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Review Article

Epidemiological Surveillance for Italian Childhood Gastroenteritis and Intussusceptions

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Abstract

In 2009 the World Health Organization recommended rotavirus vaccination for all children, and the promotion of vaccination should occur in parallel with a post-marketing surveillance strategy. We review the epidemiological data on pediatric hospitalizations for gastroenteritis and intussusceptions, a rare adverse reaction to rotavirus vaccine, in Italian children aged <6 years.

The analysis highlighted that rotavirus gastroenteritis hospitalizations in Italy are still relevant and generate significant costs to the National Health care System, the evidence of natural changes in incidence of intussusceptions that underline the importance of increasing the knowledge of the natural history of this condition, the independence of the intussusceptions with respect to rotavirus gastroenteritis.

Continuous monitoring of rotavirus gastroenteritis and intussusceptions hospital discharge database may contribute to a good management of the pediatric extensive rotavirus vaccination, once in place.

ABBREVIATIONS

GE: Gastroenteritis; RV: Rotavirus; WHO: World Health Organization; RVGE: Rotavirus Gastroenteritis; IS: Intussusceptions; VGE: Viral Gastroenteritis; HR: Hospitalization Rate; PD: Principal Diagnosis; SD: Secondary Diagnosis; HDD: Hospital Discharge Database; GEIS: Gastroenteritis with Concurrent Intussusceptions

INTRODUCTION

Acute gastroenteritis (GE) severity is linked to aetiology, and rotavirus (RV) accounts for most of severe cases [1,2].

In 2009 the World Health Organization (WHO) recommended RV vaccination for all children and post-marketing surveillance of its safety, as the first anti-RV vaccine, the Rota Shied, authorized by the FDA in 1998, was removed from the market because the incidence of cases of intussusception (IS), the most common cause of acute intestinal obstruction in infants, was higher than expected [3,4].

Currently, two new live, oral, attenuated RV vaccines (RV1, Rotarix®, GlaxoSmithKline Biological) e Rota Teq (RV5, Rotateq®, Merck & Co., Inc.) are licensed and marketed worldwide because they have been found to be safe and effective. Although it is known that RV vaccination may led to a slight increase of the baseline incidence of IS, so that possibility is included in the data sheets of the two vaccines, considering the current scientific evidence there is no objection to the recommendation of universal immunization because of the high burden of RV gastroenteritis (RVGE) and because IS remains an extremely rare event [5-7].

Nevertheless, considering the various vaccine strategies of different European countries, the promotion of vaccination should occur in parallel with a post-marketing surveillance strategy [5].

Particularly, in Italy where the two RV vaccines received the marketing authorization in 2007, the use of RV is expected to increase as the inclusion of RV vaccination in the current National Immunization Plan (NIP) in January 2017 [8].

In this article we reviewed the major epidemiological features of GE and IS in the Italian pediatrics population, with particular attention to children aged <6 years. In particular, we here synthesized the main findings of our retrospective observational studies using the Italian Hospital Discharge Database (HDD), obtained from Ministry of Health (Processing National HDD, Ministry of Health, General Directorate for Health Planning, VI Office), as information flow. All hospitalizations bearing a

primary or secondary (up to five) diagnoses coded as 560.0 (intussusceptions of the colon or of the bowel) and/or 009–009.3 (unspecified etiology gastroenteritis of presumed infectious etiology), 558.9 (unspecified etiology gastroenteritis of presumed noninfectious etiology), 008.61–69 (viral gastroenteritis, among which the rotavirus gastroenteritis, referred to as RVGE, was identified by code 008.61), 001–005 and 008–008.5 (bacterial gastroenteritis), and 006–007 (parasitic gastroenteritis), according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), were included in these studies. Then we compared our findings with national and international literature.

EPIDEMIOLOGY OF ROTAVIRUS GASTROENTERITIS

By a retrospective observational study designed to estimate the proportion of RVGE among children aged <6 years old who were diagnosed with GE and admitted to hospitals in Italy during the years 2005–2012, a total of 334,982 hospital discharge forms were collected, being 79,344 hospitalizations associated with RV, equal to 68.61% of all viral gastroenteritis (VGE) [7].

These data confirmed that RVGE still represents the greatest proportion of hospitalized VGE, in agreement with previous results either in Italy or in other parts of Europe or USA [6,9-12].

Most RVGE hospitalizations (80.79%) occurred in children younger than 3 years old, mainly infants of 12–23 months old had the highest number of cases (33.67%), then children aged 0–11 months old (28.67%).

RVGE hospitalizations seasonal peak was during December - March every year.

