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# Rotavirus vaccination

## A risk factor for intussusception?

Rotavirus (RV) infection is the leading cause of acute gastroenteritis (AGE) in infants and toddlers. In Germany, the average annual number of children below 5 years of age hospitalized from 2001 to 2008 because of acute gastroenteritis (AGE) was 25,154; 70% of these cases were related to RV infection [1].

Shortly after launch of the live, oral RV vaccine Rotashield (Wyeth-Lederle Vaccines) containing one rhesus RV serotype and three reassortant RV serotypes derived from rhesus and human strains in the United States (US) in 1998, a high risk for intussusception (IS) was demonstrated in a case–series study yielding an incidence rate ratio (IRR) of 29.4 (95% CI 16.1–53.6) for days 3–14 after the first dose and in a case–control analysis an adjusted odds ratio (aOR) of 21.7 (95% CI 9.6–48.9) [2], which translates into one additional IS case per 4,670–9,474 infants vaccinated (11–21 per 100,000 vaccinees).

In 2006, two oral new-generation RV vaccines, Rotarix® (GlaxoSmithKline Biologicals) and RotaTeq® (Sanofi Pasteur MSD), were approved by the European Commission.

Rotarix® contains a live attenuated human RV strain. The vaccine is indicated for the active immunization of infants to prevent RV gastroenteritis. The vaccination course consists of two doses. According to the product information [3],"the first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks."

RotaTeq® is a pentavalent live RV vaccine containing human bovine reassortant for active immunization of infants to prevent RV gastroenteritis. To acquire the reliable vaccine protection, three doses are necessary. The product information specifies [4]:"The first dose may be administered from the age of 6 weeks and no later than the age of 12 weeks. There should be intervals of at least 4 weeks between doses. It is preferable that the vaccination course of three doses should be completed by the age of 20–22 weeks. If necessary, the third (last) dose may be given up to the age of 32 weeks."

Marketing authorization for Rotarix® and RotaTeq® in 2006 was based on two large–scale safety clinical trials that did not demonstrate an increased IS risk. However, these studies were powered to detect a risk of IS on the magnitude of Rotashield. Two epidemiological studies were performed in Mexico and Brazil implementing both the case–series and case–control design [5]. In Mexico, receipt of the first dose was associated with an increased risk of IS between 5.3 and 5.8 within 1–7 days after vaccination. By contrast, in Brazil, administration of the second dose was associated with a slightly increased risk of IS between 1.9 and 2.6 within 1–7 days after vaccination, while there was no increased risk of IS in recipients of the first dose. The authors concluded that Rotarix® was associated with a short-term risk of IS in approximately 1 of every 51,000–68,000 vaccinees (1.5–2 per 100,000 vaccinees).

A postmarketing observed-versus-expected (OvE) analysis in Australia also revealed an increased risk of IS for both vaccines, especially in the risk windows of 1–7 days and 1–21 days following receipt of the first dose of either vaccine [1–7 days: RotaTeq®, relative risk (RR) 5.3, 95% CI 1.1–15.4; Rotarix®, RR 3.5, 95% CI 0.7–10.1; 1–21 days: RotaTeq®, RR 3.5, 95% CI 1.3–7.6; Rotarix®, RR 1.5, 95% CI 0.4–3.9] in infants aged 1–3 months [6]. However, no overall excess in cases of IS between 1 and 9 months of age compared with expected numbers for either vaccine was observed.

In Australia, a large self-controlled case series (SCCS) study [7] was performed using data of all hospitalized cases coded as IS. An interim analysis revealed a statistically significant fourfold increased risk of IS in the first 1–7 days following the first dose of either vaccine [Rotarix®: relative incidence (RI) 3.9, 95% CI 1.5–9.9; RotaTeq®: RI 4.1 95% CI 1.3–13.5] compared with other time periods after vaccine receipt. This translates into two additional cases of IS per 100,000 recipients of the first dose. The authors stressed that these findings were preliminary.

