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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.

Key words: Intussusception – Infants – case-control study – rotavirus vaccine – risk factors

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 the European Journal of Pediatrics.

In particular, each author made the following contributions:

Arnaud Fotso kamdem : Dr Fotso Kamdem, coordinated the study, aided in data collection, wrote and reviewed the manuscript.

Chrystelle Vidal: Ms Vidal designed the study and carried out the analyses.

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 approach to the study, revised and reviewed the the initial manuscript of the study.

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

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

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1 **A Case-Control Study of Risk Factors for Intussusception Among Infants in Eastern**
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3

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8 suspected IS admitted to emergency departments in the eastern region of France between 1
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10 classification were matched to 4 hospital controls. Two exposure windows were examined;
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22 an risk factor for IS. A small, non-significant increase in the risk of IS was observed after
23 rotavirus vaccination, although the low vaccine coverage rate likely precluded detection of a
24 significant increase in risk.

25

26 **Key words:** Intussusception – Infants – case-control study-rotavirus vaccine – risk factors

27

28 **Abbreviations**

29 IS, intussusception; OR, odds ratio; CI, confidence interval; CRF, case report form; GERS,
30 Groupement pour l'Élaboration et la Réalisation de Statistiques/ French statistics group;

31 GUA, geographical units of analysis / French statistics group; WA, weeks of

- 32 amenorrhea ; CNIL, French data protection authority / Commission Nationale Informatique et
33 Libertés.

34 1. Introduction

35
36 Intussusception (IS) is one of the main causes of abdominal obstruction in infants and young
37 children. It is defined as the invagination of one bowel segment into another. The majority of
38 cases of IS do not have a pathologic lead point and are classified as primary or idiopathic
39 intussusceptions. IS is a rare occurrence, with an incidence that varies between countries [1–
40 6]. The full spectrum of risk factors is not yet clearly defined. In 1999, the first vaccine
41 against rotavirus (Rotashield®, Wyeth Laboratories, USA) was withdrawn from the market in
42 the USA because it was found to be associated with an increased risk of IS [7]. The relative
43 risk of IS during the first 3 to 7 days after administration of the vaccine was 58.9 [95%
44 confidence interval (CI) 31.7-109.6] after administration of the first dose, and 11.0 (95%CI
45 4.1-29.5) after administration of the second dose [8]. New oral vaccines against rotavirus
46 were subsequently developed based on an attenuated virus, namely Rotarix® (RV1,
47 GlaxoSmithKline, Belgium), which has a 2-dose schedule, and RotaTeq® (RV5, Merck &
48 Co. Inc, USA), which has a 3-dose schedule. Recent post-marketing studies in different
49 countries have shown a slight increase in risk of IS, particularly after the first dose of these
50 vaccines [9–14]. Both of these vaccines were introduced onto the market in France in 2006.

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

56

57 2. Methods

58

59 2.1. Study design

60 We performed a case-control study based on a prospective, epidemiological registry designed
61 to record the incidence of IS, and in which all infants aged less than one year with suspected
62 IS were systematically recorded over a period of 4 years from 1 April 2008 to 31 March 2012
63 [6]. The current case-control study was performed in all hospitals with a pediatric emergency

64 department in the greater eastern region of France (namely, Alsace, Burgundy, Champagne-
65 Ardenne, Franche-Comté and Lorraine). For each case, four controls were recorded.

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

70 *2.2. Patient cases and controls :*

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

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

86

87 *2.3. Data Collection and Study Variables*

88

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

91 We recorded socio-demographic characteristics (date of birth, sex, weight and height at birth,
92 weight and height at admission); as well as medical history (Meckel's diverticulum, tumour
93 (intestinal polyp), cystic fibrosis, intestinal duplication, vascular intestinal malformations,

94 Hirschsprung disease, prior history of abdominal surgery); clinical signs (unusual crying,
95 abdominal pain, refusing bottles, vomiting, lethargy, pallor, coma, convulsions, hypovolemic
96 shock, presence of blood in the nappy or on rectal examination, palpable abdominal mass,
97 abdominal distension, or abnormal abdominal sounds); additional examinations (abdominal
98 X-ray, echography, contrast enema, abdominal computed tomography (CT scan); and type of
99 reduction (therapeutic enema or surgery), and outcome.

