analesdepediatría

www.analesdepediatria.org

ORIGINAL ARTICLE

# Post-licensure passive safety surveillance of rotavirus vaccines: Reporting sensitivity for intussusception☆,☆☆

S. Pérez-Vilar[a,*], J. Díez-Domingo[a], J. Gomar-Fayos[b], E. Pastor-Villalba[c], M. Sastre-Cantón[a], J. Puig-Barberà[a]

[a] *Área de Investigación en Vacunas, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana, FISABIO-Public Health, Valencia, Spain*
[b] *Servicio de Ordenación y Control del Medicamento, Dirección General de Farmacia y Productos Sanitarios, Valencia, Spain*
[c] *Servicio de Salud Infantil y de la Mujer, Dirección General de Salud Pública, Valencia, Spain*

Received 10 September 2013; accepted 14 October 2013
Available online 23 July 2014

**KEYWORDS**
Rotavirus vaccines;
Pharmacovigilance;
Intussusception

**Abstract**
*Introduction:* The aims of this study were to describe the reports of suspected adverse events due to rotavirus vaccines, and assess the reporting sensitivity for intussusception.
*Materials and methods:* Descriptive study performed using the reports of suspected adverse events following rotavirus vaccination in infants aged less than 10 months, as registered in the Pharmacovigilance Centre of the Valencian Community during 2007–2011.

The reporting rate for intussusception was compared to the intussusception rate in vaccinated infants obtained using the hospital discharge database (CMBD) and the regional vaccine registry.
*Results:* The adverse event reporting rate was 20 per 100,000 administered doses, with the majority (74%) of the reports being classified as non-serious. Fever, vomiting, and diarrhoea were the adverse events reported more frequently. Two intussusception cases, which occurred within the first seven days post-vaccination, were reported as temporarily associated to vaccination. The reporting sensitivity for intussusception at the Pharmacovigilance Centre in the 1–7 day interval following rotavirus vaccination was 50%.
*Conclusions:* Our results suggest that rotavirus vaccines have, in general, a good safety profile. Intussusception reporting to the Pharmacovigilance Centre shows sensitivity similar to other passive surveillance systems. The intussusception risk should be further investigated using well-designed epidemiological studies, and evaluated in comparison with the well-known benefits provided by these vaccines.


DOI of original article: http://dx.doi.org/10.1016/j.anpedi.2013.10.027
☆ Please cite this article as: Pérez-Vilar S, Díez-Domingo J, Gomar-Fayos J, Pastor-Villalba E, Sastre-Cantón M, Puig-Barberà J. Vigilancia pasiva de la seguridad postautorización de las vacunas frente a rotavirus: sensibilidad de la notificación de invaginación intestinal. An Pediatr (Barc). 2014;81:77–85.
☆☆ Previous presentation in meetings, congresses, or symposiums: summary (part of the original content) accepted for the 7th Vaccine and ISV Congress, October 27th–29th 2013, Sitges, Spain.
* Corresponding author.
*E-mail address:* perez_silvil@gva.es (S. Pérez-Vilar).

**PALABRAS CLAVE**
Vacunas frente a rotavirus;
Farmacovigilancia;
Invaginación intestinal

**Vigilancia pasiva de la seguridad postautorización de las vacunas frente a rotavirus: sensibilidad de la notificación de invaginación intestinal**

**Resumen**
*Introducción:* Los objetivos de este estudio fueron describir las notificaciones de sospechas de reacciones adversas relacionadas con las vacunas frente a rotavirus y valorar la sensibilidad de la notificación para invaginación intestinal.
*Material y métodos:* Estudio descriptivo, a partir de las notificaciones de sospechas de reacciones adversas relacionadas con las vacunas frente a rotavirus, ocurridas en niños menores de diez meses, registradas en el Centro de Farmacovigilancia de la Comunidad Valenciana durante el periodo 2007-2011.

Se comparó la tasa de notificación de invaginaciones con la tasa de invaginaciones en vacunados obtenida utilizando la base de datos de altas hospitalarias (CMBD) y el registro nominal de vacunaciones autonómico.
*Resultados:* La tasa de notificación de eventos adversos fue de 20 por 100.000 dosis administradas. El 74% de las notificaciones se clasificaron como no graves, siendo la fiebre, los vómitos y la diarrea las sospechas más frecuentes. Dos casos de invaginación, ocurridos en los siete primeros días tras la vacunación, fueron notificados como asociados temporalmente a la vacunación. La sensibilidad de la notificación de invaginación intestinal para el periodo de riesgo de uno a siete días fue del 50%.
*Conclusiones:* Los resultados sugieren que las vacunas frente a rotavirus presentan un perfil de seguridad en general adecuado, y que el Centro de Farmacovigilancia de la Comunidad Valenciana, comparado con otros sistemas de vigilancia pasiva, es igualmente sensible para detectar señales de posible asociación con invaginación intestinal. Este riesgo requiere ser investigado con estudios epidemiológicos bien diseñados y comparado con los evidentes beneficios que estas vacunas proporcionan.


## Introduction

The first vaccine against rotavirus, Rotashield®, was licensed in the United States in 1998, but was withdrawn a few months later[1] once population-based epidemiological studies [2,3] had confirmed the concern generated by the reporting of 15 cases of intussusception to the *Vaccine Adverse Events Reporting System* (VAERS) passive surveillance system after the distribution of 1.8 million doses.[4]

Two new vaccines, both live-attenuated and orally administered, were authorised several years later following various pre-licensure clinical trials designed to exclude this association[5,6]: a monovalent human vaccine, Rotarix® and a pentavalent human-bovine vaccine, RotaTeq®. These vaccines, available in Spain since 2006 and 2007 respectively, were not included in the immunisation schedule, but have been recommended by paediatricians and paid for by parents. In 2010 contamination with a virus was detected in both vaccines and they were recalled from the market.[7,8] Months later, after it was ascertained that this finding did not pose safety or efficacy problems, the distribution of RotaTeq® was authorised once again,[9] and the re-release of Rotarix® lots is imminent. The summaries of product characteristics of both vaccines recommended starting the vaccination schedule from 6 weeks of age and ending it by 24 weeks (Rotarix®) and 26 weeks (RotaTeq®) of age. In 2012 the top age limit of the RotaTeq® vaccine was raised to 32 weeks.[10]

The clinical trials and post-licensure surveillance have not shown evidence of serious adverse reactions associated to these vaccines,[5,6] except for intussusception, an association that has been monitored carefully. Post-licensure studies showed an increased risk following the first dose in Mexico (Rotarix®)[11] and Australia (RotaTeq®),[12] and following the second dose (Rotarix®) in Brazil,[11] although it was considerably smaller than the risk observed in association with Rotashield®. In the United States, no association between RotaTeq® and intussusception was found with the data available from the VAERS[13] passive surveillance system nor the data from early observational studies.[14–17] However, VAERS data on a larger number of distributed doses suggested the possibility of this association,[18] which has been recently confirmed.[19,20]

In Spain, post-licensure surveillance consists mostly of passive surveillance. However, it is known that underreporting occurs in these systems. Its degree is mostly related to the seriousness of the event, its temporal proximity to vaccination, and awareness of the association and the obligation to report such events.[21] On the other hand, reporting can increase in the first years following authorisation of a new drug[22] or be stimulated when the medication is subject to media exposure, either because there is a well-known association or because the regulatory authorities have issued some kind of warning.[23] Estimating the amount of under- and overreporting in a passive surveillance system allows for the assessment of the system's validity in detecting adverse