



A case-control study of risk factors for intussusception among infants in eastern France after the introduction of the rotavirus vaccine



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ABSTRACT

Objective: The objective of the present study was to investigate the risk factors for intussusception (IS) among infants, including vaccination against rotavirus.

Methods: Case-control study with systematic inclusion of all infants aged <1 year with suspected IS admitted to emergency departments in the eastern region of France between 1 April 2008 and 31 March 2012. All cases classed level 1 according to the Brighton classification were matched to 4 hospital controls. Two exposure windows were examined; exposure to the first dose of rotavirus vaccine in the 7 and in the 14 days prior to the occurrence of IS.

Results: A total of 115 cases were matched with 457 controls. The average vaccination coverage rate over the 4 years of study was 8.6%. Rotavirus vaccine was not found to be significantly associated with the occurrence of IS in the 7 days (odds ratio (OR) not calculated; $p = 0.99$) and in the 14 days after administration of one dose vaccine (OR 1.33, 95% confidence interval (CI) 0.14–12.82). Infant formula alone or combined with breastfeeding was associated with an excess risk of IS (OR 2.74, 95% CI 1.10–6.79). A history of gastroenteritis within 2 weeks prior to hospitalisation was also associated with an increased risk (OR 2.24, 95% CI 1.07–4.67).

Conclusion: Our study indicates that infant formula alone or combined with breastfeeding is a risk factor for IS. A small, non-significant increase in the risk of IS was observed after rotavirus vaccination, although the low vaccine coverage rate likely precluded detection of a significant increase in risk.

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Abbreviations: IS, intussusception; OR, odds ratio; CI, confidence interval; CRF, case report form; GERS, Groupement pour l'Élaboration et la Réalisation de Statistiques/French statistics group; GUA, geographical units of analysis/French statistics group; WA, weeks of amenorrhea; CNIL, French data protection authority/Commission Nationale Informatique et Libertés.

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1. Introduction

Intussusception (IS) is one of the main causes of abdominal obstruction in infants and young children. It is defined as the invagination of one bowel segment into another. The majority of cases of IS do not have a pathologic lead point and are classified as primary or idiopathic intussusceptions. IS is a rare occurrence, with an incidence that varies between countries [1–6]. The full spectrum of risk factors is not yet clearly defined. In 1999, the first vaccine against rotavirus (Rotashield[®], Wyeth Laboratories, USA) was withdrawn from the market in the USA because it was found to be associated with an increased risk of IS [7]. The relative risk of IS during the first 3 to 7 days after administration of the vaccine was 58.9 [95% confidence interval (CI) 31.7–109.6] after administration of the first dose, and 11.0 (95%CI 4.1–29.5) after

administration of the second dose [8]. New oral vaccines against rotavirus were subsequently developed based on an attenuated virus, namely Rotarix® (RV1, GlaxoSmithKline, Belgium), which has a 2-dose schedule, and RotaTeq® (RV5, Merck & Co. Inc, USA), which has a 3-dose schedule. Recent post-marketing studies in different countries have shown a slight increase in risk of IS, particularly after the first dose of these vaccines [9–14]. Both of these vaccines were introduced onto the market in France in 2006.

In this context, a large epidemiological study (EPIstudy) was conducted in the Eastern region of France, with the primary objective of investigating the incidence of IS over a period of 4 years. The results of this epidemiological study have previously been published [6]. The aim of the present analysis was to investigate the risk factors (including rotavirus vaccination) for the occurrence of IS in infants aged <1 year.

2. Methods

2.1. Study design

We performed a case-control study based on a prospective, epidemiological registry designed to record the incidence of IS, and in which all infants aged less than one year with suspected IS were systematically recorded over a period of 4 years from 1 April 2008 to 31 March 2012 [6]. The current case-control study was performed in all hospitals with a pediatric emergency department in the greater eastern region of France (namely, Alsace, Burgundy, Champagne-Ardenne, Franche-Comté and Lorraine). For each case, four controls were recorded.

The geographical area concerned by the epidemiological surveillance was defined to make it possible to estimate the incidence rate of IS with sufficient precision to detect an increase in annual incidence of around 50% after the introduction of vaccination against rotavirus (Appendix 1).

