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# The vaccines currently in use against rotavirus increase the risk of intussusception, mainly after the first dose

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**English key words:** infant; intussusception; rotavirus vaccines.
**Spanish key words:** invaginación intestinal; lactante; vacunas contra rotavirus.

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# The vaccines currently in use against rotavirus increase the risk of intussusception, mainly after the first dose

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Original article: Kassim P, Eslick GD. Risk of intussusception following rotavirus vaccination: an evidence based meta-analysis of cohort and case-control studies. Vaccine. 2017;35:4276-86.

**Abstract**

**Authors' conclusions:** from the meta-analysis carried out, it can be suggested that the vaccine against rotavirus is associated with an increased risk of intussusception, especially after the administration of the first dose.

**Reviewers' commentary:** the new rotavirus vaccines (Rotateq® y Rotarix®) are an effective tool to prevent rotavirus diarrhea, especially in children under one year of age. There is an increased risk of intussusception after the first dose, about which the patients should be informed, but this risk is much lower than with the original vaccine RotaShield®.

**Key words:** infant; intussusception; rotavirus vaccines.

**Las vacunas actuales frente a rotavirus incrementan el riesgo de invaginación intestinal, principalmente tras la primera dosis**

**Resumen**

**Conclusiones de los autores del estudio:** del metanálisis realizado se puede sugerir que la vacuna frente a rotavirus se asocia a un mayor riesgo de padecer invaginación intestinal, sobre todo tras la administración de la primera dosis.

**Comentario de los revisores:** las nuevas vacunas de rotavirus (Rotateq® y Rotarix®) son una herramienta efectiva sobre todo en el primer año de vida para prevenir la diarrea por rotavirus. Existe un riesgo aumentado de invaginación intestinal tras la primera dosis, del que debe informarse a los pacientes, pero es muy inferior a la vacuna original RotaShield®.

**Palabras clave:** invaginación intestinal; lactante; vacunas contra rotavirus.

## STRUCTURED ABSTRACT

**Objective:** to make a quantitative analysis of the available data from case-control and cohort studies conducted in different countries regarding the potential association between different time points in vaccination against rotavirus and intussusception.

**Design:** systematic review (following the PRISMA guidelines) with two separate meta-analyses (of pooled data from cohort studies and from case-control studies).

**Sources of data:** the authors conduced a search of the MEDLINE, PubMed, Embase and Google Scholar databases through May 22, 2017 using the terms "rotavirus" AND "vaccine" AND "intussusception", with no language restrictions. The authors also searched the reference lists of relevant articles.

**Study selection:** the authors included cohort and case-control studies that reported risk point estimates as odds ratios (ORs) or relative risks (RRs) or presented the necessary data to calculate them, with a sample size greater than 50 patients. Each author independently reviewed the studies to determine whether they met the inclusion criteria. Disagreements between the authors were resolved by consensus. Of the 1512 potentially relevant articles that were identified, 11 were included in the final analysis (six cohort studies and five case-control studies).

**Data extraction:** the data extraction was performed manually by the first author, and subsequently reviewed by the second author. The risk of bias was assessed independently by both authors using the Newcastle-Ottawa scale, with classification of the studies into three categories (low, moderate and high risk of bias). The intussusception outcome was assessed at two time points, within 7 days from the first dose of any RV vaccine, and after all the doses of RV vaccine. The authors performed separate meta-analyses of the cohort studies and the case-control studies using random effects models. The heterogeneity of the studies was tested with Cochran's Q statistic, and its degree quantified by means of the $I^2$ statistic. Publication bias was assessed using Egger's regression model. The authors did not perform a sensitivity analysis.

**Main results:** the overall meta-analysis of the cohort data (n = 4 506 265 first doses) revealed an increased risk of intussusception both after the first dose (RR: 3.71; 95% confidence interval (95 CI): 1.08 to 12.69; *P* = .04) and after all the doses of vaccine (RR: 3.47; 95 CI: 1.23 to 9.78; *P* = .02). The results were much clearer for the initial tetravalent vaccine, which has since been withdrawn from use (RR: 22.70; 95 CI: 14.40 to 35.78; *P* < .001), compared to the current pentavalent and monovalent vaccines (greater dispersion of results). The overall analysis of case-control studies (n = 9643 children) also found an increased probability of intussusception after the first dose (OR: 8.45; 95 CI: 4.08 to 17.50; *P* < .001) and after all doses (OR: 1.59; 95 CI: 1.11 to 2.27; *P* = .01). The heterogeneity was high in the cohort studies and moderate to low in the case-control studies.

**Conclusion:** the results of the meta-analysis suggest that there is a clear association between vaccination against rotavirus and intussusception, mainly after the first vaccine dose.

**Conflicts of interest:** none disclosed.

**Funding source:** none disclosed.

## COMMENTARY

**Justification:** international post-licensure studies of rotavirus vaccines have identified an increased risk of intussusception in children following their administration. The first vaccine against rotavirus ever developed (Rotashield® [RRV-TV]) was withdrawn from use in 1999 after its association with intussusception was confirmed.[1] Evidence has also surfaced that the second-generation rotavirus vaccines that are currently available (Rotateq® [RV5] and Rotarix® [RV1]), recommended for routine vaccination by the World Health Organization (WHO), carry a small increased risk, although temporary, of developing intussusception.[2,3]

**Validity or scientific rigour:** the review was based on a clearly defined clinical question, the methodology used for the selection and evaluation of individual studies was appropriate and well described. The results and conclusions are free from potential biases related to conflicts of interest. However, the duration of followup after vaccination and criteria used to define intussusception varied between studies.

**Clinical relevance:** the pooled data of cohort studies found a higher risk of intussusception in the first 7 days following administration of the first dose, and after completion of the RV vaccine series. The data from case-control studies also found an increased risk of intussusception after the first dose and the full series.

However, in this systematic review, the studies that included the withdrawn vaccine (RRV-TV) reported a greater RR (22.70; 95 CI: 14.8 to 35.7) and weighed more in the final results than the data from studies that only included the RV1 and RV5 vaccines. The review also excluded a study that may have influenced the final results because it only included the adverse events reported to the Vaccine Adverse Events Reporting System (VAERS), which estimated that under a worst-case scenario, the excess risk would be of 1.36 cases of intussusceptions per 100 000 doses of RV5.[4] This would amount to 55 additional cases of intussusception per year in the United States, to be weighed against a reduction of approximately 40 000 admissions for diarrhoea achieved through vaccination.

Both vaccines, RV1 and RV5, are effective in the first two years of life. RV1 reduced severe cases of diarrhoea caused by rotavirus by more than 80% in countries with a low mortality and by 40% to 57% in countries with high mortality. With the introduction of RV5, severe cases of diarrhoea from all causes dropped by 73% and 96% in countries with a low mortality and 15% in countries with a high mortality. The Cochrane review by Soares-Weiser reported that 58 cases of intussusception had been detected in 97 246 children after vaccination with RV1, and 34 cases in 81 459 children after vaccination with RV5.[2] However, other studies have not found significant differences between children given RV1 or RV5 compared to placebo in the incidence of severe adverse events in general and intussusception in particular.[2,3]

**Applicability to clinical practice:** the most recently licensed vaccines against rotavirus (RV1 and RV5) are an effective tool for preventing diarrhoea caused by rotavirus, especially in the first year of life. There is an increased risk of intussusception after the first dose of which patients need to be informed, but it is considerably smaller than the risk associated with the original RRV-TV vaccine, which seems to tip the risk-benefit balance in favour of vaccination.[5]

**Conflicts of interest:** the authors of the commentary had no conflicts of interest to declare.

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