

Burden of pediatrics hospitalizations associated with Rotavirus gastroenteritis in Lombardy (Northern Italy) before immunization program

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Abstract

Aim. Rotavirus is recognized as the main cause of acute gastroenteritis in children under 5 years old, representing a considerable public health problem with a great impact on social and public health costs in developed countries. This study aims to assess the frequency and the epidemiological aspect of the hospitalization associated with Rotavirus-gastroenteritis in Lombardy, Northern Italy, from 2005 to 2011.

Methods. The Lombardy Hospital Discharge Database was inquired from the official data of the Italian Ministry of Health and investigated for acute gastroenteritis (ICD9-CM code for bacteria, parasitic, viral and undetermined etiologic diarrhea) in primary and secondary diagnosis in children ≤ 5 years, between 2005 and 2011.

Results. Out of the 32 944 acute-gastroenteritis hospitalizations reported in Lombardy, the 50.8% was caused by Rotavirus infection; of these, the 65.5% were reported in primary diagnosis. The peak of Rotavirus-gastroenteritis hospitalization was observed in February-March in children < 2 years old, with a cumulative prevalence of 64.5%. Patients admitted to hospital with diarrhea of undetermined etiology (about 14% of overall acute-gastroenteritis) showed epidemiological characteristics similar to the Rotavirus-gastroenteritis, suggesting that the virus infection could also be involved in at least some of these.

Conclusion. Our data confirm that Rotavirus are the most important agents involving in acute gastroenteritis hospitalizations. The use of Hospital Discharge Database had proved to be a simple tool to estimate the burden and to describe the epidemiological characteristics of Rotavirus gastroenteritis and could be used as a surveillance activity before and after the introduction of mass vaccination at national and regional level in Italy.

Key words

- acute gastroenteritis
- Rotavirus hospitalization
- ICD9-CM
- Rotavirus vaccination
- public health

INTRODUCTION

Human group A Rotaviruses (RV) belong to the *Reoviridae* family and are recognized as the major cause of acute gastroenteritis (AGE) and dehydration in children worldwide. It is estimated that RV infection causes approximately 450 000 deaths annually in children < 5 years old mostly in developing countries; in industrialized countries the infection represents a relevant public health problem due to the elevated morbidity and social and health costs associated [1].

The World Health Organization (WHO) recommends to include RV immunization in all vaccination programs, in order to prevent the infection and to reduce the extent of the disease [2]. Vaccine formulations available had shown high safety and efficacy in large-scale trials [3, 4] so since 2008 the European Society for Paediatric Infectious Diseases (ESPID) and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) endorse the introduction of RV vaccines for all healthy infants in Europe [5].

An European multicenter prospective study has shown that in Italy RV infection account more than 1/3 of all children aged < 5 years hospitalized for AGE, especially infants between 3-36 months of years [6]; nevertheless, nowadays RV are not included in the Italian National Plan of Vaccinations (NPV). The offer of the RV vaccine remains highly heterogeneous in the country and the vaccination has not been identified as a priority. Some Italian regions offers the RV vaccination in co-payment or the vaccine are offered free of charge for few risk-groups identified in the population. During the drafting of this paper, only Sicily region has been introduced the vaccine in its routine immunization schedule [7].

The impact of Rotavirus gastroenteritis (RVGE) in children in Italy had been estimated through the use of ICD9-CM code extraction from HDD (Hospital Discharge Database) in previous studies [8-12], but Lombardy region (North-West Italy) was no included.

This study aims to estimate the impact of RVGE hospitalizations in Lombardy and to investigate the epidemiological characteristics of RVGE, analyzing the HDD from 2005 to 2011. The adoption of HDD to monitor RVGE cases and the potential impact of vaccination on a large scale in Lombardy are also discussed.

MATERIALS AND METHODS

Study population

The data presented in this study were obtained retrospectively from existing databases established by the Ministry of Health, in accordance with the national regulations related to clinical research. In agreement with the Italian law Decree no. 196/2003, it was not necessary to obtain informed consent of patients or specific authorization by the Ethics Committees, because the anonymity of data was assured throughout the study. The data were collected in an electronic form. The study was conducted in accordance with the Helsinki Declaration of 1975.