2.2. Patient cases and controls

Inclusion criteria for cases were: age < 12 months, infants living in the study area during the study period, and presenting with suspected IS. Exclusion criteria were: age ≥ 12 months, infants living outside the study area, patients with a prior episode of IS or occlusion, and parental refusal to consent. Cases were classified according to the Brighton collaboration definition [15] by an independent expert committee composed of radio-paediatricians, paediatricians, emergency physicians and paediatric surgeons, as level 1 (confirmed cases), level 2 (probable), level 3 (possible) and level 4 (insufficient information for classification), based on major and minor clinical and radiological criteria (Appendices 2 and 3).

Only level 1 cases were retained for this case-control study. Each case was matched with four hospital controls for sex, age (±1 week), admission period (one month before or after the admission of the case), and centre. Control subjects were infants < 12 months who admitted for minor surgery, non-chronic disease, living in the study area during the study period and not presenting suspected IS. Exclusion criteria for controls were: age ≥ 12 months, infants living outside the study area, length of stay in excess of 2 weeks in the ward, a history of IS or occlusion, and parental refusal to consent.

2.3. Data collection and study variables

Data were collected by the investigator at the time of the infant's admission to the emergency ward with suspected IS, or to the hospital ward, using a standardized case report form.

We recorded socio-demographic characteristics (date of birth, sex, weight and height at birth, weight and height at admission); as well as medical history (Meckel's diverticulum, tumour (intestinal malformations, Hirschsprung disease, prior history of abdominal surgery); clinical signs (unusual crying, abdominal pain, refusing bottles, vomiting, lethargy, pallor, coma, convulsions, hypovolemic shock, presence of blood in the nappy or on rectal examination, palpable abdominal mass, abdominal distension, or abnormal abdominal sounds); additional examinations (abdominal X-ray, echography, contrast enema, abdominal computed tomography (CT scan); and type of reduction (therapeutic enema or surgery), and outcome.

Variables for inclusion in the analysis were: signs of malnutrition (yes/no); history of infection within the previous 2 weeks (yes/no) and by type of infection: gastroenteritis (defined as the occurrence of a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (≥3 in 24 h), with or without fever or vomiting [16]), other, none; any medications received in the previous 2 weeks (defined as intake of any medication or pharmacological substance within the 2 weeks prior to hospitalization) (yes/no); concomitant disease in the 2 weeks prior to IS diagnosis (yes/no for each of: ear/nose/throat disorders, respiratory disorders, digestive disorders, other, none); weight at admission (both in categories and as a continuous variable); height at admission (in categories and as a continuous variable); gestational term (as a continuous variable, and in categories: born at term [(gestation > 37 weeks of amenorrhea (WA) or premature (22–37 WA)]; type of feeding in 3 categories (exclusive breastfeeding, infant formula, or mixed feeding (i.e. infant formula plus breastfeeding); introduction of solid food (yes/no), and rotavirus vaccine status (vaccinated/ non-vaccinated). Exposure to rotavirus vaccine was evaluated based on risk periods considered after administration of the first dose (0–2 months), the second dose (3–4 months), and the third dose (5–11 months) (RV5 vaccine).

For cases, the risk period was defined as the difference between the date of occurrence of IS (defined as the date of diagnosis) and the date of vaccination. For controls, the risk period was defined as the difference between the reference date on which the matched control subject was exactly the same age as the case patient at the time of hospitalization, and the date of rotavirus vaccination. The period not-at-risk in vaccinated children was used as the reference for the calculation of ORs.

Vaccine coverage was calculated using statistics from the French statistics group (GERS) (Groupement pour l'Élaboration et la Réalisation de Statistiques) for the period from April 2008 to March 2012, based on the number of vaccine doses dispensed by pharmacies and hospitals. Data were aggregated based on the list of geographical units of analysis (GUA) corresponding to the study zone. The equation used by the French national agency for medicines and health products safety was applied, as follows:

$$\text{Coverage rate} = \frac{\text{volume of boxes delivered to pharmacies by type of vaccine/number of doses per vaccine}}{\text{Size of the birth cohort}}$$

2.4. Data management

Data were entered in duplicate before analysis. The exhaustiveness of data collection was verified using capture-recapture analysis (Lincoln-Petersen estimation) [17], which compared information from the hospital informatics databases to data from the EPIstudy [6].

2.5. Statistical analysis

The first phase of analysis consisted in descriptive analysis of the study population (idiopathic cases). The second phase investigated risk factors for IS through the case-control study. The following analyses were performed.