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

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

122 Vaccine coverage was calculated using statistics from the French statistics group (GERS)
123 (Groupement pour l'Élaboration et la Réalisation de Statistiques) for the period from April
124 2008 to March 2012, based on the number of vaccine doses dispensed by pharmacies and
125 hospitals. Data were aggregated based on the list of geographical units of analysis (GUA)

126 corresponding to the study zone. The equation used by the French national agency for
127 medicines and health products safety was applied, as follows:

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

128 The volume of boxes delivered corresponds to the total number of single-doses of vaccine.
129 This calculation assumes that all children in the cohort receive the full dose schedule before
130 the age of one year.

131

132 *2.4. Data management*

133

134 Data were entered in duplicate before analysis.

135 The exhaustiveness of data collection was verified using capture-recapture analysis (Lincoln-
136 Petersen estimation) [17], which compared information from the hospital informatics
137 databases to data from the EPI study [6].

138

139 *2.5. Statistical analysis*

140

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

144 *2.5.1. Primary analysis*

145

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

152

153 2.5.2. *Secondary analyses*

154 One of the risk factors for which we sought to investigate the potential relation with IS was
155 receipt of an oral vaccine against rotavirus. We considered that on average, 3 to 4 confirmed
156 cases of IS would be included per month over the 4 years of the epidemiological surveillance
157 [18]. In the primary analysis, we made no distinction between vaccines; and the doses were
158 considered all together. We planned to perform secondary analyses, if the number of cases
159 recruited was sufficient, according to the type of vaccine received (RV1 or RV5), number of
160 doses received (1, 2, or 3) and the time window of exposure as per the study by Murphy et al
161 [8] (appendix 4). The prospective inclusion of 156 confirmed cases, each matched to 4
162 controls, made it possible to estimate the minimum detectable OR at 1.74 for an increase in
163 risk related to rotavirus vaccination, based on the assumption of a vaccine coverage rate of
164 30%. For reasons related to statistical power, two exposure windows were examined:
165 exposure to the first dose of rotavirus vaccine in the 7 days prior to the occurrence of IS and;
166 the exposure to any dose of rotavirus vaccine in the 14 days prior to the occurrence of IS.

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

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

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

175

176 2.6. *Ethics Statement*

177

178 The parents who agreed to participate in the study received information about the study from
179 the investigating physician in a dedicated meeting with delivery of a factsheet. Given the non-
180 interventional nature of the study, oral consent was obtained, and written informed consent

181 was not required in accordance with current French legislation (*article L 1121-1 du Code de*
182 *la Santé publique*).

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

186

187 **3. Results**

188

189 *3.1. Study population*

190

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

195 Among the population of cases, 58.3% of the infants were boys, with a boy-girl sex ratio of
196 1.4. Table 1 shows the distribution of clinical signs among the cases. Only 20 infants
197 (17.39%) had the full symptom triad associating abdominal pain, vomiting and rectal
198 bleeding.

199 The most frequently used complementary examination for the diagnosis of IS was
200 echography, which was used to confirm diagnosis in 114 (99.13%). In 78 (67.83%) infants,
201 radiological reduction was complete (Appendix 5). Surgical treatment was performed in 37
202 (32.17%) infants. The median length of hospital stay was 3 days [IQR, 2-5]. No patient died.

203

204 *3.2. Risk factor assessment*

205

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

207 Infant formula alone or with breast milk was associated with an excess risk of IS (adjusted OR
208 2.74; 95%CI 1.10-6.79) as compared to breast-feeding alone.

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

213 *3.3. Assessment of rotavirus vaccine as a risk factor*

214
215 During the study period, 12 cases of IS were recorded in infants who had received at least one
216 dose of rotavirus vaccine (5 RV5, 7 RV1). Among the controls, 42 infants had received at
217 least one dose of vaccine. The average vaccination coverage rate over the 4 years of study
218 was 8.6%. Table 4 shows the vaccine coverage rates per year. Only one case of IS occurred
219 during the 2 weeks after administration of a first dose of the vaccine.

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

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

226 In secondary analysis, after adjustment for breastfeeding and presence of concomitant disease
227 in the 2 weeks prior to hospital admission, there was no significant impact of rotavirus
228 vaccination on the risk of IS (OR 1.16, 95% CI 0.58-2.30), regardless of the time elapsed
229 between receipt of any dose of the vaccine, and occurrence of IS (maximum time observed =
230 189 days).

231

232 **4. Discussion**

233

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

236 Our findings show a predominance of boys in the study population, in line with previous
237 reports in the literature [18]. The clinical signs presented by the children in our cohort were

238 comparable to those previously described in other reports [20], with vomiting and abdominal
239 pain being the most frequent complaints.

