CAV-AEP and SEMA

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Abstract We present the consensus document on the immunization schedule for adolescents developed by 3 scientific societies: the Spanish Association of Pediatrics (AEP), through its Advisory Committee on Vaccines (CAV-AEP), the Spanish Society of Adolescent Medicine (SEMA) and the Spanish Association of Vaccinology (AEV). There are particularities in infectious disease during adolescence, such as an increased susceptibility to pertussis, poorer outcomes of chickenpox, mumps and hepatitis A, a high incidence of sexually transmitted infections or increased prevalence of meningococcal carriage. The document analyses the schedule for adolescents in the context of vaccination policy overall. It contemplates the vaccines to be included in the immunization schedule for healthy adolescents: against invasive meningococcal disease (tetravalent ACWY and B), against human papillomavirus (which should be gender-neutral), against pertussis, against influenza and against SARS-CoV-2 (in unvaccinated individuals and at-risk groups). It is worth noting that the 4CMenB vaccine appears to confer some protection against gonococcal infection, which would be a considerable added value for adolescents.

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The vaccination of adolescents belonging to risk groups or travelling abroad also needs to be contemplated, as is the case in any other age group. Vaccination against hepatitis A, which is included in the routine immunization schedule of Catalonia, Ceuta and Melilla from the second year of life, should also be considered a priority in adolescents traveling to endemic areas.

PALABRAS CLAVE
Vacunas;
Adolescente;
Grupos de riesgo;
Calendario de inmunización

Calendario de vacunaciones del adolescente. Consenso AEV, CAV-AEP y SEMA

Resumen El documento de consenso *Calendario de vacunaciones del adolescente* que se presenta tiene la autoría de tres sociedades científicas: la Asociación Española de Pediatría (AEP) con su Comité Asesor de Vacunas (CAV), la Sociedad Española de Medicina de la Adolescencia (SEMA) y la Asociación Española de Vacunología (AEV). Las infecciones tienen sus peculiaridades en la adolescencia, como la mayor susceptibilidad a la tosferina, la peor evolución de la varicela, la parotiditis y la hepatitis A, la incidencia frecuente de infecciones de transmisión sexual, o el aumento de la tasa de portadores de meningococo. Se analiza el calendario correspondiente a esta franja de edad sin perder la visión global de las inmunizaciones. Se contemplan las vacunaciones del calendario del adolescente sano: frente a la enfermedad meningocócica invasora (tetravalente MenACWY y MenB), frente al virus del papiloma humano (que debe hacerse con independencia de género), frente a la tosferina, frente a la gripe y frente a la covid (en no vacunados y en grupos de riesgo). Se destaca que la vacuna 4CMenB tiene una cierta efectividad frente a la infección por gonococo, que sería una gran ventaja añadida para el adolescente. Los calendarios del adolescente perteneciente a grupos de riesgo y del viajero deben ser considerados, al igual que en todas las edades de la vida. La vacuna de la hepatitis A que está incluida en el calendario de vacunaciones sistemáticas de Cataluña, Ceuta y Melilla, desde el segundo año de vida, debe considerarse con prioridad en el calendario del adolescente viajero.

Introduction

The consensus document we present here, the *Vaccination schedule for adolescents*, has been developed by three scientific societies in related fields: two in the field of adolescent care, the Asociación Española de Pediatría (Spanish Association of Pediatrics, AEP), including its Advisory Committee on Vaccines (CAV), and the Sociedad Española de Medicina de la Adolescencia (Spanish Society of Adolescent Medicine, SEMA), and one devoted to vaccination in all age groups from an integral and cross-cutting perspective, the Asociación Española de Vacunología (Spanish Association of Vaccinology, AEV).[1] This document analyses the immunization schedule for a specific age group, adolescents, without ever losing sight of the global perspective on vaccination that has been presented since 2019 in the recommended nationwide ''Shared Immunization Schedule for the Lifespan'' of the Interterritorial Council of the National Health System of Spain.

The adolescent immunization schedule has been enhanced in recent years with the authorization of new vaccines: the low *Bordetella pertussis* antigenic load tetanus, diphtheria and pertussis vaccine, the human papillomavirus (HPV) vaccine, the tetravalent flu vaccines (parenteral inactivated and intranasal attenuated preparations), vaccines against meningococcal disease (MenACWY and MenB) and the SARS-CoV-2. There is also the vaccine against hepatitis A, which must be given to travellers to endemic areas, whose routine administration is now included in the schedules of Catalonia, Ceuta and Melilla from age 2 years.

