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Immunisation schedule of the Pediatric Spanish Association: 2021 recommendations☆

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Abstract The CAV-AEP annually publishes the immunisation schedule considered optimal for all children and adolescent resident in Spain, taking into account the available evidence.

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schedule;
Vaccine preventable diseases;
Infant;
Child;
Adolescent

The 2 + 1 schedule is recommended (2, 4, and 11 months) with hexavalent vaccines (DTPa-VPI-Hib-HB) and with 13-valent pneumococcal conjugate. A 6-year booster is recommended, preferably with DTPa (if available), with a dose of polio for those who received 2 + 1 schemes, as well as vaccination with Tdpa in adolescents and in each pregnancy, preferably between 27 and 32 weeks.

Rotavirus vaccine should be systematic for all infants.

Meningococcal B vaccine, with a 2 + 1 schedule, should be included in routine calendar.

In addition to the inclusion of the conjugated tetravalent meningococcal vaccine (MenACWY) at 12 years of age with catch up to 18 years, inclusive, the CAV recommends this vaccine to be also included at 12 months of age, replacing MenC. Likewise, it is recommended in those over 6 weeks of age with risk factors or who travel to countries with a high incidence of these serogroups.

Two-dose schedules for triple viral (12 months and 3–4 years) and varicella (15 months and 3–4 years) will be used. The second dose could be applied as a tetraviral vaccine.

Universal systematic vaccination against HPV is recommended, regardless of gender, preferably at 12 years, and greater effort should be made to improve coverage. The 9 genotype extends coverage for both genders.

PALABRAS CLAVE
Vacunas;
Calendario de vacunación;
Enfermedades inmunoprevenibles;
Lactante;
Niño;
Adolescente

Calendario de vacunaciones de la Asociación Española de Pediatría: recomendaciones 2021

Resumen El CAV-AEP publica anualmente el calendario de vacunaciones que estima idóneo para los niños y adolescentes residentes en España, teniendo en cuenta la evidencia científica disponible.

Se mantiene el esquema 2 + 1 (2, 4 y 11 meses) con vacunas hexavalentes (DTPa-VPI-Hib-HB) y con antineumocócica conjugada 13-valente.

Se aconseja un refuerzo a los 6 años, preferentemente con DTPa (si está disponible), junto a una dosis de polio para aquellos que recibieron esquemas 2 + 1, así como vacunación con Tdpa en adolescentes y en cada embarazo, preferentemente entre las 27 y 32 semanas.

La vacuna del rotavirus debería ser sistemática para todos los lactantes.

Se insiste en la incorporación en el calendario de la vacuna antimeningocócica B, con esquema 2 + 1 en lactantes.

Además de la inclusión de la vacuna antimeningocócica conjugada tetravalente (MenACWY) a los 12 años con rescate hasta 18 años, inclusive, el CAV-AEP recomienda que esta vacuna sea introducida también a los 12 meses de edad, sustituyendo a MenC. Igualmente, se recomienda en los mayores de 6 semanas de edad con factores de riesgo o que viajen a países de elevada incidencia de estos serogrupos.

Se emplearán esquemas de dos dosis para triple vírica (12 meses y 3-4 años) y varicela (15 meses y 3-4 años). La segunda dosis se podría aplicar como vacuna tetravírica.

Se recomienda la vacunación sistemática universal frente al VPH, con independencia del género, preferentemente a los 12 años, insistiendo en un mayor esfuerzo para mejorar las coberturas. La de 9 genotipos amplía la cobertura para ambos sexos.

Introduction

The Advisory Committee on Vaccines of the Spanish Association of Paediatrics (CAV-AEP) annually updates its recommendations for the immunization of children and adolescents[1] (Fig. 1) according to the available evidence on the epidemiology of vaccine-preventable diseases in Spain and the efficacy and safety of vaccines.

The website of the CAV-AEP explains the grounds for these recommendations. The recommendations for special situations and risk groups can also be found in the online Vaccine Manual of the Asociación Española de Pediatría (Spanish Association of Paediatrics, AEP). Table 1 lists the vaccines that are currently available.