240 In around one third of cases, surgery was necessary to achieve reduction of IS, either after a
241 failed attempt at radiological reduction, or as first-line therapy. The proportion of IS cases
242 treated by surgery varies widely, ranging from 12 to 88% according to different reports in the
243 literature [3,21]. Late management (beyond 24 hours after onset) could contribute to the high
244 rate of surgery observed in certain reports [22,23].

245 After adjustment, risk factor analysis in our study suggests the implication of infant formula
246 in the occurrence of IS in infants. The implication of infant formula in the occurrence of IS in
247 infants has previously been reported by a US case-control study that included 429 cases and
248 1763 controls, with an increased risk observed in infants who consumed cow's-milk formula
249 [24]. This could be explained by the risk of allergy to the proteins in cow's milk, with the
250 development of antibodies, a chronic immunological reaction, and hypertrophy of the Peyer's
251 patches [25].

252

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

259 Unlike other studies [31][32], our study shows that the existence of concomitant disease in the
260 2 weeks prior to IS paradoxically had a significant protective effect on the occurrence of IS.
261 This could be due to a possible bias described by Berkson [33] that is inherent to case-control
262 studies performed in the hospital context. Indeed, the choice of a group of hospital controls
263 incurs the risk that this group would be composed of patients who are more exposed than the
264 general population to the risk under consideration in the study, i.e. in our case, the existence
265 of concomitant disease. In light of this, the use of non-hospital controls could be considered
266 as a possible alternative. However, this in turn would have exposed to a risk of selection bias,
267 with the risk that the physician, who would be aware of the patient's vaccination status, would
268 give precedence to children who had been vaccinated, thus leading to potential
269 underestimation of this risk factor. Choosing hospitalized children as controls also generates a

270 risk of confusion bias if, for example, controls had been chosen on their vaccination status or
271 according to the type of feeding they received. To minimize bias in our study, in particular
272 selection bias, cases and controls were matched for age, sex and centre of inclusion, based on
273 the assumption that children in a given region would all be referred to same large university
274 hospital, thus reflecting the general population of children of the same age.

275 Regarding a possible relation between rotavirus vaccination and IS, our findings showed a
276 non-statistically-significant increase in the risk of IS after administration of one dose of
277 vaccine in the 14 days prior to hospital admission, by univariate analysis, and also after one
278 first dose of vaccine, with either time-window of exposure. Despite the different study design
279 and methodological approach used in our study, our results are nonetheless in line with those
280 of the literature. Reports from other countries have also shown an increased risk especially in
281 the first week after administration of the first dose of the vaccine. For example, in a study
282 from the United States, 124 cases of IS were recorded, of which 5 occurred during the period
283 at risk, and the attributable risk was estimated at 1.1 (95%CI 0.3-2.7) during the 7 days
284 following injection of the first dose of the vaccine (RV5) [14]. In an Australian study of 306
285 cases, the vaccine attributable risk for IS was estimated to be 4.3 (95%CI 0.8-23.3) cases per
286 100,000 children vaccinated for RV1, and 7.0 (95% CI, 1.5-33.1) cases per 100 000 for RV5
287 [12]. Patel et al showed an increased risk of IS after RV1 vaccine during the week following
288 the first vaccine dose with an OR of 5.8 (95%CI 2.6-13.0) in a Mexican study of 285 cases,
289 while a Brazilian study of 330 cases showed a non-significant increase in risk (OR 1.4,
290 95%CI 0.4-4.8) [10]. In our study, the low number of cases combined with the low vaccine
291 coverage rate likely precluded detection of a significant increase in the risk of IS. A meta-
292 analysis by Rossillon et al [34] of the main post-marketing studies reported a relative risk of
293 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
294 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)
295 and 1.7 (95%CI 1.1-2.6) for RV1 and RV5 respectively. We also found that the risk
296 decreased, albeit remaining non-significant, after adjustment for breast feeding and presence
297 of concomitant disease within the 2 weeks prior to hospitalization, suggesting a protective
298 role for breastfeeding.

299 We also noted a significant relation between the occurrence of acute gastroenteritis during the
300 2 weeks prior to IS, with a two-fold increase in risk of IS. In our multivariate analysis, we
301 considered gastroenteritis as a variable of interest, and forced this variable in the model,
302 despite a p-value of 0.31 by univariate analysis. This choice was based on previous literature

303 data reporting a significant association between gastroenteritis and IS, and in this regard, our
304 findings are in line with previous publications [18] [26].

