

Unparalleled patterns of intussusception and rotavirus gastroenteritis hospitalization rates among children younger than six years in Italy

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Key words: Intussusception, intestinal invagination, children, rotavirus, hospitalization rates

Parole chiave: Intussuscezione, invaginazione intestinale, bambini, rotavirus, tassi di ospedalizzazione

Abstract

Background. No nationwide studies are available so far in Italy to analyze the annual trend of hospitalizations for intussusception (IS) comparing it with that of rotavirus gastroenteritis (GARV), therefore a survey was undertaken to assess the incidence rates of IS and GARV in children hospitalized between 2005 and 2014 in Italy.

Study design. A retrospective observational study was conducted analyzing the Italian Hospital Discharge Database (HDD), including a study on all hospitalizations bearing a primary or secondary diagnoses coded as 560.0 along the decade 2005-2014.

Methods. The trend and seasonality of hospitalizations rates (HRs) for IS were analyzed stratifying by gender and age groups. The statistical significance of temporal trend was determined using the analysis of the slope of the regression line.

For the same period, data related to national hospitalizations for GARV (code 008.61 in any diagnosis) were analyzed for comparative purpose.

Results. A total of 6,074 hospitalizations for IS in children aged <6 years were recorded. A statistically significant increase of HRs was seen for male, female, 12-23 months and 24-71 months age groups. However, in children within the first year of life there was a downward trend. The analysis of the distribution of the HRs by months of hospitalization showed the absence of seasonality, in contrast to HRs for GARV.

Conclusions. Our analysis confirmed the occurrence of the incidence peak of IS hospitalizations in children aged seven months. HRs decreased after the first year of life, replicating an age distribution that is also observed for other paediatric infectious diseases. Nevertheless, the total trend of HR was increasing.

In Italy, IS HRs in the pre-vaccination era resulted in line with those described for other European countries, with an increasing trend and the annual slope of IS hospitalization turned out to unparallel the GARV HRs.

Introduction

Intussusception (IS), a medical condition in which one segment of the intestine invaginates into a more distal segment, is the most common cause of intestinal obstruction in children younger than 2 years of age (1, 2).

The IS pathogenic mechanism is still unclear and currently defined as idiopathic (3).

The rate of spontaneous IS varies among different continents and it is higher in some Countries: globally, the incidence of intussusception without vaccination is 74/100,000 (range: 9-328) among children

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<1 year old. In Europe, the incidence ranges from 20 to 72/100,000 among children <1 year old (4, 5).

Interest in IS from the scientific community arose when an IS increased rate was associated with the first licensed rotavirus vaccine (Rotashield) implementation (6). Currently, two live, oral, attenuated rotavirus vaccines are licensed and marketed worldwide. Although it is known that rotavirus vaccination may slightly increase the risk of IS, universal immunization against rotavirus (RV) is widely recommended (7-12).

As in other parts of the world, in Italy rotavirus gastroenteritis (GARV) is the prominent cause of acute gastroenteritis (AGE) hospitalizations, being responsible of 33-50% of AGE cases (13-14). It was estimated that GARV hospitalizations in Italy are in the range of 15,000/year (15).

As no nationwide studies are available so far in Italy to analyze the annual trend of hospitalizations for intussusception (IS) comparing it with that of rotavirus gastroenteritis (GARV), a survey was undertaken to assess the incidence rates of IS and GARV in children hospitalized during the decade 2005 to 2014 in Italy.

Methods

A retrospective observational study was carried on analyzing the Italian Hospital Discharge Database (HDD) obtained from the Ministry of Health, related to the hospitalizations for IS in children <6 years in Italy in the period 2005-2014 (16). All hospitalizations bearing a primary or secondary (up to five) diagnoses coded as 560.0 (intussusception of the colon or of the bowel) according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) were included in the study. For each hospital admission, additional information as sex, age,

patient's citizenship, kind of hospitalization, length of stay, regional code and discharge month were obtained.

The characteristics of the study sample were analyzed using descriptive statistics. The discrete and nominal variables were expressed by frequencies and percentages; the continuous variables were expressed as mean values and standard deviations (SD).

Hospitalization rates (HRs/100,000) for IS and 95% confidence interval (95% CI) were calculated for every year as the ratio between the number of hospital discharges and the resident populations aged <6 years. Population data for the 2005-2014 period was obtained from the Italian Institute of Statistics (ISTAT), which registers the National population, by age group, as of the January 1st for each year (17).