These recommendations are aimed at paediatricians, family physicians, nurses, midwives, families and, gener-

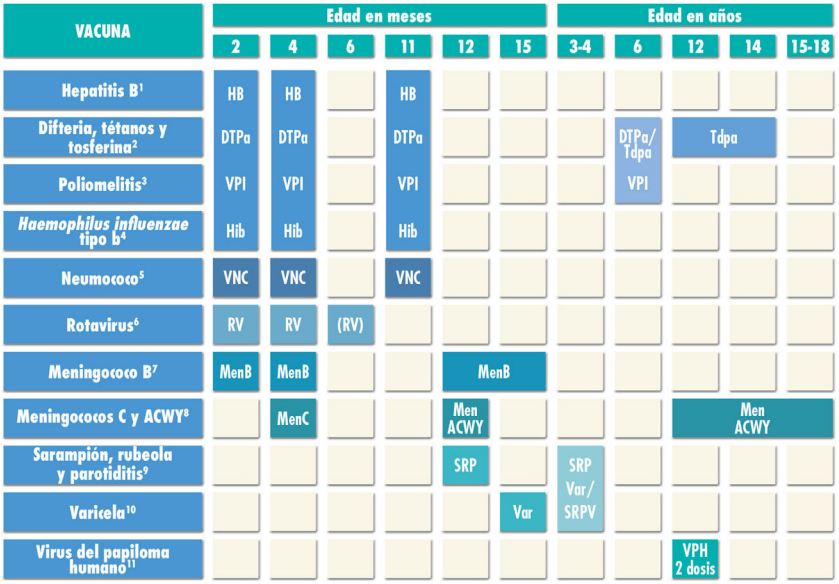

Figure 1 Routine immunisation schedule of the Spanish Association of Pediatrics 2021.

(1) Hepatitis B vaccine (HB). – Doses of hexavalent vaccine at ages 2, 4 and 11 months. Children of HBsAg-positive mothers or mothers of unknown serologic status will also be given one dose of monovalent HB vaccine at birth, in addition to 0.5 mL of hepatitis B immune globulin (HBIG) if maternal HBsAg-positive status is confirmed. Infants vaccinated at birth will adhere to the routine schedule for year 1 of life, and thus will receive 4 doses of HB vaccine. Unvaccinated children and adolescents should be given 3 doses of monovalent vaccine on a 0, 1 and 6-month schedule.

(2) Diphtheria, tetanus and acellular pertussis vaccine (DTaP/Tdap). – 5 doses: primary vaccination with 2 doses, at 2 and 4 months, of DTaP (hexavalent) vaccine; booster at 11 months (third dose) with DTaP (hexavalent) vaccine; at 6 years (fourth dose) with the standard load vaccine (DTaP-IPV), preferable to the low diphtheria and pertussis antigen load vaccine (Tdap-IPV), and at 12–14 years (fifth dose) with Tdap.

(3) Inactivated poliovirus vaccine (IPV). – 4 doses: primary vaccination with 2 doses, at 2 and 4 months, and booster doses at 11 months (with hexavalent) and 6 years (with DTaP-IPV or Tdap-IPV).

(4) *Haemophilus influenzae* type b conjugate vaccine (Hib). – 3 doses: primary vaccination at 2 and 4 months and booster dose at 11 months (with hexavalent).

(5) Pneumococcal conjugate vaccine (PCV). – 3 doses: the first two at 2 and 4 months, with a booster dose starting at 11 months of age. The vaccine recommended in Spain by the CAV-AEP continues to be the PCV13.

(6) Rotavirus vaccine (RV). – 2 or 3 doses of rotavirus vaccine: at 2 and 3–4 months with the monovalent vaccine or at 2, 3 and 4 months or 2, 4 and 5–6 months with the pentavalent vaccine. It is very important to start vaccination between 6 and 12 weeks of life in order to minimise risks, and to complete it before 24 weeks for the monovalent vaccine or 32 weeks for the pentavalent vaccine. Doses must be given at least 4 weeks apart. Both vaccines may be given at the same time as any other vaccine.

(7) Meningococcal B vaccine (MenB). – 4CMenB. 3 doses: start at age 2 months, with a primary series of 2 doses at least 2 months apart and a booster starting at age 12 months and at least 6 months after the last dose in the primary series. It can be administered at the same time as other vaccines in the schedule, although this could increase fever, so another option is to administer it 1 or 2 weeks apart from other injectable inactivated vaccines, up to age 12 months, to minimise potential reactogenicity. The separation by 1–2 weeks is not necessary for the MenACWY, MMR, varicella and rotavirus vaccines. Vaccination is also recommended at any age in risk groups: anatomic or functional asplenia, complement component deficiency, treatment with eculizumab or ravulizumab, haematopoietic stem cell transplant recipients, infection by HIV, prior episode of IMD caused by any serogroup, and contacts of an index case of IMD caused by serogroup B in the context of an outbreak.