Some of these vaccines are included in the publicly funded immunization schedule and others, for now, are prescribed on a case-by-case basis or administered after shared decision-making by the clinician, the adolescent and the parents. The MenB and HPV vaccines in male adolescents throughout adolescence (the current schedule only includes them at age 12 years) are examples of these situations. As is the case with any other age group, the vaccination of adolescents in risk groups or who travel to endemic areas must also be contemplated.

The adolescent

The World Health Organization (WHO) continues to define adolescence as ''the phase of life between childhood and adulthood, from ages 10 to 19''. It is a stage characterised by important physical changes (growth and sexual maturation) and psychosocial changes affected by brain development, which is not completed until the third decade of life.[2] The health of adolescents is influenced by their family, cultural and social environment and by their individual characteris-

tics (onset of puberty, constitutional factors...) compared to those of their peers.[3]

During adolescence, any congenital or chronic conditions with onset in childhood will continue (e.g., asthma, cystic fibrosis), conditions related to puberty (e.g., acne, gynaecological problems, scoliosis) and chronic diseases that will continue through adulthood (e.g., diabetes, inflammatory bowel disease) may develop.[4] There are also particular characteristics in infectious diseases in this period, such as an increased susceptibility to pertussis, poorer outcomes o varicella, mumps or hepatitis A, an increasing frequency of sexually transmitted diseases (STDs) and an increase in meningococcal carriage and in the incidence of invasive meningococcal disease (IMD) in late adolescence. Therefore, correct vaccination is of utmost importance.

On the other hand, too many adolescents die or experience lifelong deleterious consequences from exogenous causes resulting from risk behaviours (e.g., accidents, suicide, unwanted pregnancy). The mission of paediatrics is to provide adequate care to this age group with the goal of improving morbidity and mortality.

In regard to vaccination, every visit provides an opportunity to encourage and update vaccination in order to increase protection against the most frequent infectious diseases in adolescents.[5]

Vaccination against invasive meningococcal disease

Adolescents are the age group with the second highest risk of IMD following children aged less than 5 years. Serogroup B is the most prevalent in Europe and causes more cases in adolescents and young adults (55% of total cases) than groups A, C, W and Y combined.[6]

In Spain, there was a decreasing trend in the incidence of IMD between the 1996—97 and the 2013–2014 seasons. From the 2014–2015 season, the trend has been increasing on account of the increasing incidence of cases caused by groups W and Y, while the incidence of cases caused by group B barely changed.[7] Overall, with the advent of the coronavirus disease (COVID) 2019 pandemic and the ensuing respiratory transmission control measures, there was a substantial decrease in the incidence of IMD. Since 2021, we are witnessing an increase in cases, especially by group B. In regions of the United Kingdom (UK) and France, there have been outbreaks caused by group B in adolescents, which has prompted the implementation of specific vaccination campaigns.[8,9]

There is ample evidence of the effectiveness of the MenB and MenACWY vaccines in adolescents for controlling outbreaks and in vaccination campaigns. Routine vaccination of adolescents with the MenACWY vaccine is already established in many European countries, including Spain, the United States, Canada and Australia. Most countries also offer catch-up vaccination for unvaccinated adolescents and young adults. The MenB vaccine is funded for immunization of adolescents in the Czech Republic, some regions of Italy and the state of South Australia, and recommended, but not publicly funded, in Austria, Hungary and all other Australian states. The safety of meningococcal vaccines in adolescents and young adults is excellent, and no safety concerns have emerged with its use in routine vaccination programmes or in outbreak control.[10]

The monovalent MenA and MenC conjugate vaccines have proven effective in preventing nasopharyngeal colonization, while the evidence on the effectiveness of the MenACWY vaccine for this purpose is insufficient. Still, experiences like the one in the Netherlands (campaign for massive vaccination of adolescents with MenACWY) suggest that this vaccine can achieve herd immunity. The MenB vaccine does not reduce the carriage rate in vaccinated individuals.[11]

At present, a booster dose is not recommended in adolescence for individuals vaccinated with the Men B vaccine in infancy or childhood. As an individual measure of protection, previously unvaccinated adolescents may undergo complete vaccination with either of the 2 available vaccines (4CMenB or Menb-fHbp).[12]

Some studies have found evidence suggesting that the 4CMenB may confer protection against *Neisseria gonorrhoeae*. Meningococci and gonococci are very similar genetically and antigenically, especially in the meningococcal outer membrane vesicle protein and the subcapsular neisserial heparin-binding antigen (NHBA). Observational studies using the 4CMenB vaccine have found an effectiveness of 30%–46% in preventing gonorrhoea, which affects more than 80 million individuals at the global level and whose incidence has been increasing in recent years.[13]

Vaccination against human papillomavirus

Infection by HPV is the most prevalent STD worldwide. More than 200 genotypes have been characterised, of which 12 are oncogenic, with types 16 and 18 causing approximately 70% of cervical cancer cases.