The ICD-9-CM diagnoses and codes were obtained by Lombardy's HDD [13] and were analyzed to identify children (1 month-5 years) admitted to hospital with AGE from 2005 to 2011. Neonates younger than < 1 month were not included in the study, because no specific code exists for the identification of the illnesses, of any etiologic situation, which occur in this age group. The AGE hospitalizations were extracted by one of the seven possible diagnoses associated with patient: primary diagnosis was indicated with PD whereas the following 6 secondary diagnoses were indicated as SD. The ICD9-CM codes encompassed both etiologically determined diarrheas including bacterial [001-005, excluding 003.2 and 008.0-008.5], parasitic [006-007, excluding 006.2-006.6], or viral [008.6 and 008.8] cases, and diarrhea of undetermined etiology (NDGE), including cases of possible infective origin (8009.0-8009.3) and those presumably non-infective (558.9).

The specific ICD9-CM code for RVGE is 008.61, and the NDGE includes codes from 8009.0 to 8009.3 and 558.9.

Statistical analysis

Diarrhea coded hospitalizations for RVGE and

NDGE were examined by gender, age group (1-3, 4-6, 7-11, 12-23, 24-35, 36-47, 48-59 and 60-71 months), and month of discharge in PD and SD and tested by the chi-square test. A p -value < 0.05 was considered to indicate statistical significance (two-tailed test). The variables were expressed as frequency and percentage with the exact binomial 95% confidence intervals (CI). AGE and RVGE hospitalization rates were calculated as the estimated number of hospitalizations per 100 000 children below 6 years of age based on estimates of the resident population in Lombardy for the corresponding year retrieved by the National Institute of Statistics (ISTAT) website [14]. All statistical analyses were done using the OPENEPI software, version 3.03 updating 2014/09/22 (Copyright (©) 2003, 2008 Andrew G. Dean and Kevin M. Sullivan, Atlanta, GA, USA).

RESULTS

From 2005 to 2011, 32 944 AGE hospitalizations were reported in Lombardy. In total, 16 738 cases were diagnosed as RVGE, equal to 50.8% (95% CI 50.27-51.35) of total AGE cases. Of these, 10 961 (65.5%; 95% CI 64.76-66.2) were reported as PD and 5777 (34.5%; 95% CI 33.8-35.24) as SD. On average, 2391 cases of RVGE were reported yearly throughout the study period.