The average hospitalization rate (HR) was 296 per 100,000 children: 146 per 100,000 children for RVGE in principal diagnosis (PD) and 150 per 100,000 children for RVGE in secondary diagnosis (SD), with a downward trend for the HRs for RVGE in PD and an increasing trend for HRs for RVGE in SD. Indeed, we provided evidence that there was a switch in the position of RVGE diagnosis from PD to SD [Figure 1]: since 2008 the HRs for RVGE in SD exceeds those for RVGE in PD, with the highest peak in 2010 (total RV HR: 339 per 100,000 children). These findings support the need of including both PD and SD, which also includes nosocomial infection forms and the incidence of which was estimated in Italy by 5.3% in children under 30 months, in RV hospitalizations analysis [6,13].

No explicit reasons justifying such a switch could be found out, but we could hypothesize that the turnaround of RVGE HRs in PD than HRs in SD recorded since 2008 can be attributed in part to a strategy of containment of health spending, as well as to greater remuneration provided for the code in the PD, such as that relating to dehydration (49.77% of PD in cases of SD RVGE), when RV infections are coded in SD [14].

Another possible explanation is represented by the underestimation of the phenomenon of nosocomial RVGE, which, according to several studies, are the main cause of VGE acquired by hospitalized children and they are responsible for increased length of hospital stay compared with community-acquired RV infections, resulting, therefore, in a rise of costs for the use of additional resources [13,15-17].

Nevertheless, further studies would be needed to confirm these hypotheses. Despite some limitations due to the hospital discharge database (HDD) synthetic contents and low potential for clinical interpretation, the analysis demonstrated that RVGE hospitalizations in Italy are still relevant and generate significant

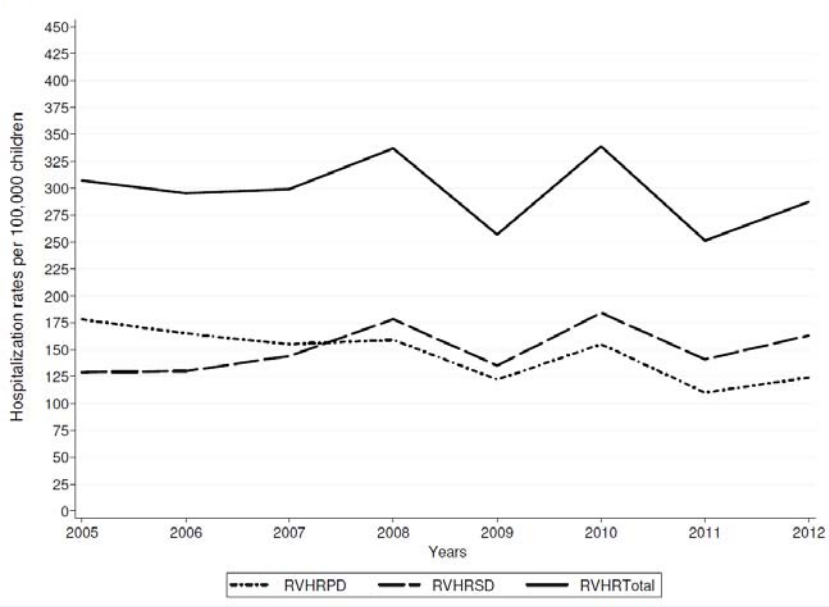

Figure 1 Hospitalization rates (HRs) per 100,000 of rotavirus gastroenteritis (RVGE) in principal (PD) and secondary (SD) diagnosis among children <6 y of age in 2005-2012.
Trend test: HRs RVGE PD (RVHRPD): β-coefficient=-8.21; p=0.010; HRs RVGE SD (RVHRSD): β-coefficient=4 .40; p=0.209; Total HRs RV (RVHR Total): β-coefficient=-3.80; p=0.487 [7].

costs to the National Health care System. As observed in other Countries, the introduction of RV universal mass vaccination in Italy might consistently reduce morbidity and associated medical costs [18].

EPIDEMIOLOGY OF INTUSSUSCEPTIONS

IS is the most common cause of intestinal obstruction in infants, with 80% of cases occurring before 2 years [19].

IS occurs when a proximal portion of the bowel invaginates into a distal portion; ileocolic (ileum invaginated into the colon) is the most common form of this condition in infants and young children [20].

According to hospital-based studies, the incidence of IS in Europe in the paediatric population ranged from 0.66 to 2.24 per 1,000 children for inpatient departments and between 0.75 and 1.00 per 1,000 children admitted to the emergency ward, with studies including different age groups [21].

In Italy, the IS incidence rate based on HDD ranged from 15.72 to 21.00 per 100,000 children, depending on the reference population and the diagnoses codes considered [22,23].

Analyzing the IS incidence background in Italy, 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) (data not shown in Tables).