The trend and seasonality of HRs for IS were analyzed stratifying by gender and by age (0-11 months, 12-23 months, 24-71 months). The statistical significance of the temporal trend was determined using the analysis of the slope of the regression line between HRs and years of observation.

For the same period, data related to national hospitalizations for GARV (ICD9-CM code 008.61 in any diagnosis), for the same age groups investigated for IS, were analyzed and HRs estimated. Repeated cases of hospitalization identified through an anonymous identification number were excluded from the analysis on incidence of hospitalizations for both of them.

The standard introduced for statistical significance was $p < 0.05$. Data analysis was performed using STATA/IC 12.1.

Results

In the decade 2005-2014 a total of 6,074 hospitalizations for IS in children aged <6 years were recorded in Italy, with a percentage of re-admission within 12 months accounting for 13.53% (822/6,074).

Excluding re-admissions (Table 1), the average of hospitalizations per year was found to be 525.20 (SD \pm 75.59) and the average length of stay of 4.25 days (SD \pm 5.76). The 64.81% (3,404/5,252) of admissions involved male children and more than a third of cases involved children within the first year of life (37.40%, 1,964/5,252). The 91.95% (4,829/5,252) of children hospitalized for IS had Italian citizenship and almost all of hospitalizations (99.35%, 5,218/5,252) were ordinary hospital admissions. The average hospitalization rate (AHR) for the studied decade amounted to 15.72/100,000 children and the stratification by geographical location showed AHR for the Centre (25.54/100,000 children) equal to about twice the AHR of the northern (13.47/100,000 children) and southern and islander regions (13.37/100,000 children) of the Country.

By the analysis of the temporal trend, a statistically significant increase of HRs was seen for both males (M) (β -coefficient = 0.78, p-value = 0.002) and females (F) (β -coefficient = 0.58, p value = 0.001), reaching the highest values in 2012 (HR M = 24.53/100,000 children; HR F = 13.89/100,000 children) (data not shown in Tables).

The stratification of HRs by age groups (Figure 1) showed that this increasing trend (HR TOT: β -coefficient = 0.68, p-value <0.001) is mainly due to 12-23 months (β -coefficient = 1.36, p-value = 0.001) and 24-71 months (β -coefficient = 0.85, p-value <0.001) age groups, as in children within the first year of life there was a downward trend (an average of 0.45/100,000 children per year; β -coefficient = -0.45, p-value = 0.143), though not statistically significant. However, in this age group, HRs were higher than the rates in the other age classes, with a peak

Table 1 - Characteristics of hospitalizations for IS in Italy (2005-2014).

Number of IS hospitalizations in the decade	N=5,252
Means of hospitalizations per year \pm SD	525.20 \pm 75.59
Days of hospitalization, mean \pm SD	4.25 \pm 5.76
Gender, n (%)	
Male	3,404 (64.81)
Female	1,848 (35.19)
Mean age (months \pm SD)	22.65 \pm 18.01
Age classes (months), n (%)	
0-11	1,964 (37.40)
12-23	1,191 (22.68)
24-71	2,097 (39.93)
Citizenship	
Italian	4,829 (91.95)
Foreign	423 (8.05)
Type of hospital admission	
Ordinary	5,218 (99.35)
Day Hospital	34 (0.65)
Average Hospitalization Rate x 100,000 children	
Total	15.72
By geographical location	
North	13.47
Centre	25.54
South and Islands	13.37

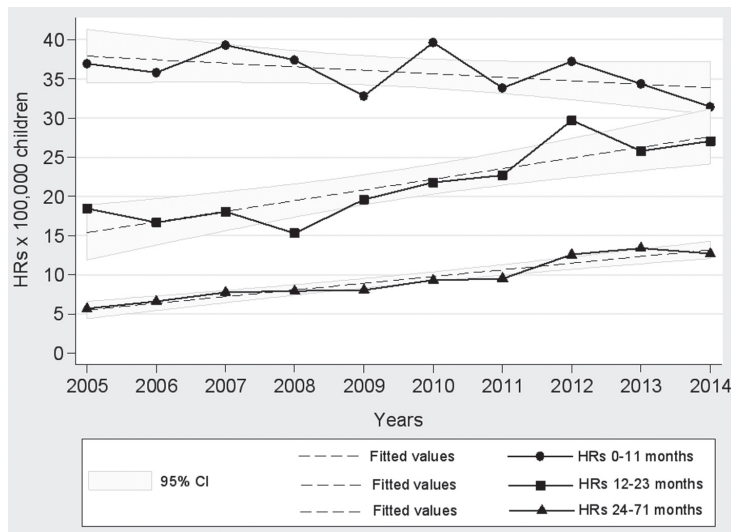


Figure 1 - Temporal trend of hospitalization rates for IS by age groups.