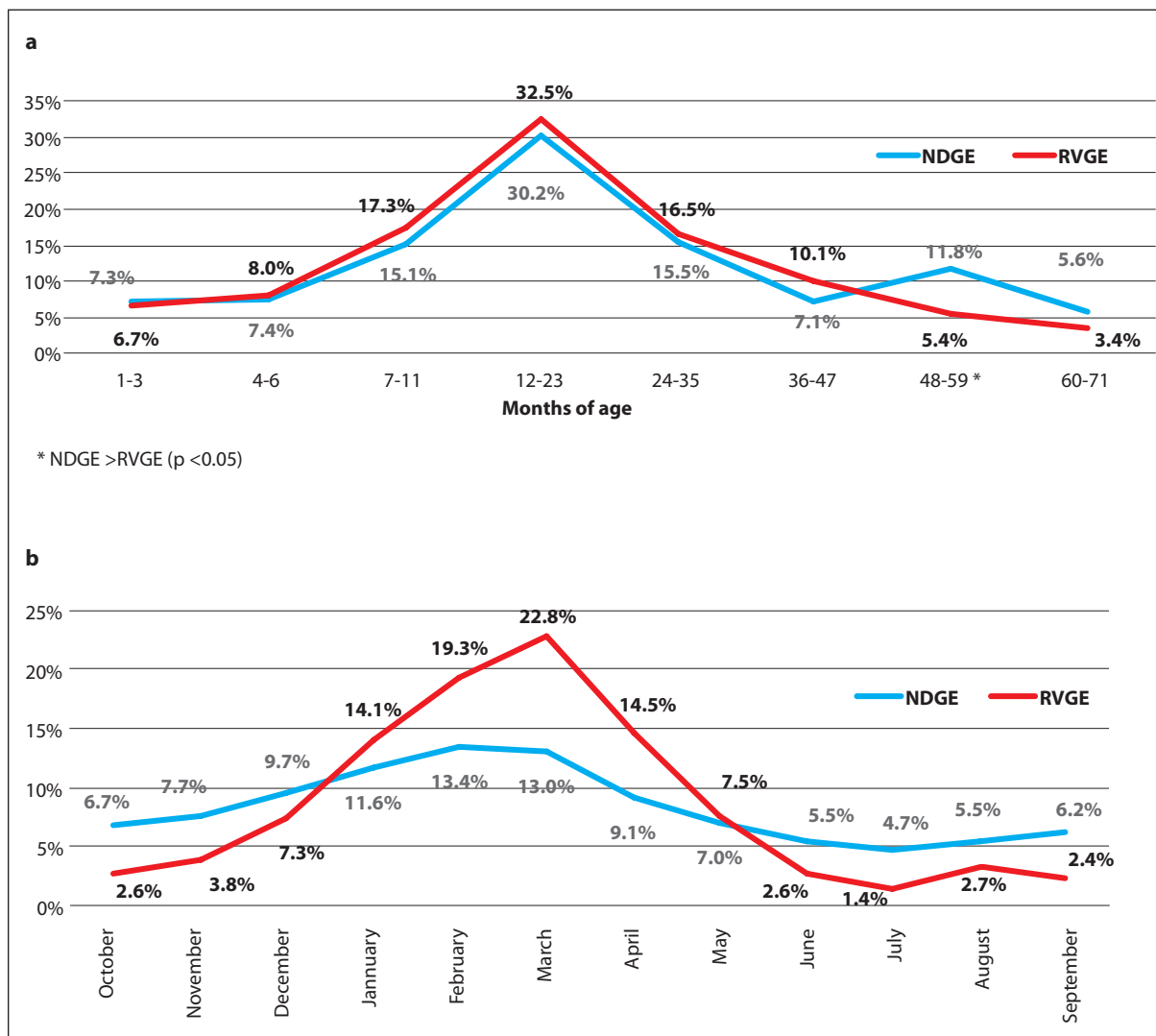
The median annual rate of AGE and RVGE hospitalizations in children \leq 5 years old was 4812 in 572 607 inhabitants (0.8%; 95% CI 0.81-0.86) and 2462 (0.4%; 95% CI 0.41-0.44), respectively. The overall AGE hospitalization rate was 825/100 000 while RVGE rate was 419/100 000 (1 child every 238).

Overall, 18 321 in 32 944 AGE cases (55.6%; 95% CI 55.08-56.15) occurred in males and 14 623 (44.4%; 95% CI 43.85-44.92) in females ($p < 0.001$), whereas 9292 in 16 738 RVGE hospitalization (55.5%; 95% CI 54.76-56.27) were recorded in males and 7444 (44.6%; 95% CI 43.72-45.23) in females ($p < 0.001$).

The monthly course of the RVGE admissions showed a recurrent seasonal trend during the whole period of study, between December and April, with a peak in February-March (*Figure 1b*)

Considering RVGE (notified in either PD or SD), 10 802 in 16 738 hospitalization (64.5%; 95% CI 63.81-65.26) were happened within the first two years of life. The rate of RVGE hospitalizations showed an increase in the children up to the 12-24 months age class followed by a reduction in the higher group (*Table 1*).

In the cohort of 1-11 months old, RVGE cases were recorded in SD more frequent than in PD (37.7% vs 29.1%, $p < 0.001$) (*Table 1*). In the *Table 2* the distribution of RVGE in PD and SD linked with ages and seasonal trend are shown; out of 3469 RVGE occurred in children below 11 months old and during winter season – from December to March, 1498 cases were recorded in SD (43.2%; 95% CI 41.22-44.5) showing an higher rate than those recorded in the other seasons – from April to November (678/1889 equal to 35.7%; 95% CI 33.76-38.08) ($p < 0.001$), while out of 6194 RVGE recorded in SD in children > 12 months old, 1382 hospitalization (22.3%; 95% CI 21.29-23.37) occurred from December to March indicating a lower rate than those

**Figure 1**

Comparison between Rotavirus gastroenteritis (RVGE) and diarrhea of undetermined etiology (NDGE) in the study population in Lombardy, 2005-2011. a) Prevalence of RVGE vs NDGE by age. b) Prevalence of RVGE vs NDGE by month.

recorded from April to November (2219/5176 equal to 42.9%; 95% CI 41.53-44.22) ($p < 0.001$) (Table 2).