Owing to the findings made in Mexico, Brazil, and Australia, the Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) initiated a Mini-Sentinel postlicensure observational study of RV vaccines and IS among infants aged 5–36 weeks within the scope of the so-called Post-Licensure Rapid Immunization Safety Monitoring Programme (PRISM). In June 2013, first results were published on the FDA homepage [8]. The retrospective co-

**Tab. 1** Characteristics of the cases of intussusception reported to the Paul-Ehrlich-Institut from 2006 to 2010 in temporal relationship with the administration of Rotavirus vaccines (Rotarix® or RotaTeq®)

| | Rotarix® | | RotaTeq® | |
|---|---|---|---|---|
| | n | % | n | % |
| IS cases reported from 2006 to 2010 | 15 | 100 | 12 | 100 |
| **Gender** | | | | |
| Male | 9 | 60 | 7 | 58.3 |
| Female | 6 | 40 | 5 | 41.7 |
| **IS occurred after receipt of the** | | | | |
| First dose | 14 | 93.3 | 6 | 50.0 |
| Second dose | 1 | 6.7 | 5 | 41.7 |
| Third dose | – | – | 1 | 8.3 |
| **Concomitant vaccination** | | | | |
| No concomitant vaccination | 13 | 86.7 | 5 | 41.7 |
| Hexavalent vaccine[a] | 1 | 6.7 | 0 | 0.0 |
| Heptavalent pneumococcal vaccine | 0 | 0.0 | 1 | 8.3 |
| Hexavalent vaccine[a] + heptavalent pneumococcal vaccine | 1 | 6.7 | 3 | 25.0 |
| Hexavalent vaccine[a] +13-valent pneumococcal vaccine | 0 | 0.0 | 2 | 16.7 |
| Pentavalent vaccine[b] + heptavalent pneumococcal vaccine | 0 | 0.0 | 1 | 8.3 |
| **Intussusception occurred (days after vaccination)** | | | | |
| 1–7 | 9 | 60.0 | 8 | 66.7 |
| 8–14 | 1 | 6.7 | 2 | 16.7 |
| 15–21 | 1 | 6.7 | 0 | 0.0 |
| 22–28 | 1 | 6.7 | 0 | 0.0 |
| 29–35 | 0 | 0.0 | 0 | 0.0 |
| 36–42 | 2 | 13.3 | 1 | 8.3 |
| 43–49 | 1 | 6.7 | 0 | 0.0 |
| 50–56 | 0 | 0.0 | 1 | 8.3 |
| **Diagnostic certainty** | | | | |
| BC level 1 | 12 | 80.0 | 11 | 91.7 |
| BC level 2 | 0 | 0.0 | 0 | 0.0 |
| BC level 3 | 0 | 0.0 | 0 | 0.0 |
| BC level not determinable | 3 | 20.0 | 1 | 8.3 |
| **Therapy** | | | | |
| Spontaneous desinvagination | 1 | 6.7 | – | – |
| Hydrostatic desinvagination | 5 | 33.3 | 5 | 41.7 |
| Surgery | 7 | 46.7 | 6 | 50.0 |
| Information n.a. | 2 | 13.3 | 1 | 8.3 |
| **Risk factors for IS** | | | | |
| No evidence for risk factors | 13 | 86.7 | 9 | 75.0 |
| Previous intussusception | 1 | 6.7 | 0 | 0.0 |
| Suspected intestinal malrotation | 1 | 6.7 | 0 | 0.0 |
| Meckel's diverticulum | 0 | 0.0 | 1 | 8.3 |
| Congenital mesenterial gap | 0 | 0.0 | 1 | 8.3 |
| Patent urachus | 0 | 0.0 | 1 | 8.3 |

[a]Diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type B. [b]Diphtheria, tetanus, pertussis, polio, hepatitis B. ***BC*** Brighton Collaboration, ***IS*** intussusception, ***n.a.*** not available

hort study based on claims data with confirmation of the IS diagnosis by chart review included 1.2 million RotaTeq® doses (of which 507,000 were first doses) and 103,000 Rotarix® doses (of which 53,000 were first doses). In contrast to previous investigations of the association between RV vaccination and IS in the US [9, 10, 11], the Mini-Sentinel PRISM study revealed an increased IS risk 1–21 days following the first administration of RotaTeq® with most of the cases occurring 1–7 days after vaccination. This translates into 1–1.5 additional IS cases per 100,000 vaccinees after receipt of the first dose. No elevated IS risk was identified after the second or third doses. Regarding Rotarix®, data were not conclusive.

In summary, postlicensure pharmacoepidemiological studies of RV vaccines and IS provide evidence that both second-generation RV vaccines are associated with an increased IS risk.

