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Reception date: December 15, 2017 • **Acceptance date:** December 18, 2017
Publication date: December 20, 2017

Evid Pediatr. 2017;13:59.

HOW TO CITE THIS ARTICLE

Montesdeoca Melián A. Rotavirus vaccines and intussusception. The controversy continues. Evid Pediatr. 2017;13:59.

This article is available at http://www.evidenciasenpediatria.es/EnlaceArticulo?ref=2017;13:59
 • ISSN: 1885-7388

Rotavirus vaccines and intussusception. The controversy continues

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Although there is wide variability between countries, it is estimated that, even today, 75 000 to 150 000 children aged less than 5 years in Europe are admitted to hospital every year due to complications of rotavirus-induce gastroenteritis (RVGE). In addition, there is a substantially higher number of patients that seek care in hospital emergency departments and primary care services due to RVGE. Fortunately, the mortality associated with RVGE in Europe remains very low (less than 0.2/100 000 children aged less than 5 years),[1] although we must not forget that every day we learn more about the extraintestinal manifestations of this microorganism, especially neurologic ones. All of the above proves a persisting and substantial economic, healthcare and social burden of disease, both direct and indirect (underestimated in cost-effectiveness analyses) that results from a vaccine-preventable disease.

In 2006, two oral attenuated vaccines were authorised for the prevention of RVGE, one of them a human rotavirus monovalent vaccine (RV1) and the other a human-bovine pentavalent vaccine (RV5). A Cochrane review published in 2012 assessed the efficacy of the RV1 and RV5 vaccines using data from 41 randomised controlled trials that included a total of 186 263 participants. The analysis showed that both vaccines prevented more than 80% of severe cases of RVGE in countries with a low rotavirus-associated mortality. These vaccines have also demonstrated considerable effectiveness in the prevention of RVGE in observational studies conducted in low-mortality countries, including cohort studies (91%; 95% confidence interval [95 CI]: 88 to 94%) and case-control studies (84%; 95 CI: 75 to 89%).[2]

Although the World Health Organization (WHO) has recommended the inclusion of these vaccines in all immunisation schedules in the world since 2009, in Spain the vaccine is administered outside the official immunisation schedules, which precludes achievement of optimal coverage, with the actual coverage, estimated based on vaccine dose sales, ranging between 8 and 74% in different provinces, with a median of 50% (unpublished data), an undesirable source of inequality.

In August 1998, an oral attenuated tetravalent human-rhesus reassortant rotavirus vaccine (RRV-TV) was authorised in the United States and started to be used at a large scale. Following a spike in the number of adverse events associated with this vaccine reported to the vaccine adverse event reporting system of the United States (VAERS), which revealed a small increase in the incidence of intussusception in the population of vaccinated infants (1/10 000 vaccinated individuals), the RRV-TV was withdrawn from the market when only a year had passed since its introduction. After this unfortunate experience, a concerted effort was made to develop safer vaccines. Aiming at detecting a potential association of vaccination with the development of a rare adverse event such as intussusception, the phase III trials of both vaccines included more than 130 000 infants, and found no evidence of an increased risk of intussusception among vaccinated individuals. Although these trials did include a large number of individuals, they did not have the power to detect an increased risk of an event should the event be infrequent enough (less than 1/10 000 vaccinated individuals). It was during post-licensure surveillance that evidence emerged in several countries of an overall risk of developing intussusception after the first dose of either vaccine (in the first 7 days post vaccination), estimated at 1 case out of 14 000 to 69 000 vaccinated individuals.[1] Until recently, there were no pooled worldwide data from cohort and case-control studies quantifying the risk of developing intussusception following vaccination with the RV1 and RV5 vaccines, which was the objective of the meta-analysis reviewed in the current issue of *Evidencias en Pediatría*.[3,4] This meta-analysis used a protocol that conformed to the PRISMA guidelines, developed for the purpose of optimising the quality and standardisation of the methods used in systematic reviews and meta-analyses.

This study reinforces previous evidence that there is an association between vaccination against rotavirus and the development of intussusception after the administration of first dose or every dose, although this event happens to be highly infrequent, while vaccination prevents tens of thousands of RVGE-related hospitalisations a year in high-income countries. This risk seems acceptable in countries where vaccination against rotavirus reduces the mortality associated with this infection—countries where intussusception carries a very high risk of death—but also in situations where the development of intussusception does not carry a high risk for the patient due to the high accessibility of health care services.

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