2.5.1. Primary analysis

Univariate analysis by logistic regression was performed for all factors listed (predisposing factors, risk factors) and adjusted for the matching variables. Qualitative variables were compared using the chi square test. Odds ratios (OR) are presented with 95% Confidence Intervals (CI). Multivariate analysis by conditional logistic regression using stepwise selection was performed; all variables that had a p-value < 0.20 by univariate analysis were included in the model.

2.5.2. Secondary analyses

One of the risk factors for which we sought to investigate the potential relation with IS was receipt of an oral vaccine against rotavirus. We considered that on average, 3 to 4 confirmed cases of IS would be included per month over the 4 years of the epidemiological surveillance [18]. In the primary analysis, we made no distinction between vaccines; and the doses were considered all together. We planned to perform secondary analyses, if the number of cases recruited was sufficient, according to the type of vaccine received (RV1 or RV5), number of doses received (1, 2, or 3) and the time window of exposure as per the study by Murphy et al [8] (Appendix 4). The prospective inclusion of 156 confirmed cases, each matched to 4 controls, made it possible to estimate the minimum detectable OR at 1.74 for an increase in risk related to rotavirus vaccination, based on the assumption of a vaccine coverage rate of 30%. For reasons related to statistical power, two exposure windows were examined: exposure to the first dose of rotavirus vaccine in the 7 days prior to the occurrence of IS and; the exposure to any dose of rotavirus vaccine in the 14 days prior to the occurrence of IS.

To investigate the relation between vaccination against rotavirus and IS, we used univariate and multivariate conditional logistic regression to estimate ORs for IS during the predefined risk periods. All variables with p-value < 0.20 by univariate analysis were included in the multivariate model, and were removed in a stepwise manner if their absence failed to affect the OR for IS after vaccination by 10% or more [8].

All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

The study was performed and reported in accordance with the STROBE criteria and recommendations [19].

2.6. Ethics statement

The parents who agreed to participate in the study received information about the study from the investigating physician in a dedicated meeting with delivery of a factsheet. Given the non-interventional nature of the study, oral consent was obtained, and written informed consent was not required in accordance with current French legislation (*article L 1121-1 du Code de la Santé publique*).

The protocol was approved by the Advisory Committee for the processing of data in health research in the French Ministry for Research on 6 April 2006 and by the French data protection authority under the number 906 127, on 18 August 2006.

3. Results

3.1. Study population

A total of 145 cases were included in the main epidemiological study. Of these, 115 (79.31%) were classified as a level 1, 8 (5.51%) as level 2, 7 (4.82%) as level 3, and 15 (10.34%) as level 4 (previous publication [6]). The 115 level 1 cases were matched to 457 in-hospital controls for the purposes of the present study.

Among the population of cases, 58.3% of the infants were boys, with a boy-girl sex ratio of 1.4. Table 1 shows the distribution of clinical signs among the cases. Only 20 infants (17.39%) had the full symptom triad associating abdominal pain, vomiting and rectal bleeding.

The most frequently used complementary examination for the diagnosis of IS was echography, which was used to confirm diagnosis in 114 (99.13%). In 78 (67.83%) infants, radiological reduction was complete (Appendix 5). Surgical treatment was performed in 37 (32.17%) infants. The median length of hospital stay was 3 days [IQR, 2–5]. No patient died.

3.2. Risk factor assessment

The results of the risk factor assessment are shown in Tables 2 and 3.

Infant formula alone or with breastmilk was associated with an excess risk of IS (adjusted OR 2.74; 95%CI 1.10–6.79) as compared to breastfeeding alone.

A history of gastroenteritis was also found to be associated with an excess risk of IS (adjusted OR 2.24; 95%CI 1.07–4.67) compared to no history of gastroenteritis in the 2 weeks prior to hospital admission. The existence of concomitant disease was associated with a reduction in the risk of having IS (adjusted OR 0.20; 95% CI 0.12–0.34).

