RESEARCH PAPER

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Temporal trends in hospitalization for rotavirus gastroenteritis: A nationwide study in Italy, 2005–2012

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Abbreviations: AGE, acute gastroenteritis; HDD, hospital discharge database; HDR, hospital discharge record; PD, primary diagnosis; RV, rotavirus; HR, hospitalization rate; RVGE, rotavirus gastroenteritis; SD, secondary diagnosis; VGE, viral gastroenteritis

AGE severity is linked to etiology, and Rotavirus (RV) accounts for most of severe cases. In 2009 the World Health Organization recommended RV vaccination for all children. Worldwide a number of Countries implemented RV vaccination in their pediatric immunisation programmes, but only a limited number in Europe. This study was designed to estimate the proportion of RVGE among children aged <6 y who were diagnosed with AGE 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. The average hospitalization rate (HR) was 146/100,000 children for RVGE in primary diagnosis (PD) and 150/100,000 children for RVGE in secondary diagnosis (SD). Since 2008 the RVGE hospitalization figures and rates (HRs) in SD exceed those in PD. The majority of RVGE hospitalizations (33.67%) were reported among children aged $\leq$ 2 years. Despite some limitations due to the hospital discharge database (HDD) synthetic contents and low potential for clinical interpretation, the analysis of national HDD, including PD and SD, documents that RV still represents a consistent cause of pediatric hospitalizations in Italy.

Introduction

Acute gastroenteritis (AGE), characterized by the onset of diarrhea with or without vomiting, still represents a major cause of morbidity even in industrialized Countries, being mortality confined in mostly resource-constrained nations. Although generally considered a mild and self-limiting disease, AGE is one of the most common causes of hospitalization and is associated with a substantial disease burden.[1-4]

Within the European Union, rotavirus gastroenteritis (RVGE) places a high demand on healthcare systems.[5-8] Surveillance studies showed that RV accounts for up to 2 thirds of admissions to hospital and emergency room visits and one third of primary care consultations for AGE among children under 5 years, being the greatest burden of disease consistently observed in children aged under 2. RVGE is estimated to occur at a rate of 1 symptomatic infection in every 7 children each year, accounting for 231 deaths, more than 87,000 hospitalizations and almost 700,000 outpatient visits.[5]

The REVEAL study, carried out in Belgium, France, Germany, Italy, Spain, Sweden, and the UK, reported that RVGE in children under 5 y of age was responsible for between 53.0% and 68.9% of cases presenting to hospitals, 35.4% and 63.3% for those seen in emergency departments, and 7.7% and 41.3% of cases seeking primary care physicians.[9]

In 2006, 2 new live, oral, attenuated RV vaccines were licensed for infants less than 6 months of age RV vaccination was first recommended to US children in 2006. Subsequently, in 2009 the World Health Organization Strategic Advisory Group of Experts (SAGE) recommended RV vaccination for all children.[10] Worldwide a number of countries have adopted this recommendation and implemented RV vaccines in their pediatric

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immunisation programmes, but only in a limited number of Countries in Europe.

Some countries, such as Austria and Luxembourg (2006), Belgium (2007), Finland (2009), United Kingdom and Germany (2013), Norway and Estonia (2014), Latvia (2015) introduced universal anti-RV vaccination until April 1st 2015, while in other countries, such as, Sweden, Denmark, and Romania the formal assessment for universal vaccination is under consideration.[11-17]

In Italy, where RVGE is an important cause of pediatric hospitalization, associated with high health care costs, as pointed out by several studies, among them, that of Marocco et al. is the only nationwide but limited only to the primary diagnosis, the National Health care System (NHS) is decentralized i.e Regions are expected to implement – free of charge - all the vaccinations included in the National Immunization Plan (NIP);[18-21] further, they are allowed to increase the vaccination offer providing that the additional budget is funded at regional level, either centrally or in co-payment with the citizens. RV in not included in the current National Immunization Plan (NIP) and most of the Regions introduced it in co-payment, sometimes reducing the co-payment to a small amount.[22-29] Sicily is the only Region were RV universal mass vaccination (UMV) free of charge was implemented in 2012.[30]

In order to provide an epidemiological picture that can be helpful in assessing the need to adopt anti-RV universal vaccination also in Italy, this study was designed to estimate the proportion of RVGE among children younger than 6 y of age who were diagnosed with AGE and admitted to hospital in Italy during the years 2005–2012.

Results

In the study time frame, 334,982 AGE hospital discharge records (HDRs) were collected in Italy (average annual number: 41,873 hospitalizations), in children aged <6 years, being AGE the primary diagnosis (PD) in 50.30% (168,509 cases) of these.