Through the study period, 4786 in 32 944 AGE hospitalizations (14.5%; 95% CI 14.15-14.91) were characterized as NDGE, among which 3173 (66.3%; 95% CI 64.95-67.62) were notified in PD and 1613 (33.7%; 95% CI 32.38-35.05) in SD.

The epidemiological characteristics of RVGE and NDGE cases were compared. With respect to the distribution by age group, RVGE and NDGE hospitalizations showed overall similar values ($p > 0.05$), except in the age group 48-59 months ($p < 0.05$), where the rate of NDGE was greater than RVGE (Figure 1a). Concerning the seasonal distribution, NDGE presented a similar trend to that observed for RVGE, with a peak between January and March, which however was remarkably smoother (Figure 1b).

DISCUSSION

Before the introduction of mass vaccination against

RV in the community, it is important to estimate the burden of the infection and the social and economic impact of RVGE hospitalizations, as well as the potential benefits of vaccine deriving from the expected reduction of admissions to hospital. In Italy, no national surveillance system of AGE or RVGE infection in children is in place, and accurate estimates of the incidence of RVGE is difficult to achieve.

This is the first study performed by the use of the ICD9-CM conducted in the whole Lombardy region for seven consecutive seasons, and its results indicate that HDD may be an easy and without additional cost tool for estimating RVGE hospitalizations in the population. As suggested by Marchetti *et al.* [9], the examination of all the diagnoses (PD and SD) available for the hospitalized patient could in fact increase the sensitivity of the measurement.

In Lombardy, about two thirds of RVGE hospitalizations were notified in PD. Because the SD is related to conditions that may either be present at the time of

Table 1
Age-specific rate of Rotavirus gastroenteritis (RVGE) hospitalizations among children aged 1-71 months in Lombardy, 2005-2011

Age group (months)	PD				SD				Total			
	RVGE		Cumulative RVGE		RVGE		Cumulative RVGE		RVGE		Cumulative RVGE	
	n.	(%)	n.	(%)	n.	(%)	n.	(%)	n.	(%)	n.	(%)
1-3 m	593	5.4	593	5.4	532	9.2	532	9.2	1125	6.7	1125	6.7
4-6 m	752	6.9	1345	12.3	591	10.2	1123	19.4	1343	8.0	2468	14.7
7-11 m	1847	16.9	3192	29.1*	1053	18.2	2176	37.7*	2900	17.3	5368	32.1
12-23 m	3647	33.3	6839	62.4	1787	30.9	3963	68.6	5434	32.5	10 802	64.5
24-35 m	1944	17.7	8783	80.1	822	14.2	4785	82.8	2766	16.5	13 568	81.1
36-47 m	1136	10.4	9919	90.5	556	9.6	5341	92.5	1692	10.1	15 260	91.2
48-59 m	642	5.9	10 561	96.4	266	4.6	5607	97.1	908	5.4	16 168	96.6
60-71 m	400	4.0	10 961	100	170	3.0	5777	100	570	3.4	16 738	100
Total	10 961	100	-	-	5777	100	-	-	16 738	100	-	-

PD: primary diagnosis; SD: secondary diagnosis; * $p < 0.001$.

Table 2
Cases of Rotavirus gastroenteritis (RVGE) identified in primary and secondary diagnosis by age of patients and season in Lombardy, 2005-2011

	Winter season (December-March)					
	PD		SD		Total	
	n.	(%)	n.	(%)	n.	(%)
1 < months < 11	1971	56.8	1498	43.2*	3469	100.0
12 < months < 71	4812	77.7	1382	22.3**	6194	100.0
All ages	6783	71.2	2880	29.8	9663	100.0
	Other seasons (April-November)					
	PD		SD		Total	
	n.	(%)	n.	(%)	n.	(%)
1 < months < 11	1221	64.3	678	35.7*	1889	100.0
12 < months < 71	2957	57.1	2219	42.9**	5176	100.0
All ages	4178	59.1	2897	40.9	7075	100.0

* $p < 0.001$; ** $p < 0.001$; PD: primary diagnosis; SD: secondary diagnosis.

admission or develop later, it is sometimes difficult to identify the real proportion of nosocomial RVGE, as occurred also in this study.