3.3. Assessment of rotavirus vaccine as a risk factor

During the study period, 12 cases of IS were recorded in infants who had received at least one dose of rotavirus vaccine (5 RV5, 7

Table 1

Distribution of clinical symptoms and signs, diagnosis method, reduction procedures and outcomes for intussusception of cases (level 1 of Brighton Collaboration Classification).

	n = 115	%
<i>Clinical symptoms</i>		
Abdominal pain (Persistent and unused crying)	79	68.70
Pallor	65	56.52
Lethargy	64	55.65
Hypovolemic shock	8	6.96
Fever (>38 °C)	5	4.35
Bloody stool	38	33.04
Refusal of baby bottle	40	34.78
Vomiting	80	69.57
Biled-stained vomiting	13	11.30
Constipation and lack of gas	14	12.17
Dehydration	9	7.83
<i>Physical signs</i>		
Abnormal or absent bowel sounds	10	8.70
Abdominal distension	25	21.74
Abdominal mass	30	26.09
Blood on rectal exam	17	14.78

Table 2
Univariate analysis of the risk factors for intussusception in infants.

	Cases n = 115	Controls n = 457	OR (95%CI) [†]	P
Birthweight				
<3.20 kg	59 (51.3)	224 (49.0)	1.0	0.68
≥ 3.20 kg	56 (48.7)	233 (51.0)	0.92 (0.61–1.38)	
Weight at admission[‡]				
<7.87 kg	64 (55.7)	222 (48.6)	1.0	0.08
≥7.87 kg	51 (44.3)	235 (51.4)	0.63 (0.37–1.06)	
Height at admission[‡]				
<67 cm	45 (39.1)	210 (46.0)	1.0	0.06
≥67 cm	70 (60.9)	247 (54.0)	1.81 (0.98–3.35)	
Gestational age at birth^{**}				
>37 SA	110 (95.70)	416 (91.0)	1.0	0.12
22–37 SA	5 (4.3)	41 (9.0)	0.47 (0.18–1.21)	
Feeding				
Exclusive Breastfeeding	6 (5.2)	56 (12.3)	1.0	0.10
Infant formula	90 (78.3)	327 (71.7)	2.597 (1.08–6.27)	0.03
Mixed feeding	19 (16.5)	73 (16.0)	2.366 (0.889–6.294)	0.08
Introduction of solid foods				
No	30 (26.1)	122 (26.7)	1.0	0.87
Yes	85 (73.9)	335 (73.3)	1.07 (0.48–2.37)	
Gastroenteritis before admission				
No	101 (87.8)	415 (90.8)	1	0.31
Yes	14 (12.2)	42 (9.2)	1.42 (0.72–2.79)	
Any medications received in the previous 2 weeks				
No	81 (70.4)	235 (51.4)	1	< 0.01
Yes	34 (29.6)	222 (48.6)	0.41 (0.26 – 0.66)	
Concomitant disease before admission				
No	86 (74.8)	194 (42.50)	1	< 0.01
Yes	29 (25.2)	263 (55.5)	0.23 (0.14–0.37)	
Exposure to first dose of rotavirus vaccine 7 days prior				
No	114 (99.1)	457 (100.0)	1.0	0.99
Yes	1 (0.9)	0 (0.0)		
Exposure to one dose of rotavirus vaccine 14 days prior				
No	114 (99.1)	454 (99.3)	1.0	0.80
Yes	1 (0.90)	3 (0.70)	1.33 (0.14–12.82)	

[†]Mean ± standard deviation = 7.73 ± 1.30 (cases); 0.77 ± 1.59 controls); OR 0.97, 95% CI 0.7–1.182.

^{*} CI, confidence interval.

[‡] Mean ± standard deviation = 67.44 ± 5.59 (cases); 66.68 ± 6.47 (controls); OR 1.06, 95% CI 1.00–1.12.

^{**} Mean ± standard deviation = 39.15 ± 1.59 (cases); 39.02 ± 2.27 (controls); OR 1.03, 95% CI 0.93–1.13.

Table 3
Multivariable logistic regression model of the risk factors for intussusception in infants.

	Adjusted OR (95% CI) ^a	p
Infant formula alone or with breastfeeding	2.74 (1.10–6.79)	0.03
Gastroenteritis before admission (yes vs no) ^b	2.24 (1.07–4.67)	0.03
Concomitant disease before admission (yes vs no)	0.20 (0.12–0.34)	<0.01

^a CI, confidence interval, adjusted for gestational term, Medication before hospitalization, weight at admission, height at admission, gastroenteritis “within fifteen day, concomitant diseases. The conditional logistic regression was performed after examining collinearity to ascertain the independence of the covariates.

^b This variable was forced in multivariate analysis despite p = 0.31 in univariate because it was a known risk factor for IS. [18] – It is a variable of clinical interest.