(8) Meningococcal C conjugate vaccine (MenC) and meningococcal ACWY conjugate vaccine (MenACWY). – 1 dose of conjugate MenC-TT at age 4 months. The CAV-AEP recommends 1 dose of the MenACWY conjugate vaccine at age 12 months and 12–14 years, and a progressive catch-up vaccination schedule to be completed by age 18 years. In ACs where vaccination with MenACWY is not included in the routine schedule, if parents choose not to administer the MenACWY vaccine at 12 months, the MenC-TT vaccine funded by the regional government must be administered instead. Administration of the MenACWY vaccine is still particularly recommended in children and adolescents that are to live in countries where the vaccine is administered at this age (United States, Canada, Argentina, United Kingdom, Austria, Greece, Netherlands, Italy and Switzerland) and for children with risk factors for IMD: anatomic or functional asplenia, complement component deficiency, treatment with eculizumab or ravulizumab, hematopoietic stem cell transplant recipients, HIV infection, prior episode of IMD caused by any serogroup, and contacts of an index case of IMD

Table 1 Abbreviation, generic names and brand names of vaccines recommended for routine immunisation by the CAV-AEP currently available in Spain.

Abbreviation/vaccine	Generic name	Brand name (manufacturer)
DTaP-IPV-Hib-HB	Hexavalent (standard-load diphtheria, tetanus, standard-load acellular pertussis, inactivated poliovirus, Hib and hepatitis B vaccine)	Hexyon (Sanofi Pasteur), Infanrix Hexa (GSK) and Vaxelis (MSD)
Tdap	Tetanus, reduced diphtheria toxoid and reduced-load acellular pertussis	Boostrix (GSK) and Triaxis (Sanofi Pasteur)
Tdap-IPV	Tetanus, reduced diphtheria toxoid, reduced-load acellular pertussis and inactivated poliovirus	Boostrix Polio (GSK)
PCV13	Pneumococcal 13-valent conjugate vaccine	Prevenar 13 (Pfizer)
MenC-TT	Meningococcal group C vaccine conjugated with tetanus toxoid	NeisVac-C (Pfizer)
MenACWY	Meningococcal A, C, W and Y vaccine conjugated with CRM	Menveo (GSK)
	Meningococcal A, C, W and Y vaccine conjugated with tetanus toxoid	Nimenrix (Pfizer)
MenB		
4CmenB	Meningococcal group B vaccine	Bexsero (GSK)
MenB-fHbp	Meningococcal group B vaccine	Trumenba (Pfizer)
MMR	Measles, mumps, rubella vaccine	MMR-VaxPro (MSD) and Priorix (GSK)
MMRV	Tetravalent vaccine (Measles, mumps, rubella and varicella)	ProQuad (MSD)
Var	Varicella	Varilrix (GSK) and Varivax (MSD)
HPV		
HPV2	2-Valent human papillomavirus vaccine	Cervarix (GSK)
HPV4	4-Valent human papillomavirus vaccine	Gardasil (MSD)
HPV9	9-Valent human papillomavirus vaccine	Gardasil 9 (MSD)
RV		
RV1	Monovalent rotavirus vaccine	Rotarix (GSK)
RV5	Pentavalent rotavirus vaccine	RotaTeq (MSD)

ally, anyone seeking updated information on paediatric vaccines.

Our objectives are: (1) to promote adherence with official immunisation schedules; (2) to offer health care providers options for catch-up vaccination in individuals with incomplete vaccination and (3) to expand individual protection with the vaccines that are currently not included in official immunisation schedules based on the current evidence.

The CAV-AEP continues to emphasise that a uniform immunization schedule for all autonomous communities (ACs) in Spain would contribute to the pursuit of health equity. It would also guarantee equal access to the recommended vaccines and cover specific vac-

caused by serogroup A, C, W or Y in the context of an outbreak. Individuals traveling to Mecca for religious reasons and to the African meningitis belt during the dry season should also receive the MenACWY vaccine.