The stratification of HRs by age groups Figure (2) showed that this increasing trend (HR TOT: β-coefficient = 0.68, p-value <0.001) was 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, the background rates were higher than the rates in the other age classes, within the European ranges and in line with those detected in different European countries [23-28].

The incidence peak of IS hospitalizations occurred in children aged seven months (data none shown in Figures).

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 (data not shown in Figures) [6,7].

An increase in IS hospitalization rates was also recently reported in France, where the incidence of IS rose from 31.9 cases per 100,000 visits in 2009 to 74.1 in 2013 and it was considered unrelated to RV vaccination [29].

These scientific evidences about natural changes in incidence of IS underline the importance of increasing the knowledge of the natural history of this condition, deepening the knowledge of the role played by individual and environmental factors in order to conduct a better epidemiological surveillance for IS.

RISK FACTORS FOR INTUSSUSCEPTIONS IN CHILDHOOD GASTROENTERITIS

Although the pathogenic mechanism of IS has not yet been clarified, its major cause is suggested to be swelling and lymph node hyperplasia of Peyer's patch in the ileum secondary to infection, that has been suggested as the 'lead point' in its pathogenesis [30].

Upper respiratory tract infection, adenovirus- and bacterial-associated gastroenteritis have been widely thought to contribute [31].

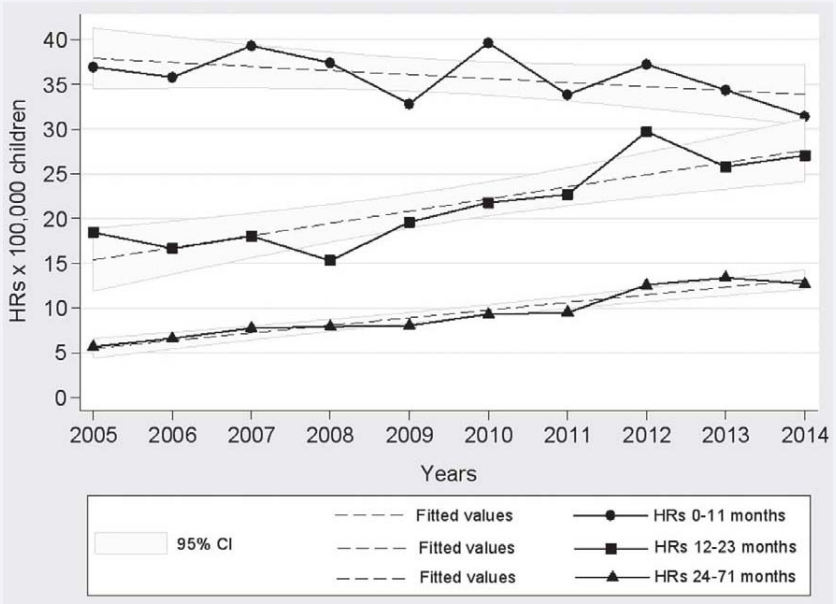

Figure 2 Temporal trend of hospitalization rates (HRs) for intussusceptions (IS) by age groups.
Trend test: HRs 0-11 months: β-coefficient = -0.45, p-value = 0.143; HRs 12-23 months: β-coefficient = 1.36, p-value = 0.001; HRs 24-71 months: β-coefficient = 0.85, p-value <0.001 [22].

Table 1: Hospitalization rates per 100,000 children for intussusceptions with concurrent gastroenteritis (GEIS) by age group [32].

	2005	2006	2007	2008	2009	2010	2011	2012	AHR	β(P-value)
0-11 months	1.80.	1.46	0.9	0.54	1.23	1.78	1.62	0.94	1.28	0.02(0.774)
12-23 months	0.55	0.72	0.54	0.53	0.71	0.87	1.06	1.84	0.85	0.14(0.019)
24-35 months	1.1	0.73	1.6	0.54	1.06	0.53	0.87	1.44	0.98	<0.1(0.950)
36-47 months	0.55	1	0.36	0.53	0.18	0.88	0.52	0.53	0.44	0.04(0.323)
48-59 months	0	1	0.18	0.18	0.18	0	0.17	0.36	0.13	0.03(0.079)
60-71 months	0	0.18	0.18	0	0	0.52	0.53	0.18	0.23	0.05(0.05(0.171)
0-71 months	0.67	0.52	0.63	0.39	0.56	0.76	0.79	0.88	0.65	0.04(0.107)

AHR: Average hospitalization rate (2005-2012); β: coefficient of the trend test
Statically significant trends shows in bold (p-value, 0.05)

We aimed to clarify the role played by enteric pathogens as potential risk factors for IS through a retrospective review of records relating to hospitalizations for GE with (GEIS) or without concurrent IS in Italian children aged <6 years old during the period 2005-2012 [32].