The clinical spectrum of disease caused by HPV ranges from genital wards (types 6 and 11) to malignant disease in the rectum, oropharyngeal region, female or male reproductive systems and even the respiratory system. Types 6 and 11 are also believed to cause most cases of recurrent respiratory papillomatosis.[14]

The prevalence of infection by HPV increases with time and with the number of sexual partners, affecting both sexes. The prevalence is higher in men than women, with an estimated average lifetime probability of 85% in individuals aged 18–70 years, remaining stable through the lifespan. The reason is that HPV persists longer in mucosal tissue.[15]

The virus can be transmitted by asymptomatic carriers and most infections resolved spontaneously within a few months, eliminated by the immune system. However, between 3% and 10% of high-risk HPV infections become persistent, giving rise to the group of individuals at risk of developing cancer.

From the time routine vaccination against HPV for girls was introduced, there has been a progressive decrease in the burden of disease in women in many parts of the world, while in men it has remained stable and, for some diseases, even continued to increase.[16]

Two vaccines against HPV are currently available in Spain. One is a bivalent vaccine against types 16 and 18, and another is a 9-valent vaccine that includes 5 oncogenic types and offers protection against genital warts. Both are safe and effective. It is important to vaccinate individuals of

both sexes before the sexual debut, as they can prevent initial infection but not the potential health effects or the transmission of a previously acquired infection.[17]

Primary vaccination can start from age 9 years, with 2 doses if starting before age 15 years and 3 doses otherwise, except in immunosuppressed individuals, who should receive 3 doses regardless of the age at the start of vaccination.[18]

Vaccination against pertussis

Pertussis is traditionally perceived as a childhood disease, but due to waning immunity adolescents are at risk of post-vaccination infection and, therefore, can play an important role in its transmission.[19] In Spain, just 70% of cases of pertussis occurred in children under 14 years in the 2005–2020 period, and in 2020 the incidence in individuals aged 15–49 years increased by a factor of 50.[20]

The vaccines against pertussis available in Spain are the reduced-antigen, combined tetanus- diphtheria-acellular pertussis (Tdap) vaccine (3- or 5-valent against pertussis), the combined Tdap-inactivated poliovirus (IPV) vaccine (3-valent against pertussis) and the combined full-load diphtheria-tetanus-acellular pertussis (DTaP)-IPV vaccine (2- or 3-valent for pertussis).[19]

The schedules for vaccination of adolescents against pertussis vary at the European and global levels. The Centers for Disease Control and Prevention (CDC) of the United States recommend vaccination of adolescents (aged 12–14 years) with the Tdap vaccine.[19] Other countries, like the UK, use the tetanus toxoid and reduced diphtheria toxoids vaccine (Td) for vaccination of adolescents.[21] In Spain, the nationwide common immunization schedule proposed for 2023 recommends vaccination with the Td vaccine at age 14 years.[22] The 2023 immunization schedule of the AEP recommends vaccination at age 12–14 years with the Tdap vaccine, and this is also the case in the regional immunization schedule of Asturias.[13]

The evidence on the effectiveness of vaccination in adolescents is heterogeneous. In the United States, the incidence of pertussis in adolescents has increased despite the high national vaccination coverage.[23] One study has shown that protection against pertussis wanes significantly in the 2 years following vaccination. However, another study conducted in the United States demonstrated that vaccination of adolescents with the Tdap vaccine can be effective in reducing the frequency of hospitalization due to pertussis in infants.[24]

On the other hand, administering the Tdap rather than the Td vaccine at 14 years can provide the opportunity to protect adolescents against pertussis, despite of the limited impact of this strategy in the general population.

More effective vaccines need to be introduced to maintain the protection against pertussis in the long term.[19,23]

Vaccination against influenza

The seasonal flu affects approximately 5%–10% of the population each season, and the incidence in children and adolescents triples the incidence in adults and the elderly.

