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Editorial

Rotavirus infections, vaccines and virus variability



Infecciones por rotavirus, vacunas y variabilidad vírica

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Among all enteric pathogens, rotavirus is the leading cause of severe acute gastroenteritis in infants and young children in Spain and worldwide.^{1,2} Rotavirus affects 95% of children by the age of 5 years and causes an estimated 2 million hospitalizations and 453,000 infant deaths, most of them in low-income countries.³ Mortality as a result of rotavirus infections is very low in high-income countries. Rotavirus gastroenteritis, however, creates a substantial economic burden on the healthcare systems in these countries.⁴ In Spain, before the introduction of rotavirus vaccines, it was estimated that 181,626 episodes of acute gastroenteritis occurred each year among children under 5. This translated into 14,342 hospitalizations, 41,701 emergency department visits and 48,320 primary care visits with important implications for the families and the society as a whole.⁵

In 2009 the World Health Organization (WHO) recommended the inclusion of either of the two licensed rotavirus vaccines into the national immunization programs of all countries.^{6,7} The Advisory Committee on Vaccines of the Spanish Association of Pediatrics (CAV-AEP) has also recommended the vaccination for rotavirus in all infants because of the morbidity and elevated healthcare burden of the virus.⁸ Rotavirus vaccines were licensed in Spain between the end of 2006 and early 2007. Currently the only rotavirus vaccine available, although not subsidized, is RotaTeq[®] (Sanofi Pasteur MSD), a pentavalent vaccine consisting of bovine-human reassortant strains expressing different viral capsid protein combinations. Other countries like Belgium, Luxembourg, Austria, Finland, and more recently the UK, have implemented universal mass vaccination programs for rotavirus using a live attenuated human-derived monovalent vaccine (Rotarix[™], Glaxo Smith Kline)⁹ and/or Rotateq[®]. The protective efficacy of these vaccines was evaluated and established by several randomized double-blind, placebo-controlled trials, demonstrating a protection rate against severe rotavirus gastroenteritis of 85% (95% CI: 72,92) for Rotarix[™]¹⁰ and 98% (95% CI: 88,100) for RotaTeq[®].¹¹

The two outer viral capsid proteins, VP7 and VP4, form the basis of the dual classification system of group A rotaviruses into G and P types. Since VP7 and VP4 are encoded by different genome segments, both type specificities segregate in an independent manner.¹² Rotaviruses, like many RNA viruses, display a great degree of genetic and antigenic diversity. Aside from showing different G and P types and an extensive variety of combinations therein, rotaviruses can accumulate point mutations leading to antigenic drift, reassortment of genome segments to drive antigenic shift, and zoonotic transmission of animal strains to introduce new antigenic types into humans.¹³ The G1P[8], G2P[4], G3P[8], G4P[8] and more recently G9P[8] have been defined as the most common human rotavirus strains. Nevertheless, other genotypes are seen more frequently in different parts of the world, mainly in low-income countries.

Both rotavirus vaccines have a high proven efficacy against severe gastroenteritis caused by rotavirus genotypes G1–G4 and G9, which account for more than 95% of all rotavirus strains circulating in Europe.¹⁴ Progress toward widespread vaccination, however, was impeded by the unexpected discovery of porcine circovirus in vaccines and by the re-emergence of intussusception as a matter of potential concern.¹⁵ The cost-effectiveness of rotavirus vaccination was also considered an impediment to the introduction of universal vaccination in some European countries like Spain, France, the Netherlands and Greece.¹⁶ Nevertheless, rotavirus vaccines are being introduced into many low-income countries with the financial support of the Global Alliance for Vaccines and Immunization (GAVI), which plans to introduce rotavirus vaccines into more than 30 countries by 2015 (<http://www.gavialliance.org/support/nvs/rotavirus>).

The implementation programs for rotavirus vaccines in both low-income and high-income countries have created a new and extremely interesting scenario for rotavirus infections and for the relatedness between vaccine and field strains. A substantial decrease in severe diarrheal disease in children in the USA has been reported by the Center for Disease Control (CDC) since the introduction of rotavirus vaccines in the national immunization program in 2006. It has exceeded the protection level expected based on vaccine coverage, as well as the extension of benefits to