Stratifying the HRs for GEIS by age group (Table 1), it was observed that the 0-11 months class was the most affected by the admission to these contributing causes (average HR for 0-11 months =1.28 per 100,000 children).

However, in this age group the trend decreased, although this decrease was not significant. In contrast, for the other age groups the trend increased; in children between their first and second year of life, in particular, a statistically significant increase of HR, equal to 0.14 x 100,000 children on average per year (trend test: β coefficient =0.14; p =0.019), was estimated.

The estimate of the adjusted ORs for the other factors in the model (Table 2), through a multivariate regression, showed the significant contribution that sex (OR 1.39, 95% CI 1.02 to 1.90) and the different associated SD of GE (unspecified GE of a presumed infectious aetiology: OR 1.82, 95% CI 1.04 to 3.17; viral GE without RV; OR 2.91, 95% CI 1.60 to 5.29; bacterial GE: OR 5.15, 95% CI 2.29 to 11.57) made in the hospitalizations for GEIS.

No association between RVGE and development of IS was observed. The probability of GEIS became statistically significant lower from 12 months of age to ≤ 23 months (OR 0.61, 95% CI 0.40 to 0.91) and for age 48-59 months (OR 0.39, 95% CI 0.17 to 0.92). In Central and Northern Italy there was a greater association with GEIS hospitalizations than in the South: this could suggest in part the influence of environmental factors on the development of IS, and in part it might indicate a different attitude to the deepening diagnostic of this condition in different areas of the country, as evidenced by the average HRs, which were higher in central and northern regions, compared to the South and the Islands.

Table 2: Multivariate logistical regression for the associations between the development of intussusceptions in the presence of gastroenteritis and the explanatory variables (sex, age, secondary diagnosis of gastroenteritis and geographical location) [32].

EXPLANATORY VARIABLES	OR	95%CI
SEX		
Female[a]	1	
Male	1.39	1.02-1.90
AGE		
0-11 months[a]	1	
12-23 months	0.61	0.40-0.91
24-35	1.24	0.83-1.84
36-47	0.87	0.52-1.45
48-59	0.39	0.17-0.92
60-71	0.83	1.41-1.68
SECONDARY DIAGNOSIS of GASTROENTERITIS(GE)		
Unspecifiied GE of Presumed non-infectious aetiology a	1	
Unspecifiied GE of Presumed infectious aetiology	1.82	1.04-3.17
Viral GE(no RV)	2.91	1.60-5.29
GERV	0.99	0.53-1.88
Bacterial GE	5.15	2.29-11.57
GEOGRAPHICAL LOCATION		
South and Islands[o]	1	
Centre	2.49	1.62-3.83
North	2.97	2.07-4.27

[a]: Reference category; [o]:adjsusted ORs for the other factor in the model

DISCUSSION & CONCLUSION

RVGE continues to cause substantial morbidity and mortality worldwide and this burden of disease indicates that an effective, safe RV vaccination is needed. Surveillance for IS may be instrumental in further assessing the safety of RV vaccines and in further understanding the epidemiology of this condition.

Our present results demonstrated that:

- The monthly distribution of HRs for RVGE in Italy, with a seasonal peak in March, did not coincide with that of HRs for IS, with the highest HR in June [6,7].
- The peak of HRs for IS was recorded in children of 7 months of age, while the peak of HRs for RVGE was observed in children 12-23 months of age [6,7,15,35].
- The temporal trend of HRs for GEIS (increasing) and RVGE (decreasing) for the same timeframe and for the same range of age had a countertendency [7,22].

Confirming the independence of the two phenomena, as it was confirmed by the logistical regression that highlighted no association between GEIS and RV [32].

Moreover, the total trend of HR for IS was increasing, as it was also recently reported in Sicily and in France, where it was

considered unrelated to RV vaccination [29,36]. This increasing trend was mainly due to ≥ 12 month's age groups as in children within the first year of life there was a decreasing trend, even if they had background rates higher than the rates in the other age classes, in line with those reported for some other European countries [22-28].

A statistically significant increase of HRs for IS was seen especially for males, who had the higher HRs for IS, according to the already available data, and who also had a higher risk of developing IS in the presence of GE compared to females, confirming an already known fact [21,25,33-35,37].

An explanation of this male predominance in the incidence of IS observed worldwide, has not yet been identified [27,33-36]. Future study should enhance the possible effects caused by sexual hormones through specific analysis [36].

As RV still has a heavy burden on child health in Italy, the implementation of a universal RV vaccination program should be an important public health achievement. Although the risk/benefit balance is definitely in favors of vaccination, an epidemiological surveillance for childhood gastroenteritis and intussusceptions may contribute to a good management of the pediatrics extensive RV vaccination, once in place.

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