RV vaccines have been on the German market since 2006 and both currently authorized RV vaccines are being used. In 2010, the five eastern federal states had a moderate (58%) and the 11 western federal states a low (22%) vaccine coverage [12]. An impact analysis revealed that RV vaccination in Germany was associated with a significant reduction in RV-related hospitalizations in 6- to 23-month-old children; it was calculated that—independent of the geographic region—vaccination of 50% of infants would lead to an estimated 42% decrease in hospitalization of 6- to 11-month-old infants [12]. In Mecklenburg-Western Pomerania, vaccine effectiveness for the prevention of RV infection requiring medical attention or hospitalization was estimated to be 68% (95% CI 61–71) and 80% (95% CI 77–83), respectively; breastfeeding and attending daycare were identified as risk factors for breakthrough infections [13].

In July 2013, the German Standing Committee on Vaccination (STIKO) recommended the routine use of the second-generation RV vaccines for infants [14, 15]. Previously, Saxony, Brandenburg, Mecklenburg–West Pomerania, Thuringia, and Schleswig–Holstein had already introduced RV vaccination into the respective vaccination schedules. We aimed at performing an OvE analysis stratified by vac-

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## Rotavirus vaccination. A risk factor for intussusception?

**Abstract**

Recently published pharmacoepidemiological studies associate the currently authorized Rotavirus (RV) vaccines with intussusception (IS). We aimed at investigating whether, in Germany, there are excess IS cases in RV vaccinees compared with the background incidence before market authorization in 2006. Suspected cases of IS following receipt of RV vaccines reported to the Paul-Ehrlich-Institut (PEI) from 2006 to 2010 were reviewed and validated against the criteria of the Brighton Collaboration's definition for IS. An observed-versus-expected analysis was conducted using standardized morbidity ratio (SMR) methods based on age-specific incidence rates for IS ranging from 19.2 to 98.5 per 100,000 person–years. A total of 27 cases of suspected IS in RV vaccinees were reported to the PEI. No excess of IS cases could be detected 1–7 days after receipt of either RV vaccine after any dose in the first year of life; however, in infants aged 3–5 months, a significantly increased SMR for IS was found in a risk window of 1–7 days after the first dose of either RV vaccine [SMRs: Rotarix® 4.6 (95% CI 1.5–10.7); RotaTeq® 5.8 (95% CI 1.2–17.1)]. A significantly increased risk of IS in a risk window of 1–7 days after RV vaccination was not found when the first dose was administered earlier. Therefore, it is recommended to start the vaccination course at 6–12 weeks of age.

**Keywords**

Rotavirus · Vaccination · Intussusception · Risk factors · Adverse drug reaction

## Rotavirusimpfung. Ein Risikofaktor für Invagination?

**Zusammenfassung**

Vor Kurzem publizierte pharmakoepidemiologische Studien weisen auf eine Assoziation zwischen den zurzeit zugelassenen Rotavirus (RV)-Impfstoffen und Invagination hin. Untersucht werden sollte, ob es in Deutschland mehr Fälle von Invagination (IV) bei RV-Impflingen gibt als aufgrund der Hintergrundinzidenz vor Marktzulassung im Jahr 2006 erwartet. Dem Paul-Ehrlich-Institut zwischen 2006 und 2010 gemeldete IV-Verdachtsfälle nach RV-Impfung wurden analysiert und gemäß der IV-Falldefinition der Brighton Collaboration validiert. Mithilfe von „Standardized-morbidity-ratio" (SMR)-Methoden wurde basierend auf altersspezifischen Inzidenzraten für IV zwischen 19,2 und 98,5 pro 100.000 Personenjahre eine „Observed-versus-expected-Analyse" durchgeführt. Das Paul-Ehrlich-Institut erhielt insgesamt 27 IV-Verdachtsfälle nach RV-Impfung. Obwohl für jeden der beiden RV-Impfstoffe und nach jeder Dosis in den ersten 7 Tagen nach Gabe nicht mehr IV-Fälle im 1. Lebensjahr als erwartet gemeldet wurden, zeigte sich für beide Impfstoffe bei 3 bis 5 Monate alten Kindern ein signifikant erhöhtes SMR für IV in einem Risikofenster von 1 bis 7 Tagen nach der 1. Dosis [SMR: Rotarix® 4,6 (95%-KI 1,5–10,7); RotaTeq® 5,8 (95%-KI 1,2–17,1)]. Ein signifikant erhöhtes Risiko in den ersten 7 Tagen nach der Impfung zeigte sich nicht, wenn die 1. Dosis davor verabreicht wurde. Daher empfiehlt es sich, die 1. Dosis ab der vollendeten 6. Lebenswoche bis zur vollendeten 12. Lebenswoche zu verabreichen.