(9) Measles, mumps and rubella vaccine (MMR). – 2 MMR vaccine. The first at age 12 months and the second at age 3–4 years. The tetravalent MMRV vaccine may be administered for the second dose. Susceptible patients outside the specified ages will be vaccinated with 2 doses of MMR at least 1 month apart.

(10) Varicella vaccine (Var). – 2 doses: the first at age 15 months (age 12 months is also acceptable) and the second at age 3–4 years. The tetravalent vaccine (MMRV) may be used for the second dose. Susceptible patients outside the specified ages will be vaccinated with 2 doses of monovalent Var vaccine at least 1 month apart.

(11) Human papillomavirus vaccine (HPV). – Universal routine vaccination of all girls and boys, at age 12 years, to prevent HPV-related oncological diseases. All 3 HPV vaccines are authorised for use in male individuals, although there is little evidence on the use of the HPV2 vaccine in this sex. Administration of 2 doses at age 12 years. The vaccination schedule depends on the vaccine used: for the tetravalent vaccine, a 2-dose series (at 0 and 6 months) between ages 9 and 13 years and a 3-dose series (at 0, 2 and 6 months) in those aged $\geq$14 years; for the 2-valent and 9-valent vaccines, a 2-dose series (at 0 and 6 months) between ages 9 and 14 years and a 3-dose series (at 0, 1–2 [depending on the vaccine used] and 6 months) in those aged $\geq$15 years. The HPV vaccine may be administered at the same time as the MenC, MenACWY, hepatitis A and B and Tdap vaccines. There are no data on its coadministration with the varicella vaccine, although it should not cause any problems.

cination of risk groups or in special epidemiological circumstances.

We need to structure systems for debate on the subject of: (1) the role of Primary Care as the cornerstone of the National Health System and vaccination; (2) gaps in vaccination coverage and their causes; (3) the approaches to co-funding vaccines that are not included in official immunization schedules; (4) the investigation of and compensation for any potential, rare and unpredictable harm caused by vaccines, and (5) the need to create a platform offering information on all aspects of vaccination.

As has been done in other countries, we need to promote a new infrastructure at the national level for researching and providing evidence-based advice on policy issues related to vaccination, as recommended by the WHO, which would allow the synchronization of the various scientific, social and health administration perspectives at play.

The AEP is open to collaborate with the Ministry of Health, of Spain, the governments of the different autonomous communities and any other parties involved in tasks and processes aimed at improving immunisation. In a year dominated by the coronavirus disease 2019 (COVID-19) pandemic, our response to emerging uncertainties and needs requires the involvement of scientific societies such as the AEP.

Vaccination against hepatitis B

2021 recommendation: 3 doses of hexavalent vaccine at 2, 4 and 11 months of age. Spain, with 700 annual cases of hepatitis B, is a low-endemic country. In 2019, 577 cases were notified, corresponding to an incidence of 1.24 cases per 100,000 inhabitants. The prevalence of carriage is 1%.[2]

Since 2017, vaccination against hepatitis B virus (HBV) starts at age 2 months with the hexavalent vaccine.

The strategy for prevention of vertical transmission of HBV in children born to HBsAg-positive mothers includes administration of the monovalent vaccine and hepatitis B immune globulin (0.5 mL) in the first 12 h post birth, thereafter completing vaccination in adherence with the current immunization schedule, with administration of a total of 4 doses of vaccine.

Unvaccinated children and adolescents should be given three doses of monovalent vaccine on a 0, 1 and 6 month schedule. If vaccination against hepatitis A virus (HAV) is indicated, the combined hepatitis A and B vaccine can be given in a similar schedule.

Vaccination against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b.

2021 recommendation: 2 + 1 schedule with the hexavalent vaccine at 2, 4 and 11 months. Children that have received the 2 + 1 series should be given DTaP-IPV, preferably, or Tdap-IPV at age 6 years and Tdap at age 12–14 years. The first dose can be administered earlier starting at 6 weeks post birth. We recommend vaccination with Tdap of all pregnant women in each pregnancy, preferably between 27 and 32 weeks of gestation, as early as possible within this window. In case of high risk of preterm birth, vaccination could be given starting at 20 weeks.