In Spain, in the 2019/2020 season, the incidence was highest in children aged less than 15 years, with 744.7 new cases per 100 000 in the 5-to-14 years age group. The burden of disease caused by influenza in the child and adolescent population tends to be underestimated[25] by both health care professionals and the general population, chiefly due to a lack of awareness of its clinical significance at the individual level and in terms of the use of health care resources. In adolescents, compared to adults, infection by influenza tends to cause more severe fever and associated symptoms in addition to a higher frequency of complications, especially in those with underlying disease.

The flu should not be considered a benign disease in adolescence, for, while it is usually self-limiting,[26] it may cause complications such as pneumonia, otitis, myositis, encephalitis or myocarditis.

Limitations to daily activities and social interactions are more frustrating for adolescents. Closer physical contact (sports, friend groups) makes the transmission of influenza more likely. Sleep deprivation, poor dietary habits, substance use—in short, specific lifestyle habits—can make them more vulnerable. In the short and medium term, the indications for vaccination in adolescence will increasingly lean towards universal vaccination, along with recommendation of healthy lifestyle habits.

A recent review of the evidence of vaccination against seasonal influenza found an efficacy of 25.6%–74.2% and an effectiveness of 26%–78.8%,[27] which suggests that vaccination is an effective preventive measure in healthy adolescents, in line with international recommendations.

Information on the currently available inactivated vaccines and intranasal attenuated vaccine, all of them quadrivalent, can be found at the online immunization manual of the AEP.[28]

The perception that influenza is a mild disease in adolescents must change. We must raise awareness of its significance among health care professionals and promote public vaccination strategies in this age group, independently of any potential risk factors.

Vaccination against COVID

According to the national epidemiological surveillance network of Spain,[29] from the start of the pandemic to April 21, 2023, 6374 individuals aged 10–19 years were hospitalised, 383 admitted to intensive care units (ICUs) and 34 died due to SARS-CoV-2 infection. In the last year, there were 1374 related hospital admissions, 69 ICU admissions and 7 deaths.

As of March 31, 2023, a total of 105 733 320 doses of COVID vaccine had been administered in Spain. Of the 42 350 585 inhabitants aged more than 12 years, 92.6% are fully vaccinated, with a percentage of 95.8% in the 12-to-19 years subset.[30]

In May 2023, the omicron variant continues to be the most prevalent in Spain. It is characterised by greater immune evasion compared to previous variants, is more easily transmitted and causes less severe disease in vaccinated individuals.[31]

The European Medicines Agency has authorised 3 monovalent vaccines (original strain) (Comirnaty® 30 μg, Spikevax® 100 μg and Nuvaxovid®), 2 bivalent messenger RNA vaccines (Comirnaty® and Spikevax® Original/Omicron BA.1 and Original/Omicron BA.4-5) for vaccination of adoles-

cents aged 12 or more years, and one bivalent recombinant vaccine (Bimervax®) for individuals aged more than 16 years.[32] Most doses administered to adolescents in Spain were of Comirnaty® vaccine. Monovalent vaccines continue to reduce the risk of hospitalization and severe disease. Bivalent vaccines are preferred for seasonal booster doses.[31]

Vaccination of previously unvaccinated adolescents is recommended. In addition, in those belonging to risk groups, regardless of the number of doses received in the past, a booster dose is recommended in autumn-winter, at least 5 months apart from the last received dose or known infection, except in the immunosuppressed (3 months), although as the vaccination campaign progressed, any individual aged more than 5 years could be vaccinated upon request.[33]

The COVID vaccines are very safe. The most frequent adverse events in adolescents are local, such as pain, redness or swelling at the site of injection. Constitutional symptoms, like fever, headache, fatigue or myalgia, are infrequent. They develop within 24–48 hours of vaccination and usually last one or two days. They develop more frequently after the second dose than after the first.[34]

With universal vaccination, there were reports of cases of myocarditis and/or pericarditis associated with the mRNA vaccines (although the risk is greater with the actual infection), a rare adverse event that generally develops within 14 days of vaccination (more frequently after the second dose in male recipients aged 12–29 years). In most cases, the course was benign, with resolution in 2–3 days. We do not recommend the use of the mRNA vaccine in any individual who experienced an episode of myocarditis or pericarditis following a previous dose.[33,34]

Vaccination of at-risk adolescents

Individuals at risk are those with medical conditions, behaviours or histories of exposure that may increase the likelihood of contracting an infectious disease and/or the severity of the disease. Belonging to a risk group generally warrants the provision of specific protection against vaccine-preventable diseases, which may require additional vaccines or doses.[35]

Although historically adolescents have not been a focus of attention when it comes to the risk groups to consider for vaccination, this population has characteristics that must be taking into account in developing recommendations.[36] For instance, they start to travel without parental supervision, they may become sexually active, with the corresponding risk of contracting STDs,[37] and the number of adolescents with chronic diseases has increased due to the increased survival for diseases such as cystic fibrosis, congenital heart defects, cancer or spina bifida and the increased incidence of diseases like diabetes.[38] Some of the risk groups in the adolescent population include adolescents with immunosuppressed status, chronic diseases or engaging in risk behaviours, all of who require specific management.