Trend test. HRs 0-11 months: β -coefficient = -0.45, p-value = 0.143; HRs 12-23 months: β -coefficient = 1.36, p-value = 0.001; HRs 24-71 months: β -coefficient = 0.85, p-value <0.001.

of 39.66/100,000 children hospitalizations in 2010.

As highlighted by Figure 2, the HRs for IS according to the age progressively increases to reach a peak of 4.4/100,000 children for those 28 weeks old, then

decreases progressively until the age of 52 weeks, to remain practically the same until the age of 92 weeks.

The analysis of the distribution of the HRs by months of hospitalization for IS (Figure 3) showed the absence of seasonality,

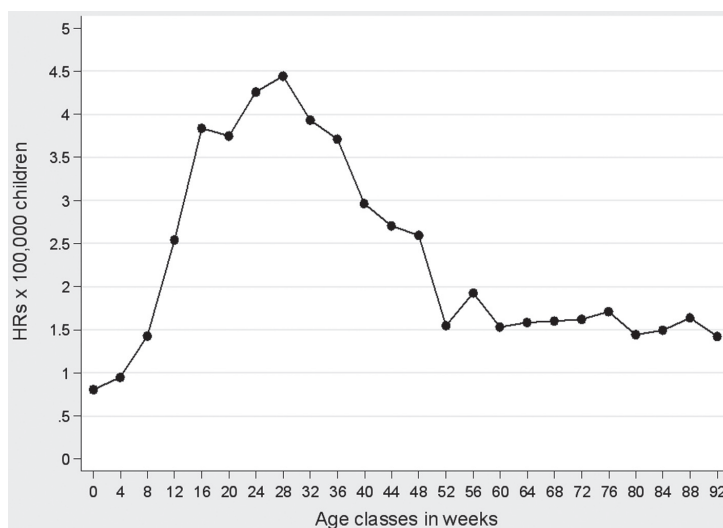


Figure 2 - Age distribution (weeks) of the hospitalization rates for IS in children aged <2 years.

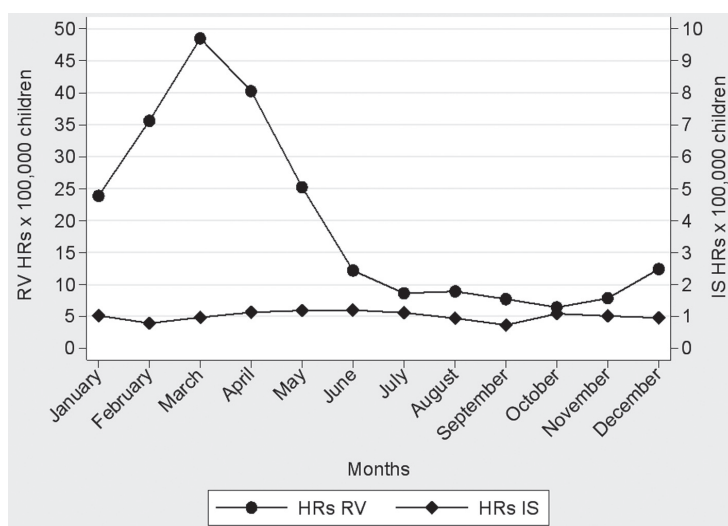


Figure 3 - Comparison of seasonality of hospitalization rates for IS and RV.

in contrast to HRs for RV, for which a typical seasonality, with a peak in March (AHR = 49/100,000 children) was observed.

A total of 3,270 admissions were coded by 560.0 code alone, not associated with Secondary Diagnoses. The most frequent conditions coded with IS among the 1,982 remaining admissions were abdominal pain (4.2%, 84/1,982), melena-rectal bleeding (9.1%, 181/1,982), Meckel's diverticulum (6.0%, 120/1,982) and mesenteric lymphadenitis (7.2%, 142/1,982).

Discussion and conclusions

WHO recommends epidemiological surveillance for IS, evaluating the baseline incidence before the introduction of vaccination (18). Although the risk/benefit balance is definitely in favour of vaccination, the IS risk assessment should be available before the paediatric programs of RV vaccination are implemented (7, 12, 19).