RV1). Among the controls, 42 infants had received at least one dose of vaccine. The average vaccination coverage rate over the 4 years of study was 8.6%. Table 4 shows the vaccine coverage rates per year. Only one case of IS occurred during the 2 weeks after administration of a first dose of the vaccine.

Fig. 1 shows the intervals between the administration of a dose of rotavirus vaccine and the occurrence of IS among the cases, and between injection of a dose of rotavirus vaccine and the reference date in controls.

In primary analysis, rotavirus vaccination was not found to be significantly associated with the risk of IS, either after administration of a first vaccine dose within the previous 7 days, or after any vaccine dose within the previous 14 days in univariate analysis (Table 2).

In secondary analysis, after adjustment for breastfeeding and presence of concomitant disease in the 2 weeks prior to hospital admission, there was no significant impact of rotavirus vaccination on the risk of IS (OR 1.16, 95% CI 0.58–2.30), regardless of the time elapsed between receipt of any dose of the vaccine, and occurrence of IS (maximum time observed = 189 days).

4. Discussion

To the best of our knowledge, this case-control study is the first in France to provide new insights into the risk factors for IS.

Our findings show a predominance of boys in the study population, in line with previous reports in the literature [18]. The clinical signs presented by the children in our cohort were comparable to those previously described in other reports [20], with vomiting and abdominal pain being the most frequent complaints.

In around one third of cases, surgery was necessary to achieve reduction of IS, either after a failed attempt at radiological reduction, or as first-line therapy. The proportion of IS cases treated by surgery varies widely, ranging from 12 to 88% according to

Table 4
Vaccine coverage rate calculated from the GERS data over the study period.

	1st year April 08–March 09	2 nd Year April 09–March 10	3rd Year April 10–March 11	4th year April 11–March 12	Total April 08–March 12
Numbers of doses (GERS* data)					
RV1 (Rotarix®)	15 003	16 845	685	9 734	42 267
RV5 (Rotateq®)	3 553	4 417	17 283	11 143	36 936
Number of births in Eastern region	97 829	97 176	96 946	95 164	387 115
RV1 (Rotarix®) Vaccination Coverage rate	7.67%	8.67%	0.36%	5.11%	5.46%
RV5 (Rotateq®) Vaccination Coverage rate	1.21%	1.52%	5.94%	3.90%	3.18%
Rotavirus vaccine coverage	8.88%	10.19%	6.30%	9.01%	8.64%

* GERS, Groupement pour l'Élaboration et la Réalisation de Statistiques/French statistics group.