Another issue that may arise in this age group is a reduction in vaccination coverage, something that is also common in risk groups. Consequently, vaccination at this age is key for the health of our youth, especially those who exhibit risk behaviours. Vaccination of household members and health care professionals who serve adolescents is an essential protective strategy that has not been usually evaluated in the scientific literature.

Vaccination of travelling adolescents

Any adolescents who plan to travel, as well as their parents, should be aware and mature enough to schedule a visit with their medical provider at least one month before departure.[39]

We must convey the need to avoid situations that carry a risk of contracting infections through consumption of water or foods, mosquito bites and risk behaviours.

Depending on the vaccination schedule of the adolescent, the travel destination, duration of the trip, time of the year and type of activity that will take place, pharmacological prophylaxis, primary vaccination or advancing a dose of vaccine may be indicated. The recommendations for vaccination of Spanish adolescents that are going to travel can be found in the online manual of the AEP.[40]

Some vaccines are required to enter certain countries, such as the yellow fever vaccine (an endemic disease in large part of Africa and South America, which requires 1 dose of vaccine 10 days before departure and a booster for adolescents who received primary vaccination before age 2 years), the MenACWY vaccine (African meningitis belt, students, attendees to concerts or festivals with massive audiences; with repeat vaccination every 5 years for risk groups) and the poliovirus vaccine (stays longer than 4 weeks in countries with circulation of wild or vaccine-derived strains, with administration of 1 dose 1 months before departure if more than one year elapsed from primary vaccination); and other indicated based on individual risk, such as vaccines against cholera, Central European encephalitis, Japanese encephalitis, typhoid fever, hepatitis A (included in the immunization schedules of Catalonia, Ceuta and Melilla and indicated as a priority for travellers) or rabies, in addition to ensuring vaccination status is up to date according to the routine immunization schedule.[40]

Pharmacological prophylaxis for prevention of malaria is also indicated depending on the destination, in addition to the use of insect repellents and adequate clothing.

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Conflicts of interest

FJAG has collaborated in educational activities funded by Alter, AstraZeneca, GlaxoSmithKline, MSD, Pfizer and Sanofi-Pasteur and as a consultant in GlaxoSmithKline, MSD, Pfizer and Sanofi-Pasteur advisory boards.

AMGT has collaborated in educational activities funded by AstraZeneca, GlaxoSmithKline, MSD, Ordesa, Pfizer, Sanofi-Pasteur and Seqirus and as a consultant in MSD and Sanofi-Pasteur advisory boards, and has received funding to attend educational activities in Spain and abroad.

IGH has collaborated as a researcher with Ordesa and Nestlé, and received aid to attend congresses from GlaxoSmithKline.

AIA has collaborated in educational activities funded by GlaxoSmithKline, MSD and Pfizer, as a consultant in GlaxoSmithKline advisory boards and received funding from GlaxoSmithKline, MSD and Pfizer to attend educational activities in Spain.

FML has collaborated with GlaxoSmithKline, Hipra, MSD and Pfizer as a consultant and as a speaker in educational activities.

FNH has collaborated with GlaxoSmithKline as a speaker in various meetings and educational activities, with Ordesa in epidemiological studies and with Nestlé and Pfizer through the funding of activities.

JJPM has collaborated with GlaxoSmithKline, Hipra, MSD, Novavax, Pfizer and Sequirus as a speaker in educational activities.

PSM has collaborated in educational activities funded by AstraZeneca, GlaxoSmithKline y MSD, as a researcher in clinical trials for Sanofi-Pasteur and as a consultant in GlaxoSmithKline advisory boards, and has received funding to attend educational activities in Spain and abroad from GlaxoSmithKline, MSD and Pfizer, and grants supported by GlaxoSmithKline.

JVR has had not conflicts of interest in the past 5 years, as he has not received any fees or direct funding from the pharmaceutical industry.

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