**Schlüsselwörter**

Rotavirus · Impfung · Invagination · Risikofaktoren · Unerwünschte Arzneimittelreaktion

cine type, dose, and age for the risk window at 1–7 days after vaccination based on the most recent data available regarding vaccine exposure as well as age-specific IS incidence rates in Germany in order to investigate whether there is an indication of excess IS cases in RV vaccinees in Germany when compared with the background incidence before marketing authorization in 2006.

## Methods

### Spontaneous reporting of IS cases in temporal relationship with RV vaccination

According to the German Protection Against Infection Act (*Infektionsschutzgesetz*, IfSG), it is mandatory for physicians and nonmedical practitioners to report adverse events following immunization (AEFI) to the local health authority and to the national competent authority, the Paul-Ehrlich-Institut. Furthermore, marketing authorization holders have to report suspected serious adverse reactions to the PEI according to the German drug law (*Arzneimittelgesetz*, AMG). All suspected cases of IS following RV vaccinations reported to the PEI between 2006 and 2010 were reviewed and validated according to Brighton Collaboration's (BC) definition for acute IS [16]. Only cases fulfilling BC level 1 (highest level of diagnostic certainty) were eligible.

### Annual birth data

Annual birth data from 2006 to 2009 were provided by the German Federal Statistics Office (*Statistisches Bundesamt*); date of data delivery: 13 April 2011. Since birth data were not yet available for 2010 at the time the data were received, the figures for 2009 were used.

### Number of vaccinees by vaccine type, dose, and age

A retrospective survey was performed in November/December 2010 in two representative panels of German households with children aged 0–4 years using a self-administered written questionnaire. Participants were asked whether their child had been vaccinated with RV vaccine and, if yes, to specify the vaccination date, vaccine type, and batch number. These details that are documented in the child's international certificate of vaccination should be transcribed to the questionnaire. For the 5-year cohort (year of birth 2006–2010) vaccine-specific immunization rates were calculated stratified by dose and age at vaccine administration. A weight factor was used to account for disproportionate sampling regarding federal state, age, and gender. Vaccine type and dose- and age-specific immunization rates were multiplied with the number of live births registered in Germany from 2006 to 2010.

### Age-specific incidence rates for IS

Age-specific IS incidence rates reported by Weiß et al. [17] for the era when RV

**Tab. 2** Observed and expected cases of intussusception (Brighton Collaboration level 1) from 2006 to 2010 by age in days in children vaccinated with Rotarix®

| | | | | 1–7 days after vaccination | | |
|---|---|---|---|---|---|---|
| **Dose** | **Age (days)** | **Age-specific incidence rate[a,b]** | **Number of vaccinees[a]** | **Cases** | **Expected** | **SMR[a]** |
| 1 | 0–89 | 19.2 (12.5–30.4) | 209,394 (169,855–248,932) | 2 | 0.8 | 2.6 (0.3–9.4) |
| 1 | 90–179 | 61.4 (48.0–79.4) | 92,611 (75,124–110,098) | 5 | 1.1 | **4.6 (1.5–10.7)** |
| 1 | 180–269 | 98.5 (80.9–120.6) | 2,860 (2,320–3,400) | 0 | 0.1 | – |
| 1 | 270–365 | 67.8 (53.6–86.5) | 1,749 (1,419–2,080) | 0 | 0.02 | – |
| 1 | >365 | – | 4,805 (,3898–5,712) | 0 | – | – |
| 1 | 0–365 | 61.7 (54.5–70.1) | 306,614 (248,718–555,332) | 7 | 3.6 | 1.9 (0.8–4.0) |
| 2 | 0–89 | 19.2 (12.5–30.4) | 52,802 (42,832–62,772) | 0 | 0.2 | – |
| 2 | 90–179 | 61.4 (48.0–79.4) | 201,039 (163,078–239,000) | 0 | 2.4 | – |
| 2 | 180–269 | 98.5 (80.9–120.6) | 8,142 (6,604–9,679) | 0 | 0.2 | – |
| 2 | 270–365 | 67.8 (53.6–86.5) | 947 (768–1,126) | 0 | 0.0 | – |
| 2 | >365 | – | 1,458 (1,183–1,734) | 0 | – | – |
| 2 | 0–365 | 61.7 (54.5–70.1) | 262,930 (213,282–312,577) | 0 | 3.1 | – |
| 1+2 | 0–365 | 61.7 (54.5–70.1) | 569,544 (462,000–677,087) | 7 | 6.7 | 1.0 (0.4–2.1) |

