



Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc



Editorial

The effect of maternal pertussis vaccination on the epidemiology of pertussis in Spain



El efecto de la vacunación materna contra la tos ferina en la epidemiología de la tos ferina en España

Pertussis is a worldwide public health problem. Many countries have reported a disease emergency despite well-established vaccination programs.¹ This increase in the incidence has been attributed to several factors as a waning of immunity over time, an increase in detection when introducing PCR tests in the diagnosis, antigenic changes in *Bordetella pertussis* that would allow escaping of vaccine's immunity and a change in the vaccination programs from whole cell vaccine to acellular vaccine.²

In Spain pertussis vaccination was introduced in the 1960 decade. According to the epidemiology of the disease and the availability of vaccines some changes have been introduced in the schedule along the time. In 1998, the acellular vaccine started to replace the whole cell pertussis vaccine and in 2005 the acellular vaccine completely replaced it. Since 2017, the schedule of the pertussis vaccination program includes two primary doses at 2 and 4 months of age, a first booster at 11 months and a second booster at 6 years of age with tetravalent vaccine (DTPa-IPV).³

In Spain, pertussis vaccination coverages have remained very high in the last decades, above 95% for the primary doses and between 93% and 95% for the first booster.⁴ However, reports show a steadily increase in the incidence of pertussis through the four epidemic periods described in the last twenty years (2002–2005; 2006–2009; 2010–2013; 2014–2019). From the lowest incidence rate ever registered (around 1 case per 100,000 population) in 2002–2005, pertussis experienced a sharply increases, reaching 7.3 cases per 100,000 population in the period 2010–2013 and reaching up to 19.9 cases per 100,000 population in 2015 (epidemic period 2014–2019).^{5,6}

Hospitalizations for pertussis show an epidemic pattern similar to that of incidence but more stable. Children under one year of age, especially those under 2 months, have the highest rates of hospitalization for pertussis and have also experienced consistent increased in the last two decades. The annual rate of hospitalization due to pertussis among infants under 3 months of age was 615 per 100,000 population in the epidemic period 2010–2013, and

peaked until 880 hospitalizations per 100,000 population in 2015 (epidemic period 2014–2019).⁶

A study in Catalonia and Navarra found that 14.9% of pertussis cases were hospitalized of whom 91% were aged <6 months.⁷ In Spain 59.5% of hospitalizations due to pertussis, correspond to infants younger than 3 months, and 91.7% to infants under one year of life.⁶ Household contacts, especially mothers and siblings, were the source of infection in most cases.⁸ Between 2000 and 2006 the national mean of death from pertussis was 1 death per year; between 2007 and 2015 deaths picked to 5.1 per year, while along the period 2016–2019 annual deaths due to pertussis fell to 2.5, all of them in newborns aged <3 months.^{6,9}

In response to this increase in pertussis, in 2015, the Council of National Health System recommended a single dose of acellular pertussis vaccine (dTpa in every one pregnancy) in pregnant women between 27 and 36 weeks of gestation to protect newborns¹⁰ following similar recommendations in the United States and the UK.¹¹ Spanish regions started to implement vaccination in pregnancy along 2014 and 2015 so that by early 2016 all regions had available the pertussis vaccination in pregnancy.⁹ National coverage of vaccination in pregnancy is high, ranging from 80.1% to 83.6% in 2016–2019.⁴

The foundation for this intervention is based on evidence of the transplacental transfer of maternal antibodies.¹² A dose of pertussis vaccine during pregnancy improves maternal antibody levels and should, therefore, offer passive protection to new born in the first weeks of life, before initiation of the primary infant vaccination calendar at 2 months of age.¹² The strategy provides the additional benefit of protecting the mother against pertussis infection, which is important as mothers may be a source of infection for infants.¹³ The recommendation for vaccination during pregnancy was made with limited evidence and, although some studies suggested a high effectiveness of vaccination against pertussis during pregnancy, post-implementation studies are recommended to assess the effectiveness and long-term success of the strategy.¹⁴

Recent studies in Spain, included the studies published in this issue of EIMC^{15,16} show a high impact of maternal pertussis vaccination in the hospitalization rate due to pertussis among infants. The article of Botia et al.¹⁵ shows an important reduction of risk of hospitalisation in children aged <2 months and the study of

DOIs of original articles: <https://doi.org/10.1016/j.eimc.2021.04.004>,
<https://doi.org/10.1016/j.eimc.2021.07.007>

<https://doi.org/10.1016/j.eimc.2022.03.002>

0213-005X/© 2022 Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Published by Elsevier España, S.L.U. All rights reserved.

Leon-Morillo et al.¹⁶ suggests a reduction of cases and severity of pertussis in children aged <6 months. The national rate of hospitalization among infants younger than 3 months dropped dramatically and consistently along the post-vaccination period (2016–2019): in 2019, the hospitalization rate (161 per 100,000 population) was more than five times lower than the hospitalization rate (880 per 100,000) reached in 2015.⁶

Other epidemiological studies had shown a high vaccine effectiveness (VE) of maternal vaccination in reducing the risk of pertussis in the first two months of life. Amirthalingam et al.,¹⁷ with the screening method, found a VE of 90% in infants aged <2 months. Using a case–control study design Bellido et al.¹⁸ and Godoy et al.¹⁹ found an estimated VE of 90.9%, of 88.0% respectively.