To our knowledge, this is the first Italian nationwide study analyzing the patterns of IS and GARV hospitalization rates among

children younger than 6 years. The analysis confirmed the occurrence of the incidence peak of IS hospitalizations in children aged 7 months (28 weeks). IS incidence in Italy was previously estimated at about 5/100,000 persons/year by using a paediatric database as information flow (20). In the present study AHR turned out to be 19.84/100,000 in paediatric population and 35.89/100,000 in <1 year children. Such a discrepancy might be addressed considering that children in the first year of life with suspected IS are more likely to refer directly to the hospital, and the episode may not be transcribed into the consulting paediatrician database. Previous work reported at national level a peak of cumulative HR in children between 25 and 32 weeks of life in line with the present study; however, HRs should not be directly compared as other codes, in addition to 560.0, and a broader study population (children 0-15 years old) were considered (21). Further, a IS peak at 8 month of age was recently described in Sicily (22). In line with previous reports, a male predominance in the incidence of IS hospitalizations was confirmed (22-27).

Unlike what was found in other contexts, the monthly distribution of HRs for RV in Italy, with a seasonal peak in March, did not coincide with that of HRs for IS, with the highest HR in June (28, 29). In addition, while the peak of HRs for IS was recorded in children of 7 months of age, the peak of HRs for RV was observed in children 12-23 months of age (26, 28-30).

HRs decreased after the first year of life, replicating an age distribution that is observed also for other paediatric diseases of infectious origin (31). Nevertheless, the total trend of HR was increasing. An increase in IS HR was also recently reported for Sicily by Costantino et al (22). Such a trend was reported also in France, where the incidence of IS rose from 31.9 cases per 100,000 visits in 2009 to 74.1 in 2013 (odds ratio, 2.32; 95% confidence interval 1.74 - 3.11) and it was considered unrelated with rotavirus vaccination (32).

The limitations of the study presented here are mainly linked to the HDD features. As a matter of fact, neither the database allows us to detect the cases treated in Emergency Departments, nor it was possible to collect data on clinical severity of IS.

As a conclusion, in Italy, IS HRs in the pre-vaccination era resulted in line with those described for other European countries, with an increasing trend. The annual slope of IS hospitalizations turned out to unparallel the GARV hospitalization trend. Continuous monitoring of IS and GARV HDD may contribute to a good management of the paediatric extensive RV vaccination, once in place.

Riassunto

Modelli dissimili per i tassi di ospedalizzazione per intussuscezione e gastroenterite da rotavirus nei bambini di età inferiore ai 6 anni in Italia

Premessa. In Italia non sono disponibili studi su scala nazionale che analizzino l'andamento annuale dei ricoveri per intussuscezione (IS) confrontandolo con

quello delle gastroenteriti da rotavirus (GARV), pertanto è stata condotta un'indagine volta a valutare l'incidenza dei ricoveri per IS e per GARV nei bambini ospedalizzati tra il 2005 e il 2014 in Italia.

Disegno dello studio. È stato condotto uno studio osservazionale retrospettivo analizzando le Schede di Dimissione Ospedaliera (SDO), includendo nello studio tutte le ospedalizzazioni recanti il codice 560.0 in diagnosi principale o in una delle diagnosi secondarie per la decade 2005-2014.

Metodi. Il trend e la stagionalità dei tassi di ospedalizzazione (TO) per IS sono stati analizzati stratificando per genere e classi di età. La significatività statistica del trend temporale è stata determinata attraverso l'analisi della pendenza della retta di regressione. Per lo stesso periodo a scopo comparativo sono stati analizzati i tassi di ospedalizzazione per GARV (codice 008.61 in qualsiasi diagnosi).

Risultati. Sono state registrate un totale di 6.074 ospedalizzazioni per IS nei bambini di età < 6 anni. È stato osservato un aumento statisticamente significativo dei TO nei maschi, nelle femmine e nelle fasce d'età 12-23 mesi e 24-71 mesi. Per i bambini entro il primo anno di vita, invece, i TO sono risultati in controtendenza. L'analisi della distribuzione dei TO per mese di ospedalizzazione ha mostrato l'assenza di stagionalità al contrario di quanto osservato per i TO per GARV.

Conclusioni. La nostra analisi conferma il picco di incidenza delle ospedalizzazioni per IS nei bambini di 7 mesi di vita. I TO sono diminuiti dopo il primo anno di vita, replicando una distribuzione per età che si osserva anche per altre malattie infettive pediatriche. Tuttavia, il trend totale dei TO è risultato in aumento.

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