[a]Point estimate and 95% confidence intervals. [b]Age-specific incidence rates (per 100,000 person–years) were taken from Weiß et al. [17]. *SMR* standardized morbidity ratio

vaccination had not yet or had just been introduced in Germany (2006 and 2007, see discussion) were used. This estimate was based on a two-source capture-recapture calculation (CRC) including data from ESPED reports (source 1)—the methods and results of the ESPED (*Erhebungseinheit für seltene pädiatrische Erkrankungen*) in Deutschland study are described elsewhere [18, 19]—and hospital discharge records for 2006 and 2007 (source 2).

## Standardized morbidity ratio

Standardized morbidity ratio (SMR) point estimates and 95% CI (exact Poisson CI) values were calculated stratified by vaccine type, dose, and age (subgroups: 0–2, 3–5, 6–8, and 9–11 months) for the risk window (interval between vaccination and AE occurrence) of 1–7 days following immunization. The following parameters entered the SMR calculation: observed number of confirmed cases, estimated number of vaccinees, and age-specific incidence rate. The OvE analysis method applied in this investigation has been used previously to analyze AEs following vaccination [20]. All statistical tests were two-sided and $p<0.05$ was considered statistically significant.

## Sensitivity analyses

### Vaccine exposure

In the main analysis, point estimates for the number of vaccinees were used to calculate the SMRs. In order to account for the uncertainty of immunization rates, the analyses were repeated with the upper 95% CI of the estimated number of vaccinees.

### Vaccine exposure and age-specific incidence rates

In the second step, the upper 95% CI of the number of vaccinees as well as the upper 95% CI of the age-specific incidence rate were used instead of the point estimators in order to perform a strictly conservative analysis.

### Risk factors for IS

A third sensitivity analysis was conducted to account for preexisting medical conditions that might foster IS. The OvE analysis was repeated excluding subjects with known or potential risk factors for IS.

## Statistical software

Statistical analyses were performed using the software package SAS version 9.3 (SAS Institute Inc., Cary, NC/USA).

# Results

## Spontaneous reporting of IS cases in temporal relationship with RV vaccination

From 2006 to 2010, a total of 27 AEFI of suspected IS following administration of RV vaccines (15 after Rotarix®, 12 after RotaTeq®) were reported to the PEI (**Tab. 1**). Thirteen infants (48.1%) experiencing IS underwent surgical reduction. Twelve cases of IS after administration of Rotarix® and 11 cases following RotaTeq® met the definition of BC level 1. In four cases (three following receipt of Rotarix® and one after RotaTeq®), the BC level could not be determined because of missing information regarding diagnostics and therapy. A total of 15 confirmed cases occurred within 1–7 days after vaccination.

## Estimated number of vaccinees by vaccine type, dose, and age

A total of 4,402 households were contacted, of which 3,711 (84.3%) returned the completed questionnaire. As several households comprised more than one child under the age of 5 years (year of birth 2006–2010), data on 4,565 children – 2,369 (51.9%) boys and 2,196 (48.1%) girls – were obtained, which were all included in the analysis. The estimated numbers of vaccinees by vaccine type, dose, and age are presented in **Tab. 2** and **Tab. 3**.