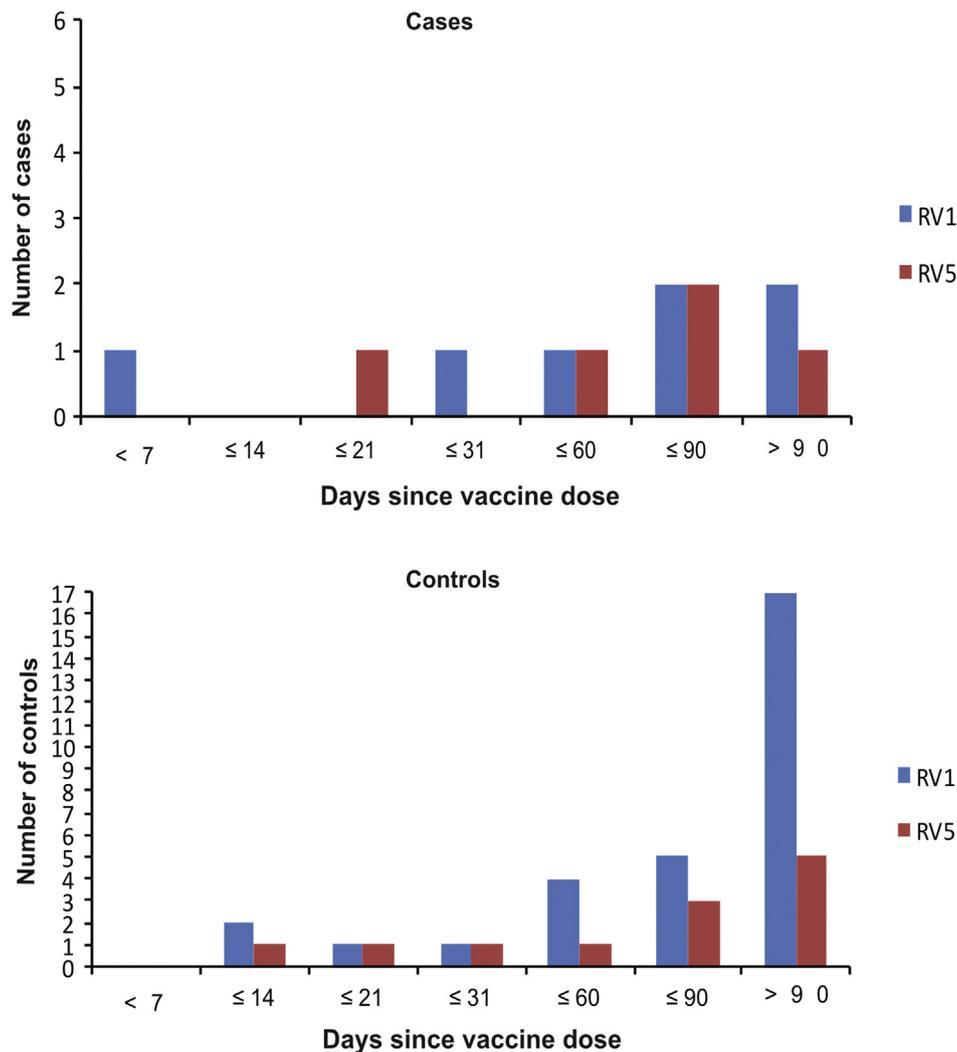


Fig. 1. Interval between Rotavirus Vaccination and Hospitalization in cases and controls.

different reports in the literature [3,21]. Late management (beyond 24 h after onset) could contribute to the high rate of surgery observed in certain reports [22,23].

After adjustment, risk factor analysis in our study suggests the implication of infant formula in the occurrence of IS in infants. The implication of infant formula in the occurrence of IS in infants has previously been reported by a US case-control study that included 429 cases and 1763 controls, with an increased risk observed in infants who consumed cow's-milk formula [24]. This could be explained by the risk of allergy to the proteins in cow's

milk, with the development of antibodies, a chronic immunological reaction, and hypertrophy of the Peyer's patches [25].

We observed a significant relation between IS and the presence of gastroenteritis during the 2 weeks prior to IS, with a twofold increase in risk in those with a recent history of gastroenteritis. These findings are in agreement with other reports in the literature [26,27]. The role of rotavirus infection in the occurrence of IS remains controversial [28–30], and the conflicting results between studies could be explained by the lack of statistical power or the different methodologies used.

Unlike other studies [31,32], our study shows that the existence of concomitant disease in the 2 weeks prior to IS paradoxically had a significant protective effect on the occurrence of IS. This could be due to a possible bias described by Berkson [33] that is inherent to case-control studies performed in the hospital context. Indeed, the choice of a group of hospital controls incurs the risk that this group would be composed of patients who are more exposed than the general population to the risk under consideration in the study, i.e. in our case, the existence of concomitant disease. In light of this, the use of non-hospital controls could be considered as a possible alternative. However, this in turn would have exposed to a risk of selection bias, with the risk that the physician, who would be aware of the patient's vaccination status, would give precedence to children who had been vaccinated, thus leading to potential underestimation of this risk factor. Choosing hospitalized children as controls also generates a risk of confusion bias if, for example, controls had been chosen on their vaccination status or according to the type of feeding they received. To minimize bias in our study, in particular selection bias, cases and controls were matched for age, sex and centre of inclusion, based on the assumption that children in a given region would all be referred to same large university hospital, thus reflecting the general population of children of the same age.