Recent systematic reviews on safety and effectiveness of acellular pertussis vaccination during pregnancy conclude that maternal vaccination has an overall positive benefit-risk ratio.²⁰ The effectiveness in preventing pertussis disease in <2–3 months old infants were consistently high (69–93%); about 70–90% of pertussis disease and up to 90.5% of pertussis hospitalizations in infants under 3 months of age can be avoided.²¹

Regarding the ideal moment of maternal vaccination, some studies have reported a decrease in the VE with the increase in weeks of gestation at vaccination and a higher concentration of antibodies in children of mothers vaccinated in the first part of the third trimester. Higher concentrations and greater avidity of antibodies in the cord serum of newborns of mothers vaccinated between 27–30 weeks of gestation have been observed compared with mother vaccinated after 30 weeks of gestation.²²

In the light of these findings the time for vaccination in pregnancy was brought forward in Spain; since 2020, it is recommended to administer a dose of dTpa from week 27 and preferably in week 27 or 28.^{3,10}

The effect of maternal vaccination in reducing transmission in household is also consistent with studies that indicate that pertussis transmission occurs primarily at home⁸ and that mother and siblings are a potential source of infection for new born.¹³ In addition, a recent study in Spain shows that having an immigrant mother and having a school-aged sibling increases the risk of pertussis.¹⁹ Having an immigrant mother may be a risk marker in communities with a higher risk of pertussis, due to lower vaccination coverage in pregnancy and exposure to cases of pertussis. Reports have associated having a school-aged sibling with transmission at home. In a study about the risk of pertussis among household, the siblings of the pertussis cases were identified as the cohabitants with the greatest risk.⁸

All these studies provide strong evidence for helping pregnant mothers and health professionals to make informed decisions about the advisability of vaccination during pregnancy, which is important because advice from health professionals on maternal vaccination during pregnancy has been shown to be the most important factor in improving vaccination coverages.²³

Non-pharmacological measures taken to reduce transmission during the COVID-19 pandemic may have had a significant impact on reducing respiratory infections from viruses and bacteria. In the study by Leon-Morillo et al.,¹⁶ no cases of pertussis were observed during the first year of pandemic and suggests the potential usefulness of these measures to prevent cases among household, especially if there are newborns at risk of developing pertussis. This issue would encourage more detailed studies in the future.

In conclusion, most studies show a high VE of maternal pertussis vaccination in protecting children aged <2 months. Living with school-aged siblings is a risk factor for pertussis in children aged <2 months. Vaccines are well accepted by the population in Spain, but there is still room for improvement of coverage of dTpa vaccination during the pregnancy. Vaccines against pertussis are safe and protective; pregnant women,

infants and children should receive timely the scheduled doses to prevent serious pertussis disease among newborns. Development of new vaccines with more durable protection should be promoted.

Funding

This study was supported by the Ministry of Science and Innovation, Institute of Health Carlos III (Project PI15/01348) and the European Regional Development Fund (ERDF-A way of making Europe).