Infection by *Bordetella pertussis* affects individuals of all ages, but the risk of severe disease, hospital admission or death is greater in young infants. Vaccination during pregnancy is not only effective in preventing the disease, but also in reducing its severity.[3] This is an effective strategy for prevention of severe forms of disease in infants, reducing the risk of hospital admission, admission to the intensive care unit (ICU) and the length of stay.[4] At present, more than 40 countries implement this strategy, which is essential before initiation of the primary vaccine series.

Vaccination in the second or third trimester of pregnancy is highly effective in preventing pertussis (69–93%) and can prevent up to 90.5% of hospital admissions in infants aged less than 3 months.[5] If there is a known risk of preterm birth, vaccination starting from 20 weeks would be an option after performance of the routine prenatal ultrasound scan.

The optimal timing of vaccination in pregnancy and the potential interference of maternal antibodies with infant responses to vaccination (blunting) continue to be subjects of debate.

The reported effectiveness of vaccination in pregnancy does not vary significantly based on the timing (80.7%); for instance, a study in Argentina did not find differences based on the administration of the vaccine in the second versus the third trimester.[6]

The blunting effect is greater when primary vaccination starts at 2 months rather than 3. The benefits of maternal vaccination extend beyond 3 months, but delaying primary vaccination past this point does not seem justified given that this affects immunization against other pathogens such as tetanus, diphtheria, *Haemophilus influenzae* type b, polio and hepatitis B. To date, the Netherlands is the only country that has modified its vaccination schedule for this reason.

The primary vaccine series and booster doses at 11 months, 6 years and 12–14 years are needed to maintain adequate protection against the diseases prevented by combined vaccines that include pertussis.

Although poliomyelitis has been eradicated in Africa, caution should be exerted in case of international travel due to the increase in cases caused by the wild virus in Pakistan and Afghanistan.

Vaccination against pneumococcal disease

2021 recommendation: *Vaccination against pneumococcal disease is recommended for all children younger than 5 years and children of any age that belong to any risk group with the 13-valent pneumococcal conjugate vaccine (PCV13). A 2 + 1 series (at 2, 4 and 11–15 months) is recommended for routine vaccination of infants.*

The evidence on the decrease in the burden of invasive pneumococcal disease (IPD) and non-invasive forms of disease (pneumonia and acute otitis media) with administration of pneumococcal conjugate vaccines (PCVs) continues to grow. The decrease in the incidence of IPD has approximately matched the predictions made in efficacy trials, but the reduction in pneumonia and otitis media has exceeded expectations. The use of PCVs is associated with a reduction

in antibiotic resistance and antibiotic use, even in low-resource countries.[7] In Spain, routine childhood vaccination with PCV13 has led to substantial decreases in the overall burden of IPD in children and adults.[8]

It is agreed that active surveillance of IPD is necessary to remain aware of emerging nonvaccine serotypes,[9] a phenomenon observed in all countries that use PCVs[8–10] and that could compromise the impact of vaccination in the medium to long term.[10]

The routine use of PCV10 is associated with an increase in the incidence of IPD caused by nonvaccine serotypes, especially 19A,[9] although to a variable degree. In Belgium, the switch to the PCV10 from the PCV13 in the childhood immunization schedule has been associated with an increased incidence of IPD, especially in children aged less than 2 years, an mainly on account of serotype 19A.[11] Although a causal relationship with the switch in the vaccine used cannot be established with certainty, all the existing evidence supports this hypothesis.

Vaccination against rotavirus

2021 recommendation: *Vaccination against rotavirus (RV) should be included in the routine immunisation schedule for al infants*. The European Academy of Paediatrics and the European Society of Paediatric Infectious Diseases support this recommendation.[12]

At present, more than 110 countries include the RV vaccine in their routine immunisation schedules. The public health benefits of this vaccine are spectacular. In Spain, hospital admissions associated with RV infection have decreased by 83–96% in the past 10 years, proving that the vaccine is highly effective.[13]

The indirect positive effects of vaccination also extend to the unvaccinated, which increases the impact and efficiency of the vaccine considerably. Preterm infants, for who vaccination is publicly funded on account of membership in a risk group, should be vaccinated without delay, even if they are hospitalised, before 12 weeks post birth.[14]

The benefits of vaccination far exceed the risk of intussusception, the only severe adverse event associated with the RV vaccine, which is very rare (1–5 cases per 100,000 vaccinated children).[15]