## Observed-versus-expected analysis: Rotarix®

Regarding Rotarix® (**Tab. 2**), the OvE ratio calculated over the first dose ad-

**Tab. 3** Observed and expected cases of intussusception (Brighton Collaboration level 1) from 2006 to 2010 by age in days in children vaccinated with RotaTeq®

| | | | | 1–7 days after vaccination | | |
|---|---|---|---|---|---|---|
| **Dose** | **Age (days)** | **Age-specific incidence rate[a,b]** | **Number of vaccinees[a]** | **Cases** | **Expected** | **SMR[a]** |
| 1 | 0–89 | 19.2 (12.5–30.4) | 217,424 (174,849–259,999) | 2 | 0.8 | 2.5 (0.3–9.0) |
| 1 | 90–179 | 61.4 (48.0–79.4) | 43,622 (35,081–52,164) | 3 | 0.5 | **5.8 (1.2–17.1)** |
| 1 | 180–269 | 98.5 (80.9–120.6) | 2,948 (2,370–3,525) | 0 | 0.1 | – |
| 1 | 270–365 | 67.8 (53.6–86.5) | 915 (736–1,094) | 0 | 0.0 | – |
| 1 | >365 | – | 3,357 (2,699–4,014) | | | |
| 1 | 0–365 | 61.7 (54.5–70.1) | 264,909 (213,036–316,782) | 5 | 3.1 | 1.6 (0.5–3.7) |
| 2 | 0–89 | 19.2 (12.5–30.4) | 69,011 (55,498–82,524) | 0 | 0.3 | – |
| 2 | 90–179 | 61.4 (48.0–79.4) | 172,382 (138,627–206,137) | 3 | 2.0 | 1.5 (0.4–4.3) |
| 2 | 180–269 | 98.5 (80.9–120.6) | 2,152 (1,730–2,573) | 0 | 0.0 | – |
| 2 | 270–365 | 67.8 (53.6–86.5) | 2,005 (1,613–2,398) | 0 | 0.0 | – |
| 2 | >365 | – | 2,752 (2,213–3,291) | | | |
| 2 | 0–365 | 61.7 (54.5–70.1) | 245,550 (197,468–293,632) | 3 | 2.9 | 1.0 (0.2–3.0) |
| 3 | 0–89 | 19.2 (12.5–30.4) | 2,689 (2,163–3,216) | 0 | 0.0 | – |
| 3 | 90–179 | 61.4 (48.0–79.4) | 195,425 (157,158–233,692) | 0 | 2.3 | – |
| 3 | 180–269 | 98.5 (80.9–120.6) | 20,405 (16,409–24,400) | 0 | 0.4 | – |
| 3 | 270–365 | 67.8 (53.6–86.5) | 1,532 (1,232–1,832) | 0 | 0.0 | – |
| 3 | >365 | – | 4,436 (3,567–5,305) | – | – | – |
| 3 | 0–365 | 61.7 (54.5–70.1) | 220,051 (176,962–263,140) | 0 | 2.6 | – |
| 1, 2, 3 | 0–365 | 61.7 (54.5–70.1) | 730,510 (587,466–849,398) | 8 | 8.6 | 0.9 (0.4–1.8) |

[a]Point estimate and 95% confidence intervals. [b]Age-specific incidence rates (per 100,000 person–years) were taken from Weiß et al. [17]. *SMR* standardized morbidity ratio

ministered within 1–7 days after vaccination in infants up to 12 months of age was slightly increased (SMR 1.9, 95% CI 0.8–4.0) without reaching significance. A slightly elevated, albeit not significant, SMR for vaccinees aged 0–2 months and a significantly increased SMR for infants aged 3–5 months of life was found 1–7 days after receipt of the first dose (SMR 4.6, 95% CI 1.5–10.7). No excess cases were detected after receipt of the second dose. SMR calculation over dose 1 and 2 revealed no increased OvE ratio.

## Observed-versus-expected analysis: RotaTeq®

With respect to RotaTeq® (**Tab. 3**), the results were similar. No statistically increased SMR for IS (1.6, 95% CI 0.5–3.7) was observed in recipients of the first dose administered in the first year of life 1–7 days after vaccination. There was an elevated, but not significant, SMR in vaccinees aged 0–2 months and a significantly elevated SMR in infants aged 3–5 months within 1–7 days following the first dose (SMR 5.8, 95% CI 1.2–17.1). There was an OvE ratio of 3 vs. 2 (SMR 1.5, 95% CI 0.4–4.3) within 1–7 days following the second dose in infants aged 3–5 months and there was no evidence for excess cases after receipt of the third dose. Similar to the results observed for Rotarix®, there was no higher number of IS cases than expected when calculating the SMR over dose 1, 2, and 3.