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older unvaccinated age groups, thus demonstrating both the direct and indirect impacts of rotavirus vaccination in the USA.¹⁷ That notwithstanding, the efficacy of these vaccines has been reported to be remarkably lower in low-income countries.¹⁸ For example, a vaccine efficacy against severe diarrhea of only 58% was observed in a 2007–2009 Nicaraguan study using RotaTeq.¹⁹ It has been suggested that this high level of vaccine failure in Nicaraguan children was probably not a result of antigenic drift or the emergence of new genetically distinct virus strains, but of the introduction of vaccine strain genes into circulating human rotaviruses.¹⁹ In Brazil, the predominance of G2P[4] strains after the establishment of a national vaccination program using the monovalent G1P[8] vaccine, Rotarix™, was observed. This led to the speculation that Rotarix is less effective against G2P[4] rotavirus, allowing the emergence of this genotype as the primary cause of diarrheal disease.²⁰ It is, however, unclear if the predominance of G2P[4] genotype is related to the vaccination program or if this is attributable to normal genotype fluctuations. Rotavirus surveillance will be crucial to clarifying these questions. It is a matter of concern that the immune pressure and herd immunity raised by universal mass vaccination against rotavirus might drive the emergence of vaccine escape mutants.

The long-term impact of immunization with rotavirus vaccines on viral strain evolution needs to be monitored by conducting surveillance studies of the circulating rotavirus strains during the post-introduction period. The European Rotavirus Network (EuroRotaNet) was established in January 2007 and has conducted rotavirus strain surveillance for 7 consecutive years in 17 European countries. The network includes three Spanish laboratories: Departamento de Microbiología y Ecología, Facultad de Medicina, Universidad de Valencia; Hospital Donostia of San Sebastián, and Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid. This network has detected a total of 47 different combinations of G and P types between 2006 and 2012 in single rotavirus infections. Six rotavirus genotypes, G1P[8], G4P[8], G2P[4], G9P[8], G3P[8] and G12P[8], accounted for 91% of all characterized strains. The G1P[8] strains were the most prevalent year after year, whereas the prevalence of the other five most common genotypes varied significantly over time and among countries.¹⁴ To date, studies assessing rotavirus molecular epidemiology and genotype diversity have not reached clear conclusions regarding the effects of vaccination.

It is both interesting and useful to gain information on the impact of vaccines on the prevalence of circulating rotavirus strains. The study by Sánchez-Fauquier et al.²¹ published in this issue, describes the rotavirus genotype distribution during two consecutive years, from 2010 to 2011, in the Hospital Severo Ochoa in Leganés, Madrid, after the vaccine's introduction. They found that the most prevalent genotype was G1P[8] (60.7%), followed by G2P[4] (16.09%), G9P[8] and G12P[8], albeit no rotavirus vaccine coverage rate in the study population was estimated. Aside from this, vaccine coverage rates in Spain are highly variable among the different autonomous regions. Based on the number of doses sold, the mean vaccine coverage in the 2-year period 2009–2010 was estimated to be as low as 11% in the province of Gipuzkoa²² and 51% between July 2008 and June 2009 in Galicia.²³ National vaccine coverage rates increased from an estimated 16% in 2007 to 43% in 2009, followed by a decline to 22% in 2010.¹⁶

It is difficult to determine if vaccination influences on the fluctuations of rotavirus genotypes, especially with a modest coverage. Significant annual changes in genotype distribution have usually been detected by molecular epidemiology studies of rotavirus gastroenteritis; they were even in the prevaccine era. A good example is the global emergence of the G9P[8] genotype since the mid-1990s, now considered a common genotype. The emergence of G12P[8] strains was detected in the Basque Country in

2004–2005.²⁴ It was later found to be the predominant genotype (65% of 223 strains in the 2010–2011 rotavirus season).²² The high prevalence of G12P[8] has occurred mainly in Northern Spain, whereas a much lower G12P[8] prevalence has been reported in Madrid in 2010–2011 (4.3% of 117 strains) and in a collaborative study performed by laboratories in Valladolid, Zaragoza, Barcelona and Valencia (13.3% of 511 strains in 2011–2012).²⁵

In conclusion, a better understanding of the long-term effects of rotavirus vaccines on the prevalence, epidemiology and evolutionary dynamics of circulating viral genotypes requires continuous strain surveillance.

Conflict of interest

Javier Buesa participates in a research project financially supported by GSK and Sanofi Pasteur MSD.