Vaccination against meningococcal disease

2021 recommendation: *Routine vaccination against meningococcus B is recommended in all infants starting at 2 months of age with a 2 + 1 schedule, with the decision whether to vaccinate made on a case-by-case basis in all other paediatric age groups, including adolescents.*

We also recommend administration of the MenC-TT vaccine at age 4 months and replacing the MenC dose at age 12 months by a dose of MenACWY. It is essential that, should a child not be given the latter vaccine, the dose of MenC is administered without fail. We continue to recommend administration of the MenACWY vaccine to adolescents at age 12 years, and catch-up vaccination is recommended up to age 18 years. For all other paediatric age groups, the decision to vaccinate will be made on a case-by-case basis.

In Spain, 2 vaccines containing subcapsular antigens are currently available for prevention of invasive meningococcal disease (IMD) due to group B meningococcus (MenB): the MenB-fHbp vaccine (authorised in Europe for use from age 10 years) and the 4CMenB vaccine (from age 2 months).

Since IMD caused by group B meningococcus is very rare, conventional cost-benefit analyses of this vaccine (in terms of quality-adjusted life years, or QALY) are unfavourable. However, the CAV-AEP considers that routine vaccination of infants with 4CMenB worthwhile, as IMD has devastating consequences. Group B meningococcus is the most frequent serogroup isolated in infants aged less than 12 months in Spain, and the impact observed in the United Kingdom after inclusion of this vaccine in the routine vaccination schedule in 2015 proves its effectiveness. Some ACs, such as Canary Islands and Castilla y Leon, have already introduced it in their schedules.

In the United Kingdome, after administration of nearly 4 million doses, the impact on vaccinated cohorts has been evident. In infants aged 12–23 months vaccinated with a 2 + 1 schedule, the incidence decreased by 57% (95% confidence interval [CI], 34–72%) compared to the 2016–2017 period (incomplete vaccination), and by 80% (95% CI, 64–89%) compared to the 2017–2018 period. The effectiveness against vaccine serotypes was of 70.5%, with prevention of 277 (95% CI, 236–323) cases of IMD by MenB in the first 3 years of the programme, with no evidence of safety concerns. There was no significant decrease in the incidence of disease in unvaccinated cohorts, which indicated that vaccination with 4CMenB was the factor determining this outcome.[16] Similar results have been recently reported in two regions in Italy, with evidence of a considerable reduction in the incidence of IMD by MenB following the introduction of routine vaccination with 4CMenB.[17] The data from the United Kingdom motivated a change in the summary of product characteristics of this vaccine in 2020 with authorization of a 2 + 1 schedule starting at 2 months. Also in the United Kingdom, routine vaccination with the 4CMenB vaccine has led to a reduction in IMD by MenW.[18]

Although some questions remain, the CAV-AEP considers the vaccine impact and safety data sufficient to support routine administration of 4CMenB to infants, the age group with the highest incidence of IMD, with a 2 + 1 schedule starting at age 2 months. In other paediatric age groups, including adolescents, the decision whether to vaccinate will be made on a case-by-case basis, as there is no evidence of this vaccine reducing the prevalence of nasopharyngeal carriage or generating herd immunity.[19]

In recent years, there has been a considerable increase in the incidence of IMD by serogroups W and Y worldwide.[20] In Europe, serogroup W accounted for 18.5% of the total cases of IMD in 2018, and serogroup Y for 12%.[21] This increase has been reflected in the immunisation schedules of several countries through the substitution of a dose of MenACWY for the MenC dose given during adolescence and/or the second year of life.[22] At present, only Saudi Arabia, Argentina, Libya and Colombia recommend vaccination before age 12 months, although other countries are contemplating this option.

In Spain, there has been a progressive increase in IMD caused by serogroups W and Y since 2014–2015. However, this trend was not sustained in the most recent

period: the latest data reported to the Centro Nacional de Epidemiología (National Epidemiology Centre) through week 40 of 2020 show a decrease in the incidence of IMD by serogroups W (40 cases, incidence of 0.08/100,000) and Y (24 cases, incidence of 0.05/100,000). Some factors may have affected these figures, such as vaccination with the MenACWY and underreporting associated with the COVID-19 pandemic in some ACs.