## Sensitivity analyses

### Vaccine exposure

Using upper 95% CIs of vaccine exposure data instead of point estimates, there was still an elevated SMR (3.9, 95% CI 1.3–9.0) for IS occurring in a risk window of 1–7 days after the first dose in recipients of Rotarix® aged 3–5 months. For RotaTeq®, a still elevated SMR (4.9, 95% CI 1.0–14.3) was also obtained when inserting the upper 95% CI of the estimated number of vaccinees.

### Vaccine exposure and age-specific incidence rates

The strictly conservative analysis of IS occurring in a risk window of 1–7 days after the first dose using upper 95% CIs for both the number of vaccinees and the age-specific incidence rate yielded an SMR of 3.0 (95% CI 1.0–7.0) for Rotarix® and an SMR of 3.8 (95% CI 0.8–11.0) for RotaTeq® in recipients aged 3–5 months.

### Risk factors for IS

Regarding Rotarix®, one infant in the 3–5-month age group experienced recurrent IS within 1–7 days after receipt of the first dose. Excluding this case from analysis, there was still a significantly increased SMR for IS (3.7, 95% CI 1.0–9.4). With respect to RotaTeq®, two patients aged 3–5 months diagnosed with IS within 1–7 days following the first dose had risk factors (congenital mesenteric gap, patent urachus). Excluding these infants from analysis, there was still an elevated but no longer significant SMR for IS (SMR 1.9, 95% CI 0.05–10.9).

## Discussion

Pharmacoepidemiological studies showed an association between the currently authorized RV vaccines [5, 7, 8] and IS, especially 1–7 days after receipt of the first dose. As rates of natural IS differ among countries (e.g., IS incidence rate in infants below 1 year of age: Australia 81.0/100,000 person–years [21], USA 47.0/100,000 person–years [9], Germany 61.7/100,000 person–years [17]), it is important to analyze country-specific data.

On the basis of the most recent available data on vaccine exposure and age-

specific IS incidence rates in Germany, we performed an OvE analysis for IS cases stratified by vaccine type, dose, and age for the risk window 1–7 days after vaccine administration, which revealed an elevated risk—albeit not significantly—with either RV vaccine following receipt of the first dose. In infants aged 3–5 months, a significantly increased risk to develop IS 1–7 days after the first dose of either RV vaccine was observed. Notably, in our analysis, 32.7% (95% CI 28.3–37.2) of all"consumed" first doses with respect to Rotarix® and 19.0% (95% CI 14.9–23.0) regarding RotaTeq® were given after the third month of life. Age restrictions for the initiation of RV vaccination have been criticized [22] because of unnecessary withholding of vaccination with a positive risk–benefit ratio. The Committee for Medicinal Products (CHMP) therefore adopted a change to the indication of RotaTeq® in January 2012 extending the upper recommended age from 26 to 32 weeks of life [23]. Although the absolute numbers of our analysis were small, our results indicate that a delay of the first dose beyond the third month of life might result in additional cases of IS. Considering the age-related background incidence of IS, our results appear to be biologically plausible.

## Strengths

All IS cases included in the OvE analysis were validated according to the BC's definition of IS [16]. Only cases with the highest level of diagnostic certainty were eligible. This high level of case ascertainment minimizes the risk of SMR overestimation due to misclassification. In Germany, there are no local or national immunization registries by which immunization coverage levels could be tracked. Therefore, precise data on RV vaccine uptake in children eligible for vaccination were not available. However, we conducted a large representative survey by utilizing two panels of households with young children. A high participation rate guaranteed that the risk for a selection bias is low. The data on vaccine type, dose, batch number, and vaccination date originate from the international certificate of vaccination, a document that is completed and signed by the attending pediatrician(s). It is usually sufficiently accurate and complete. Vaccine-, dose-, and age-specific immunization rates were used to estimate the number of doses administered in the respective strata. The calculated estimates of doses administered were checked against the number of doses approved by the PEI until 31 December 2010 and found to be 26.2% (95% CI 12.0–40.5) lower than the number of doses approved. As batches released by the PEI may also be marketed in other countries, the provided estimates for the doses administered appear to be reliable.