305 One of the strengths of this study is the quality of the data recorded. Indeed, exhaustiveness of
306 the recorded data was verified using diagnostic codes from the medical informatics systems
307 with capture-recapture analysis [17,35], and showed excellent overall exhaustiveness. A
308 further strength is the reliable quality of the data thanks to systematic monitoring and quality
309 control systems implemented to ensure the data recorded were verified and accurate.

310 The main limitation of our study is the lack of statistical power due to poor vaccine coverage
311 rates. There are two main reasons for this poor vaccine coverage. First, at the time of the
312 study, there were no recommendations regarding the rotavirus vaccine from the national
313 health authorities and therefore no reimbursement for this vaccine by the national health
314 insurance system .Secondly, scepticism in relation to vaccination in general is highly
315 prevalent in France [36]. This attitude probably impacted negatively on the power of this
316 study, and more generally, poses a problem for the statistical power of analyses linked to risk
317 factors where exposure is the lowest. Finally, there may be potential for residual confounding.
318

319 **5. Conclusion**

320
321 This study highlights potential risk factors implicated in the occurrence of IS. The occurrence
322 of acute gastroenteritis in the 2 weeks prior to hospitalization is a significant risk factor for IS.
323 Infant formula alone or combined with breastfeeding was also found to be a significant risk
324 factor for the occurrence of IS. The limited statistical power and the low vaccine coverage
325 likely preclude detection of a significant increase in the risk of IS related to rotavirus
326 vaccination.

327

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350 **References**

- 351 [1] Samad L, Cortina-Borja M, Bashir HEI, Sutcliffe AG, Marven S, Cameron JC,
352 et al. Intussusception incidence among infants in the UK and Republic of
353 Ireland: a pre-rotavirus vaccine prospective surveillance study. *Vaccine*
354 2013;31:4098–102. doi:10.1016/j.vaccine.2013.06.084.
- 355 [2] Jenke AC, Klaassen-Mielke R, Zilbauer M, Heininger U, Trampisch H, Wirth
356 S. Intussusception: incidence and treatment -insights from the nationwide
357 German surveillance. *J Pediatr Gastroenterol Nutr* 2011;52:446–51.
358 doi:10.1097/MPG.0b013e31820e1bec.
- 359 [3] Buettcher M, Baer G, Bonhoeffer J, Schaad UB, Heininger U. Three-year
360 surveillance of intussusception in children in Switzerland. *Pediatrics*
361 2007;120:473–80. doi:10.1542/peds.2007-0035.
- 362 [4] Chen YE, Beasley S, Grimwood K, New Zealand Rotavirus Study Group.
363 Intussusception and rotavirus associated hospitalisation in New Zealand.
364 *Arch Dis Child* 2005;90:1077–81. doi:10.1136/adc.2005.074104.
- 365 [5] Justice FA, Auldist AW, Bines JE. Intussusception: trends in clinical
366 presentation and management. *J Gastroenterol Hepatol* 2006;21:842–6.
367 doi:10.1111/j.1440-1746.2005.04031.x.
- 368 [6] Fotso Kamdem A, Vidal C, Pazart L, Leroux F, Pugin A, Savet C, et al.
369 Incidence of acute intussusception among infants in eastern France:
370 results of the EPIstudy trial. *Eur J Pediatr* 2017;176:301–9. doi:10.1007/s00431-
371 016-2838-z.
- 372 [7] Centers for Disease Control and Prevention (CDC). Withdrawal of
373 rotavirus vaccine recommendation. *MMWR Morb Mortal Wkly Rep*
374 1999;48:1007.
- 375 [8] Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA,
376 et al. Intussusception among infants given an oral rotavirus vaccine. *N*
377 *Engl J Med* 2001;344:564.
- 378 [9] Leino T, Ollgren J, Strömberg N, Elonsalo U. Evaluation of the
379 Intussusception Risk after Pentavalent Rotavirus Vaccination in Finnish
380 Infants. *PLoS One* 2016;11:e0144812. doi:10.1371/journal.pone.0144812.
- 381 [10] Patel MM, López-Collada VR, Bulhões MM, De Oliveira LH, Bautista
382 Márquez A, Flannery B, et al. Intussusception risk and health benefits of
383 rotavirus vaccination in Mexico and Brazil. *N Engl J Med* 2011;364:2283–92.
384 doi:10.1056/NEJMoa1012952.
- 385 [11] Rha B, Tate JE, Weintraub E, Haber P, Yen C, Patel M, et al. Intussusception
386 following rotavirus vaccination: an updated review of the available
387 evidence. *Expert Rev Vaccines* 2014;13:1339–48.
388 doi:10.1586/14760584.2014.942223.
- 389 [12] Carlin JB, Macartney KK, Lee KJ, Quinn HE, Buttery J, Lopert R, et al.
390 Intussusception risk and disease prevention associated with rotavirus
391 vaccines in Australia's National Immunization Program. *Clin Infect Dis*
392 2013;57:1427–34. doi:10.1093/cid/cit520.
- 393 [13] Buttery JP, Standish J, Bines JE. Intussusception and rotavirus vaccines:
394 consensus on benefits outweighing recognized risk. *Pediatr Infect Dis J*