In 2019, the Comisión de Salud Pública (Public Health Committee) published the recommendations for vaccination against IMD. When it came to the MenACWY vaccine, the committee considered vaccination of adolescents and young adults a priority, replacing the MenC dose at 12 years by a dose of MenACWY and planning catch-up vaccination of adolescents aged 13–18 years in the span of 2–3 years to achieve an epidemiologically significant impact as soon as possible. Castilla y Leon and Andalusia have included the MenACWY in their routine immunisation schedules at ages 12 months and 12 years.

The CAV-AEP supports the replacement of the dose of MenC by a dose of MenACWY in adolescence and at age 12 months. In case the MenACWY vaccine is not given at 12 months, it is important to ensure administration of a dose of MenC to prevent a decrease in vaccination coverage.

In other paediatric age groups, the decision whether to vaccinate will be made on a case-by-case basis.

Vaccination against measles, mumps and rubella (MMR)

2021 recommendation: *The first dose of MMR will be given at age 12 months and the second at age 3–4 years. The quadrivalent vaccine (MMRV) may be used for the second dose.*

Although Spain continues to be considered free of indigenous measles, in recent years, as observed in neighbouring countries and all other regions of the World Health Organization (WHO), there has been a progressive increase in the number of cases in our country,[23] a situation that may get worse if we do not remedy the drop in vaccination coverage that has occurred during the COVID-19 pandemic. It is essential that coverage rates greater than 95% be maintained for each of the doses of this vaccine.

We recommend administration of the first dose at age 12 months and of the second dose at 3–4 years (possibly giving the MMRV), although this may change in the near future. Administration of the second dose is essential to remedy the potential failure of the first dose an ensure adequate herd immunity. When it comes to rubella, only sporadic cases have been reported in Spain since 2013, including 3 in 2019, and there have been no cases of congenital rubella syndrome since 2014. There are still paediatric outbreaks of mumps.

We continue recommending separate administration of the MMR and varicella vaccines for the first dose of the series in children aged less than 2 years.[24]

Vaccination against varicella

2021 recommendation: *We recommend vaccination of all children against varicella with 2 doses administered at ages 15 months and 3–4 years (the MMRV vaccine may be used for the second dose). For children and adolescents that have not had the disease that have not received any prior doses, we recommend catch-up vaccination with a 2-dose series, or, in those that have received a single dose, completion of the series with a second dose.*

Since 2016, all ACs in Spain has included vaccination against varicella with a 2-dose schedule (15 months and 3–4 years). There are two monovalent and two tetravalent MMRV vaccines with evidence of a high effectiveness (92–97.3%) in both the vaccinated and unvaccinated population.[25]

In 2020, 9 of the 19 ACs in Spain had introduced the use of the MMRV for the second dose.

The inclusion of the varicella vaccine in childhood immunisation schedules is one of the safest and cost-effective public health measures.[26] After more than 20 years of routine childhood vaccination, many countries have reported benefits not only in children, but also at the level of the entire population.[27] To prevent varicella in vaccinated individuals and circulation of the virus, a 2-dose series is necessary.[28] There is no evidence to date of a significant impact of vaccination against varicella in the incidence of herpes zoster in unvaccinated age groups in the population.[29,30]

Vaccination against human papillomavirus (HPV)

2021 recommendation: *Routine vaccination against HPV is recommended in both girls and boys, preferably at age 12 years, with 2 doses of vaccine.*

The recommended age for vaccination is 12 years, with administration of a 2-dose series prior to sexual debut, with the aim of maximizing its possible benefits and pursuing the broadest possible vaccination coverage. We also recommend catch-up vaccination and vaccination of individuals in risk groups.

The causal role of human papillomavirus (HPV) has been demonstrated not only in cervical cancer, but also in other cancers affecting individuals of both sexes, such as anal cancer or head and neck cancers.[31] The excellent effectiveness of the available vaccines for prevention of the persistent infection by HPV associated to precancerous cervical lesions translates to a reduction of nearly 85% in the incidence of high-grade lesions, even after 10 years,[32] anogenital cancer in males[33,34] and genital warts in both sexes. There is also evidence suggesting an impact on oropharyngeal cancer.[35]

The HPV vaccines are extremely safe and offer a very favourable risk-benefit ratio. Although a causal relationship has not been proven in any of the adverse events described with these vaccines,[33] the coverage rates in many ACs continues to be inferior compared to other routine vaccines, and efforts must be made to improve them.