Since it is known that the IS incidence is highly dependent on age, using age-specific incidence rates constitutes a strength of this investigation. The background incidence rates were estimated for data collected from 1 January 2006 to 31 December 2007 within the scope of the ESPED study when RV vaccination had not yet or had just been approved by the European Commission. Thus, the influence of RV vaccination on IS incidence rates in this publication is believed to be negligible. In addition, all IS cases included met the BC criterion of level 1 so that overestimation of the age-specific background incidence due to misclassification is unlikely. After an unexplained decline of the incidence of hospitalizations due to IS in infants up to 12 months of age in Germany from 2000 to 2002 and a further decline from 2004 to 2005 probably owing to a change to the DRG system [17], the figures stabilized on a lower level from 2006 to 2009 (66.0, 62.1, 64.3, 65.0 per 100,000 child–years; data provided by the German Federal Statistics Office on 1 December 2011). Thus, using background incidence rates based on cases recruited from 2006 to 2007 appears appropriate. Furthermore, we used the same criterion (BC level 1) to ascertain IS cases as has been used in the ESPED study, a fact that enables a reliable comparison of observed cases versus background incidence rates.

Hitherto, IS incidence rates <1 year in Germany were reported in three recent research articles by Bissantz et al. [18], Jenke et al. [19], and Weiß et al. [17] of which the estimates were all based on data originating from the ESPED study. Only the last study provided IS incidence estimates stratified by month (quarter) of life, which were therefore used in this OvE analysis. Within the scope of a sensitivity analysis (strictly conservative analysis), using upper 95% CIs for both the number of vaccinees and the age-specific incidence rate still revealed an increased risk in recipients of the first dose aged 3–5 months 1–7 days after vaccine administration. This indicates that this analysis is sufficiently robust in the permissible error range.

## Limitations

The small total number of cases affects the precision of the estimates. Despite the obligation to report postvaccinal complications, there is of course underreporting, although it is not clear to what extent. The relatively high rate of surgical reduction (about 50%) found in this analysis as compared with the rate observed within the scope of the surveillance study [17], which was about 30% (personal communication), may be explained by better reporting of more serious cases. Considering the suspected underreporting of AEFI, which would result in SMR underestimation, a well-powered epidemiological study is needed to provide a proper quantification of the attributable risk.

Another shortcoming is the uncertainty regarding preexisting medical conditions that might foster IS. In the literature, IS recurrence rates of 14% [24] and 8% [25] have been reported. There are several reports on the association between intestinal malrotation and IS—so-called Waugh's syndrome [26, 27, 28, 29]. Meckel's diverticulum has also been frequently described in the literature as a lead point for IS in children and adults [30, 31, 32, 33, 34, 35], whereas the association with a mesenteric gap or a patent urachus is less clear. Nevertheless, we found a total of three published IS cases linked to traumatic or congenital mesenteric defects [36, 37, 38]. A literature search yielded two IS case reports on infants with patency of both the omphalomesenteric duct and urachus [39, 40], thus patent urachus was also considered as a potential risk factor. Enlarged lymph nodes were not classified as a risk factor since RV infection was shown to be associated

with increased distal ileum wall thickness and lymphadenopathy during the illness period [41]. To elucidate the role of the above-mentioned confounders—an interaction between risk factor, e.g., a distinct lead point, and RV vaccine should also be considered—more complex study designs are required.

The role of concomitant vaccination is even less clear. The currently authorized pentavalent, hexavalent combined, and pneumococcal vaccines, however, have hitherto never been associated with IS. An adverse drug reaction database search for IS following vaccination with penta- and hexavalent combined, and/or pneumococcal vaccines alone, i.e., without concomitant administration of RV vaccine, delivered only one report of suspected IS in a 4-month-old infant after receipt of a hexavalent combined vaccine together with a pneumococcal vaccine. The risk of an interaction appears negligible although it cannot be completely ruled out.

## Conclusion

**This observed-versus-expected analysis indicates a risk for excess cases of IS 1–7 days after receipt of the first dose of either RV vaccine in infants aged 3–5 months. This finding needs to be addressed in a well-powered epidemiological study. In summary, our observed-versus-expected analysis suggests that starting RV vaccination as early as possible in infancy would minimize the risk for IS.**

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## Compliance with ethical guidelines

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