- 395 2014;33:772–3. doi:10.1097/INF.0000000000000359.
- 396 [14] Yih WK, Lieu TA, Kull dor ff M, Mar tin D, McMahill -Wal raven CN, Platt R,
397 et al. Int ussusception risk after rot avirus vaccination in U.S. infants. *N*
398 *Engl J Med* 2014;370:503–12. doi:10.1056/NEJMoa1303164.
- 399 [15] Bines JE, Kohl KS, For ster J, Zanardi LR, Davis RL, Hansen J, et al. Acute
400 int ussusception in infants and children as an adverse event following
401 immunization: case definition and guidelines of data collection, analysis,
402 and present ation. *Vaccine* 2004;22:569–74.
- 403 [16] Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H.
404 European society for pediatric gastroenterology, hepatology, and
405 nutrition/european society for pediatric infectious diseases evidence-
406 based guidelines for the management of acute gastroenteritis in
407 children in Europe: Update 2014. *J Pediatr Gastroenterol Nutr* 2014;59:132–
408 52. doi:10.1097/MPG.0000000000000375.
- 409 [17] Böhning D, Patilea V. A capture--recapture approach for screening using
410 two diagnostic tests with a availability of disease status for the test
411 positives only. *J Am Stat Assoc* 2008;103.
- 412 [18] Bines J, Ivanoff B. Acute int ussusception in infants and children.
413 Incidence, clinical present ation and management: a global perspective.
414 *World Heal Organ Dep Vaccines Biol Geneva*, Oct 2002, WHO/V&B/0219 2002.
- 415 [19] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP,
416 et al. The Strengthening the Reporting of Observational Studies in
417 Epidemiology (STROBE) Statement: guidelines for reporting observational
418 studies. *Int J Surg* 2014;12:1495–9. doi:10.1016/j.ijsu.2014.07.013.
- 419 [20] Blanch AJ, Perel SB, Acworth JP. Paediatric int ussusception: epidemiology
420 and outcome. *Emerg Med Australas* 2007;19:45–50. doi:10.1111/j.1742-
421 6723.2007.00923.x.
- 422 [21] Bines JE, Patel M, Parashar U. Assessment of Post licensure Safety of
423 Rotavirus Vaccines, with Emphasis on Int ussusception. *J Infect Dis*
424 2009;200:S282. doi:10.1086/605051.
- 425 [22] Khumjui C, Doung-ngern P, Sermgew T, Smit suwan P, Jiraphongsa C.
426 Incidence of int ussusception among children 0–5 years of age in Thailand,
427 2001–2006. *Vaccine* 2009;27:F116–9. doi:10.1016/j.vaccine.2009.09.003.
- 428 [23] Navarro OM, Daneman A, Chae A. Int ussusception: The Use of Delayed,
429 Repeated Reduction Attempts and the Management of Int ussusceptions
430 due to Pathologic Lead Points in Pediatric Patients. *Am J Roentgenol* 2004.
431 doi:10.2214/a.jr.182.5.1821169.
- 432 [24] Johnson B, Gargiullo P, Murphy TV, Parashar UD, Patel MM.
433 Sociodemographic and dietary risk factors for natural infant
434 int ussusception in the United States. *J Pediatr Gastroenterol Nutr*
435 2010;51:458–63. doi:10.1097/MPG.0b013e3181d3273f.
- 436 [25] Iyngkaran N, Yadav M, Boey CG, Lam KL. Severity and extent of upper
437 small bowel mucosal damage in cow's milk protein-sensitive enteropathy.
438 *J Pediatr Gastroenterol Nutr* 1988;7:667–74. doi:3183870.
- 439 [26] Mansour AM, El Koutby M, El Barbary MM, Mohamed W, Shehata S, El
440 Mohammady H, et al. Enteric viral infections as potential risk factors