The CAV-AEP upholds its recommendation of routine vaccination against HPV independently of sex. Vaccination for boys is included in the immunisation schedule of 35 countries.[31,36] The immunogenicity and safety in boys are similar to those achieved in girls.[37,38]

In Spain, vaccines authorised for use in individuals of both sexes contain 2 (VHP2) or 9 (HPV9) genotypes. The vaccine that contains 4 genotypes (HPV4), which is still

Table 2 Bibliographic sources and literature search strategies used in the development of this document.

-TripDatabase: Advanced search: (disease) (vaccine) (vaccination)
-Cochrane Library: Disease AND vaccine
-MEDLINE/Pubmed: (''disease/microorganism'' [MeSH Terms]) AND (''vaccine'' [MeSH Terms] OR ''vaccination'' [MeSH Terms]). Filters activated: Childbirth-18 years, Human (Sort by: Best Match)
-EMBASE: ''disease''/exp AND ''vaccine''/exp
-Communications and presentations in national and international congresses
-Primary sources (textbooks, references of articles selected in the search)
-Data obtained directly from authors (unpublished)
-Publications not indexed in databases
-Information obtained from the pharmaceutical industry
-Official websites of the Ministry of Health of Spain and the Instituto de Salud Carlos III

used in some ACs for routine vaccination, is no longer being manufactured. All offer protection against cervical cancer and precancerous lesions associated with HPV. The HPV9 vaccine offers the broadest direct coverage against cervical cancer (90%) and potential prevention of 85% to 95% HP-related vulvar, vaginal and anal cancers.[39,40] The HPV4 and HPV9 vaccines confer direct protection against genital warts. The CAV-AEP recommends that in the ACs, the HPV vaccine selected by the regional government be used for routine vaccination.

Table 2 shows the bibliographic sources and literature search strategies used in the development of this document.

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Conflicts of interest (last 5 years)

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

MJCO has collaborated in educational activities funded by GlaxoSmithKline, Novartis, MSD, Pfizer and Sanofi, as a researcher in clinical trials for GlaxoSmithKline and Pfizer, and as a consultant in GlaxoSmithKline, Novartis, MSD, Pfizer and Sanofi advisory boards.

JAA has collaborated in educational activities funded by Astra, GlaxoSmithKline, Pfizer and Sanofi, as a researcher in clinical trials for GlaxoSmithKline, Novartis and Sanofi and as a consultant in GlaxoSmithKline, MSD, Pfizer and Sanofi advisory boards.

MGS has collaborated in educational activities funded by Astra, GlaxoSmithKline, MSD, Pfizer and Sanofi, as a researcher in clinical trials for GlaxoSmithKline, Janssen, MSD and Sanofi and as a consultant in GlaxoSmithKline and Novartis advisory boards.

NGS has collaborated in educational activities funded by MSD and Sanofi and attended educational activities funded by Novartis y Pfizer.

EGL has received funding to attend domestic educational activities, and has participated in educational activities funded by GlaxoSmithKline, MSD, Pfizer and Sanofi, as a researcher in clinical trials for GlaxoSmithKline and MSD and as a consultant in a GlaxoSmithKline advisory board.

AHM has received funding to attend domestic educational activities and has participated in educational activities funded by Pfizer.

AIA has collaborated in educational activities funded by GlaxoSmithKline, MSD, Pfizer and Sanofi, has received funding from Pfizer to attend domestic educational activities, and has participated in educational activities funded by GSK, MSD and Pfizer.

AMM has received funding from Pfizer to attend educational activities in Spain and abroad, but stopped accepting any type of direct sponsoring from any pharmaceutical laboratories for any type of activity (as an educator or as an attendant) since becoming a member of the CAV-AEP.

MLNG has collaborated in educational activities funded by Gilead, GlaxoSmithKline, Janssen, MSD, Pfizer and ViiV, as a consultant for Abbott, Astra Zeneca, Novartis and ViiV advisory boards and as a researcher in clinical trials sponsored by GlaxoSmithKline, Pfizer, Roche and Sanofi.

JRC has collaborated in educational activities funded by GlaxoSmithKline, MSD, Pfizer and Sanofi and as a researcher in clinical trials for GlaxoSmithKline and Pfizer.

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Appendix A. Appendix A

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