Regarding a possible relation between rotavirus vaccination and IS, our findings showed a non-statistically-significant increase in the risk of IS after administration of one dose of vaccine in the 14 days prior to hospital admission, by univariate analysis, and also after one first dose of vaccine, with either time-window of exposure. Despite the different study design and methodological approach used in our study, our results are nonetheless in line with those of the literature. Reports from other countries have also shown an increased risk especially in the first week after administration of the first dose of the vaccine. For example, in a study from the United States, 124 cases of IS were recorded, of which 5 occurred during the period at risk, and the attributable risk was estimated at 1.1 (95%CI 0.3–2.7) during the 7 days following injection of the first dose of the vaccine (RV5) [14]. In an Australian study of 306 cases, the vaccine attributable risk for IS was estimated to be 4.3 (95%CI 0.8–23.3) cases per 100,000 children vaccinated for RV1, and 7.0 (95% CI, 1.5–33.1) cases per 100 000 for RV5 [12]. Patel et al showed an increased risk of IS after RV1 vaccine during the week following the first vaccine dose with an OR of 5.8 (95%CI 2.6–13.0) in a Mexican study of 285 cases, while a Brazilian study of 330 cases showed a non-significant increase in risk (OR 1.4, 95%CI 0.4–4.8) [10]. In our study, the low number of cases combined with the low vaccine coverage rate likely precluded detection of a significant increase in the risk of IS. A meta-analysis by Rossillon et al. [34] of the main post-marketing studies reported a relative risk of IS after the first dose of rotavirus vaccine of 5.4 (95%CI 3.9–7.4) for the RV1 and 5.5 (95%CI 3.3–9.3) for RV5. The risk is lower after the second dose, with ORs of 1.8 (95%CI 1.3–2.5) and 1.7 (95%CI 1.1–2.6) for RV1 and RV5 respectively. We also found that the risk decreased, albeit remaining non-significant, after adjustment for breast feeding and presence of concomitant disease within the 2 weeks prior to hospitalization, suggesting a protective role for breastfeeding.

We also noted a significant relation between the occurrence of acute gastroenteritis during the 2 weeks prior to IS, with a two-fold increase in risk of IS. In our multivariate analysis, we considered gastroenteritis as a variable of interest, and forced this variable in the model, despite a p-value of 0.31 by univariate analysis. This choice was based on previous literature data reporting a significant association between gastroenteritis and IS, and in this regard, our findings are in line with previous publications [18,26].

One of the strengths of this study is the quality of the data recorded. Indeed, exhaustiveness of the recorded data was verified

using diagnostic codes from the medical informatics systems with capture-recapture analysis [17,35], and showed excellent overall exhaustiveness. A further strength is the reliable quality of the data thanks to systematic monitoring and quality control systems implemented to ensure the data recorded were verified and accurate.

The main limitation of our study is the lack of statistical power due to poor vaccine coverage rates. There are two main reasons for this poor vaccine coverage. First, at the time of the study, there were no recommendations regarding the rotavirus vaccine from the national health authorities and therefore no reimbursement for this vaccine by the national health insurance system. Secondly, scepticism in relation to vaccination in general is highly prevalent in France [36]. This attitude probably impacted negatively on the power of this study, and more generally, poses a problem for the statistical power of analyses linked to risk factors where exposure is the lowest. Finally, there may be potential for residual confounding.

5. Conclusion

This study highlights potential risk factors implicated in the occurrence of IS. The occurrence of acute gastroenteritis in the 2 weeks prior to hospitalization is a significant risk factor for IS. Infant formula alone or combined with breastfeeding was also found to be a significant risk factor for the occurrence of IS. The limited statistical power and the low vaccine coverage likely preclude detection of a significant increase in the risk of IS related to rotavirus vaccination.

6. Authors' contributions

We confirm that all authors have made substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data, or to the drafting of the article or its critical revision of important intellectual content. Further, we confirm that all authors have given final approval of the version to be published and its submission to *Vaccine*.

In particular, each author made the following contributions: Arnaud Fotso Kamdem coordinated the study, aided in data collection, wrote and reviewed the manuscript.

Chrystelle Vidal: Ms Vidal designed the study, carried out the analyses, revised and reviewed the initial manuscript of the study.

Lionel Pazart: Dr Pazart designed the study, revised and reviewed the initial manuscript of the study.

Aurore Pugin: Ms Pugin carried out the analyses.

Caroline Savet: Ms Savet was the clinical research assistant and carried out data collection.

Franck Leroux: Mr Leroux was data manager and aided in data collection.

Geoffroy Sainte-Claire Deville: Mr Sainte-Claire Deville managed regulatory, ethical and administrative issues related to the study, revised and reviewed the initial manuscript of the study.

Didier Guillemot: Prof. Guillemot conceptualized, designed the study, revised and reviewed the initial manuscript of the study.

Jacques Massol: Prof. Massol conceptualized, designed the study, revised and reviewed the initial manuscript of the study.

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Appendix A. Supplementary material

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