- 441 for intussusception. *J Infect Dev Ctries* 2013;7:28–35.
- 442 [27] Nylund CM, Denson LA, Noel JM. Bacterial enteritis as a risk factor for
443 childhood intussusception: a retrospective cohort study. *J Pediatr*
444 2010;156:761–5. doi:10.1016/j.jpeds.2009.11.026.
- 445 [28] Bahl R, Saxena M, Bhandari N, Taneja S, Mathur M, Parashar UD, et al.
446 Population-based incidence of intussusception and a case-control study
447 to examine the association of intussusception with natural rotavirus
448 infection among Indian children. *J Infect Dis* 2009;200 Suppl :S277-81.
449 doi:10.1086/605045.
- 450 [29] El-Hodhod MA, Nassar MF, Ezz El-Arab S, Ahmed EF. Rotavirus fecal
451 antigen retrieval in infantile intussusception. *Eur J Clin Microbiol Infect*
452 *Dis* 2008;27:879–81. doi:10.1007/s10096-008-0506-6.
- 453 [30] Velázquez FR, Luna G, Cedillo R, Torres J, Muñoz O. Natural rotavirus
454 infection is not associated to intussusception in Mexican children.
455 *Pediatr Infect Dis J* 2004;23:S173–8.
- 456 [31] Bines JE, Liem NT, Justice FA, Son TN, Kirkwood CD, de Campo M, et al. Risk
457 factors for intussusception in infants in Vietnam and Australia:
458 adenovirus implicated, but not rotavirus. *J Pediatr* 2006;149:452–60.
459 doi:10.1016/j.jpeds.2006.04.010.
- 460 [32] Hsu HY, Kao CL, Huang LM, Ni YH, Lai HS, Lin FY, et al. Viral etiology of
461 intussusception in Taiwanese childhood. *Pediatr Infect Dis J* 1998;17:893–8.
- 462 [33] Berkson J. Limitations of the application of the fourfold contingency
463 table. *Biometrics Bull* 1946;2:47–53. doi:10.2307/3002000.
- 464 [34] Rosillon D, Buyse H, Friedl and LR, Ng S-P, Velázquez FR, Breuer T. Risk of
465 Intussusception After Rotavirus Vaccination: Meta-analysis of
466 Postlicensure Studies. *Pediatr Infect Dis J* 2015;34:763–8.
467 doi:10.1097/INF.0000000000000715.
- 468 [35] Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods
469 and limitations. *Epidemiol Rev* 1995;17:243–64.
- 470 [36] Larson HJ, de Figueiredo A, Xiaohong Z, Schulz WS, Verger P, Johnston IG, et
471 al. The state of vaccine confidence 2016: global insights through a 67-
472 country survey. *EBioMedicine* 2016.

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

	n= 115	%
Clinical symptoms		
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
Bil ed-st ained vomiting	13	11.30
Constipation and lack of gas	14	12.17
Dehydration	9	7.83
Physical signs		
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

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

	Cases n=115	Controls n= 457	OR (95%CI*)	P
Birth weight				
< 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 Breast feeding	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	< .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	< .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)	

489 * : CI, confidence interval
490 † mean ± standard deviation = 7.73 ± 1.30 (cases); .77 ± 1.59 controls ; OR 0.97, 95% CI 0.7–
491 1.182
492 ‡ mean ± standard deviation = 67.44 ± 5.59 (cases); . 66.68 ± 6.47 (controls) ; OR 1.06, 95% CI
493 1.00-1.12
494 ** mean ± standard deviation = 39.15 ± 1.59 (cases); . 39.02 ± 2.27 (controls) ; OR 1.03, 95% CI
495 0.93-1.13
496

497 **Table 3** Multivariable logistic regression model of the risk factors for intussusception in
 498 infants

	Adjusted OR (95% CI) ^a	p
Infant formula alone or with breast feeding	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

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

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

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

	1st year	2nd Year	3rd Year	4th year	Total
	April 08 - March 09	April 09 – March 10	April 10 – March 11	April 11 – March 12	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					
RV1 (Rotarix®) Vaccination Coverage rate	97 829	97 176	96 946	95 164	387 115
	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

510 **Figure Legend:**

511 **Figure 1** Interval between Rotavirus Vaccination and Hospitalization in cases and controls

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