References

- Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis.* 2012;12:136–41.
- Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. *Pediatr Infect Dis J.* 2006;25 1 Suppl.:S7–11.
- Parashar UD, Breese JS, Glass RI. The global burden of diarrhoeal disease in children. *Bull WHO.* 2003;81:236.
- Rheingans RD, Heylen J, Giaquinto C. Economics of rotavirus gastroenteritis and vaccination in Europe: what makes sense? *Pediatr Infect Dis J.* 2006;25 1 Suppl.:S48–55.
- Díez-Domingo J, Surinach NL, Alcalde NM, Betegón L, Largeron N, Trichard M. Burden of paediatric Rotavirus Gastroenteritis (RVGE) and potential benefits of a universal Rotavirus vaccination programme with a pentavalent vaccine in Spain. *BMC Public Health.* 2010;10:469.
- World Health Organization. Rotavirus vaccines: an update. *Wkly Epidemiol Rec.* 2009;84:533–40.
- World Health Organization. Rotavirus, vaccines. WHO position paper – January. *Wkly Epidemiol Rec.* 2013;88:49–64.
- Moreno-Pérez D, Álvarez García FJ, Arístegui Fernández J, Cilleruelo Ortega MJ, Corretger Raut JM, García Sánchez N, et al. Calendario de vacunaciones de la Asociación Española de Pediatría: recomendaciones 2014. *An Pediatr (Barc).* 2014;80:55.e1–37.
- Iturriza-Gómara M, Cunliffe N. Rotavirus vaccine: a welcome addition to the immunisation schedule in the UK. *BMJ.* 2013;346:f2347.
- Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med.* 2006;354:11–22.
- Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med.* 2006;354:23–33.
- Estes MK, Kapikian AZ. Rotaviruses. In: Knipe DM, Howley PM, editors. *Fields virology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1917–74.
- Matthijssens J, Bilcke J, Ciarlet M, Martella V, Banyai K, Rahman M, et al. Rotavirus disease and vaccination: impact on genotype diversity. *Future Microbiol.* 2009;4:1303–16.
- Iturriza-Gómara M, Dallman T, Banyai K, Bottiger B, Buesa J, Diedrich S, et al. Rotavirus genotypes co-circulating in Europe between 2006 and 2009 as determined by EuroRotaNet, a pan-European collaborative strain surveillance network. *Epidemiol Infect.* 2011;139:895–909.
- Glass RI, Parashar U, Patel M, Gentsch J, Jiang B. Rotavirus vaccines: successes and challenges. *J Infect.* 2014;68 Suppl. 1:S9–18.
- Giaquinto C, Jackson AE, Vesikari T. Report of the second European expert meeting on rotavirus vaccination. *Vaccine.* 2012;30:2237–44.
- Rha B, Tate JE, Payne DC, Cortese MM, Lopman BA, Curns AT, et al. Effectiveness and impact of rotavirus vaccines in the United States – 2006–2012. *Expert Rev Vaccines.* 2014;13:365–76.
- Lopman BA, Pitzer VE, Sarkar R, Gladstone B, Patel M, Glasser J, et al. Understanding reduced rotavirus vaccine efficacy in low socio-economic settings. *PLoS ONE.* 2012;7:e41720.
- Bucardo F, Rippinger CM, Svensson L, Patton JT. Vaccine-derived NSP2 segment in rotaviruses from vaccinated children with gastroenteritis in Nicaragua. *Infect Genet Evol.* 2012;12:1282–94.
- Gurgel RQ, Cuevas LE, Vieira SC, Barros VC, Fontes PB, Salustino EF, et al. Prevalence of rotavirus P[4]G2 in a vaccinated population Brazil. *Emerg Infect Dis.* 2007;13:1571–3.
- Sánchez-Fauquier A, González-Galán V, Arroyo S, Cabornero A, Ruiz-Burrueros A, Wilhelmi-De Cal I. Monitoring of children with acute gastroenteritis in

- Madrid, Spain during 2010–2011: rotavirus genotype distribution after the vaccines introduction. *Enferm Infecc Microbiol Clin.* 2014;**32**:280–4.
22. Cilla G, Montes M, Gomariz M, Alkorta M, Iturzaeta A, Perez-Yarza EG, et al. Rotavirus genotypes in children in the Basque Country (North of Spain): rapid and intense emergence of the G12[P8] genotype. *Epidemiol Infect.* 2013;**141**:868–74.
 23. Martínón-Torres F, Bouzón Alejandro M, Redondo Collazo L, Sánchez Lastres JM, Pértega Díaz S, Seoane Pillado MT, et al. Effectiveness of rotavirus vaccination in Spain. *Hum Vaccine.* 2011;**7**:757–61.
 24. Cilla G, Montes M, Gomariz M, Pineiro L, Pérez-Trallero E. Rotavirus genotypes in children in the Basque Country (Northern Spain) over a 13-year period (July 1996–June 2009). *Eur J Clin Microbiol Infect Dis.* 2010;**29**:955–60.
 25. Fernández-Jiménez M, Téllez-Castillo CJ, Carmona-Vicente N, Prat-Fornells J, Escoms R, Bartolomé R, et al. Surveillance of human rotaviruses in Spain from 2006 to 2012. In: Abstract Book of the 5th European Rotavirus Biology Meeting, October 6–9, 2013. 2013. p. 64–5.