Our data confirm that RV was the most important agent involved in AGE hospitalization, being present in more than half of the cases investigated. On a population basis, these data indicate that at least 0.4% of all Lombard children under 6 years of age were hospitalized for episodes of RVGE, annually. The RVGE hospitalization rate found in Lombardy (419/100 000 inhabitants) is greater than that found in other national studies in Italy [9, 12], but is in line with those of other regions [8, 10, 15] and with the estimates for Italy generated by mathematical prediction models (290-565/100 000) [16]. It should be considered that the present estimates for Lombardy might be lower than the actual data; in fact, some authors have shown that only 65.26% of all RVGE are diagnosed or encoded cor-

rectly, and that therefore they underestimate the real burden [15, 17].

The results obtained through the HDD study confirm the epidemiological characteristics of RVGE hospitalizations observed in previous studies in other part of Italy. The age group at higher risk of admission to hospital with RVGE were children of less than 24 months of age. The rate of RVGE hospitalization had shown a increase trend up to the 12-24 months age-class, followed by a decrement. As expected, the youngest children was protective against RV thank to maternal antibody and the reduction in the rate of RVGE in the children over 2 years old could be linked with the develop of the children protective antibody after previously infection. Interesting, the rate of RVGE as well as AGE hospitalization was higher in male than in female children ($p < 0.001$). A clear seasonal distribution of cases was constantly revealed in all years investigated, with the

greater rate collected between winter and early spring, peaking in February-March.

The higher rate of RVGE cases identified in SD in children aged 1-11 months may suggest that patients within this age group had developed a hospital-acquired RV infection more frequently than the other, confirming previous findings [18]. In fact, considering the severe clinical picture usually associated with RV infection in children of less than 1 year, it is reasonable to assume that a PD of RV infection would have been recorded if it was present on admission. Interestingly, RVGE cases among children 1-11 months old were identified in SD more frequently during the winter season than in children over 12 months ($p < 0.001$). It is known that cases of RVGE share a same seasonal trend as the respiratory syndromes due to influenza virus, respiratory syncytial virus (RSV) and others etiological agent, which cause hospitalization particularly of younger children. Thus, our findings of a higher risk of nosocomial RV infection among children 1-11 months old, particularly in the cold months, might reflect a higher rate of hospital admission in this age class due to respiratory disease, as suggested by other authors [19, 20].

In this study, NDGE hospitalizations (4786 cases, about 14% of overall AGE) presented epidemiological characteristics similar to those associated with RVGE. The trend of RVGE and NDGE by age classes and seasonality was well overlapped.

In some European countries where vaccination has been in place since 2006, a significant reduction of both RVGE infections and hospital admissions has been demonstrated [21]; moreover, using mathematical models, Giammanco *et al.* [22] and Vitale *et al.* [23] has estimated that the introduction of mass vaccination in Italy would allow a significant saving for societal perspective costs without additional workload for the health-care service.

Disease surveillance based on HDD data is retrospective and is characterized by a low sensitivity despite its high specificity [7]. Additional actions would be needed, including enrolment of "sentinel hospitals" which could provide both current data on admissions and stool sam-

ples for genotyping of circulating RV strains.

Since 2008, the Lombardy region is part of the RotaNet-Italy Study Group [24], including "sentinel hospitals" and research centers throughout the country and coordinated by the Istituto Superiore di Sanità and by the Ministry of Health. The RotaNet-Italy network is linked to the EuroRotaNet [25] providing genotyping data on the RV strains circulating in the Italian paediatric population and investigating the possible emergence of imported, zoonotic or recombinant RV strains that might prove resistant to current vaccines and require re-evaluation of vaccine composition [26].

CONCLUSIONS

In conclusion, data obtained from the regional HDD indicate that RV were the major cause of AGE hospitalization in children in Lombardy in the period between January 2005 and December 2011. The disease presented a recurring peak of admissions to hospital in winter and early spring especially in children up to 2 years of age, based on both primary and secondary diagnosis. Using the results of this study as a baseline, continuing HDD-based surveillance may be useful to assess the impact of RV vaccine on the epidemiology of RVGE before and after mass vaccination.

Authors' contribution statement

Pellegrinelli L, Binda S, Primache V, designed the study and wrote the first draft of the paper. Bubba L, Fiore L, participated to the conception of the work and data analysis. Chiaramonte I, Ruggeri FM, substantially collaborated to the statistical analysis and in writing of the manuscript.

All authors worked together to interpret the results and to review the final draft of the manuscript.

Conflicts of interest statement

The authors declare that they have no conflicts of interest.

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