References

1. WHO. Pertussis vaccines: WHO position paper – Wkly Epidemiol Rec. 2015;385–400. <https://www.who.int/publications/i/item/who-position-paper-pertussis-vaccines>.
2. Decker MD, Edwards KM. Pertussis (Whooping Cough). J Infect Dis. 2021;224(Suppl. 4):S310–20. doi:10.1093/infdis/jiaa469.
3. Consejo Interterritorial del Sistema Nacional de Salud. Calendario común de vacunación a lo largo de toda la vida. Calendario recomendado año 2022. <https://www.msbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/calendario-y-coberturas/docs/CalendarioVacunacion.Todalavida.pdf> [accessed 13.01.22].
4. Ministerio de Sanidad. Coberturas de vacunación, España 2010–2020. <https://www.msbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/calendario-y-coberturas/coberturas/home.htm> [accessed 4.01.22].
5. Sizaire V, De Aragon MVM. Increase of pertussis incidence in 2010–2012 after 12 years of low circulation in Spain. Euro Surveill. 2014;19. <http://dx.doi.org/10.2807/1560-7917.es2014.19.32.20875>, pii=20875.
6. Centro Nacional de Epidemiología. CIBERESP. ISCIII. Informe epidemiológico sobre la situación de la tos ferina en España, 2005–2019. Resultados preliminares. Madrid, 31 January 2022. <https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documentos/archivos%20A-Z/TOSFERINA/Informe.Tosferina.2005-2019.preliminar.pdf> [accessed 02.02.22].
7. Crespo I, Toledo D, Soldevila N, Jordán I. Characteristics of hospitalized cases of pertussis in Catalonia and Navarra, two regions in the north of Spain. PLOS ONE. 2015;10:e0139999. <http://dx.doi.org/10.1371/journal.pone.0139999>.
8. Godoy P, Toledo D, Carmona G, Caylà JA, Alseda M, Álvarez J, et al. Factors influencing the spread of pertussis in households: a prospective study, Catalonia and Navarre Spain, 2012–2013. Euro Surveill. 2016;21. <http://dx.doi.org/10.2807/1560-7917.ES.45.30393201621>, pii=30393.
9. Centro Nacional de Epidemiología. ISCIII. Situación de la Tosferina en España, 1998–2016. Análisis preliminar del Impacto de la Vacunación de Tos ferina en Embarazadas. April 2018. <https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documentos/archivos%20A-Z/TOSFERINA/Situacion%20de%20la%20Tosferina%20en%20Espana%20B1a,%201998-2016.pdf> [accessed 10.01.22].
10. Ministerio de Sanidad. Preguntas y respuestas sobre la Vacunación de la tos ferina en embarazadas. https://www.msbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/programasDeVacunacion/docs/Embarazadas.Preguntas_respuestas.VacunacionTosferina.profsanitarios.pdf [accessed 10.01.22].
11. Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, et al. Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. Clin Infect Dis. 2016;63 Suppl. 4:S236–43. <http://dx.doi.org/10.1093/cid/ciw559>.
12. Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014;311:1760–9. <http://dx.doi.org/10.1001/jama.2014.3633>.
13. Wendelboe AM, Njamkepo E, Bourillon A, Floret DD, Gaudelus J, Gerber M, et al. Transmission of Bordetella pertussis to young infants. Pediatr Infect Dis J. 2007;26:293–9. <http://dx.doi.org/10.1097/01.inf.0000258699.64164.6d>.
14. Furuta M, Sin J, Ng ESW, Wang K. Efficacy and safety of pertussis vaccination for pregnant women – a systematic review of randomised controlled trials and observational studies. BMC Pregnancy Childbirth. 2017;17:2–20. <http://dx.doi.org/10.1186/s12884-017-1559-2>.
15. Ruiz-Botía I, Riera-Bosch MT, Rodríguez-Losada O, Soler-Palacín P, Melendo S, Moraga-Llop F, et al. Impact of vaccinating pregnant women against pertussis on hospitalizations of children under one year of age in a tertiary hospital in Catalonia. Enferm Infecc Microbiol Clin (Engl Ed). 2022;40:473–8.
16. Leon-Morillo MR, Gomez-Pastrana D, Diaz-Colom MD, Quecuty-Vela S, Alados-Arboledas JC, Aragon-Fernández C. Effect of pertussis vaccine in pregnancy and Covid-19 pandemic in the cases of whooping cough. Enferm Infecc Microbiol Clin (Engl Ed). 2022;40:499–502.
17. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014;384:1521–8. [http://dx.doi.org/10.1016/S0140-6736\(14\)60686-3](http://dx.doi.org/10.1016/S0140-6736(14)60686-3).

18. Bellido-Blasco J, Guiral-Rodrigo S, Míguez-Santiyán A, Salazar-Cifre AG-MF. A case–control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian Community Spain, 1 March 2015 to 29 February 2016. *Euro Surveill.* 2017;22:30545, <http://dx.doi.org/10.2807/1560-7917.ES.22.30545201722>.
19. Godoy P, García-Cenoz M, Rius C, Muñoz-Almagro C, Carmona G, Alseda M, et al. Effectiveness of maternal pertussis vaccination in protecting newborn: a matched case–control study. *J Infect.* 2021;83:554–8, <http://dx.doi.org/10.1016/j.jinf.2021.08.022>.
20. Vygen-Bonnet S, Hellenbrand W, Garbe E, von Kries R, Bogdan C, Heininger U, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. *BMC Infect Dis.* 2020;20:136, <http://dx.doi.org/10.1186/s12879-020-4824-3>.
21. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. *Expert Rev Vaccines.* 2020;19:621–38, <http://dx.doi.org/10.1080/14760584.2020.1791092>.
22. Abu Raya B, Srugo I, Bamberger E. Optimal timing of immunization against pertussis during pregnancy. *Clin Infect Dis.* 2016;63:143–4, <http://dx.doi.org/10.1093/cid/ciw233>.
23. Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among

pregnant women in South Australia. *PLOS ONE.* 2018;13:e0197867, <http://dx.doi.org/10.1371/journal.pone.0197867>.

Pere Godoy^{a,b,c,*}, Josefa Masa-Calles^{b,d}

^a *Agència de Salut Pública de Catalunya, Barcelona, Spain*

^b *Ciber de Epidemiología y Salud Pública, CIBERESP, Madrid, Spain*

^c *Institut de Recerca Biomèdica de Lleida, IRBLleida, Lleida, Spain*

^d *Centro Nacional de Epidemiología. Instituto de Salud Carlos III, Madrid, Spain*

* Corresponding author.

E-mail address: pere.godoy@gencat.cat (P. Godoy).