Table 1 shows the number of hospital admissions only coded as AGE of any etiology in PD: 63.09% of AGE (106,326 cases) presented the code of gastroenteritis of non-specified origin, and 33.75% of cases were viral gastroenteritis (VGE), that were the leading cause of admissions for gastroenteritis of specified origin; RVGE were 39,024 (23.16%), and represented 68.61% of all VGE. Considering the total admissions for AGE (in PD), over the 8-years study period, a significant and consistent reduction of the total number of admissions for AGE, from 27,555 in 2005 to 14,988 in 2012, (a decrease of 45.60% - AGE trend-test: β coefficient=-1,939; $p < 0.001$) was observed. In parallel, a minor, but statistically significant, decrease for RVGE of 29.72% (from 5,824 in 2005 to 4,093 in 2012; RVGE trend-test: β coefficient $= -253$; $p = 0.014$) was found out.

Figure 1A shows the trend of hospitalizations for RVGE in children under 6 y of age over the study period, but including secondary diagnosis (SD). SD inclusion leads to a total of 79,344 hospitalizations associated with RV, of which 40,320 (50.81%) in SD.

Overall, the percentage of hospital admissions for RVGE in PD has gradually and significantly decreased from 57.93% in 2005 to 43.18% in 2012. On the contrary, the incidence of RVGE SD admissions has increased from 42.07% in 2005 to 56.82% in 2012.

The annual incidence rates of RV hospitalizations among children <6 y of age are shown in **Figure 1** B. The average hospitalization rate (HR) was 296/100,000 children: 146/100,000 children for RVGE in PD and 150/100,000 children for RVGE in SD. Since 2008 the HRs for RVGE in SD exceeds those for RVGE in PD, with the highest peak in 2010 (total RV HR: 339/100,000 children). The decrease of the HRs for RVGE in PD is 8.21 per year ($p = 0.01$), while considering the trend of HRs for RVGE in any diagnosis (PD and SD) it is not statistically significant ($p = 0.487$).

Most RVGE hospitalizations (80.79%) occurred in children younger than 3 y (**Table 2**), mainly infants ≤2 years (12–23 months) had the highest number of cases (33.67%), followed by children aged up to 3 y (24–35 months), with 18.45% of annual hospitalizations, then children aged 0–11 months (28.67%).

RVGE hospitalizations seasonal peak was during December - March every year, with maximum values of 2,850 cases in PD during 2006 and 3,139 cases in SD over 2008 y (data by Italian HDD database; data not shown).

In RVGE SD cases, 26,675 (66.16%) main diagnoses were related to symptoms or conditions attributable to AGE (**Fig. 2**): the most frequent were dehydration (49.77%) syncopations and convulsions (6.59%) and acidosis and electrolyte fluid disorders (5.35%). The main (52%) DRG code for RVGE SD was 298 (symptoms concerning nutrition and metabolism <18 years).

Total hospital charges for the admissions for RV in the overall period were approximately € 112 million. They, however, decreased from € 7,238,739 in 2005 to € 3,158,220 in 2012, considering only PD.

Discussion

Hospital admission rates for RV AGE in children aged <6 y still remain a relevant topic in Italy. The hospital discharge data (HDD) analysis confirmed that RVGE still represents the greatest proportion of hospitalized VGE, in agreement with previous results either in Italy and in other parts of Europe or USA.[7,9,18,21-32]

As in the study time frame the RV vaccine coverage (estimated less than 10%) did not reach yet significant levels to affect the overall epidemiology of the disease, the figures reported here can be considered as a pre-vaccination picture.[28] A progressive reduction of all hospitalizations for acute diarrhea in children, in the study period, which is more evident for AGE of unspecified etiology and of bacterial and parasitic origin was observed.

Indeed, we provided evidence that there was a switch in the position of RV AGE diagnosis from PD to SD. No explicit reasons justifying such a switch could be found out. Vitale et al, using the Markov model and considering a cohort of 555,791 births in 2011 in Italy, in the absence of vaccination, estimated

Table 1. Number (percentage) of all hospitalizations for gastroenteritis in PD among children <6 y of age in the 2005–2012 period

	2005	2006	2007	2008	2009	2010	2011	2012	2005–2012
UNSPECIFIED ETIOLOGY									
Infectious: ICD9CM 009–009.3	12,569 (45.61%)	12,500 (47.57%)	10,619 (44.96%)	9,191 (42.55%)	7,743 (43.47%)	8,794 (43.46%)	7,145 (46.92%)	7,013 (46.79%)	75,574 (44.85%)
Non-infectious: ICD9CM 558.9	5,244 (19.03%)	5,352 (19.51%)	4,684 (19.83%)	4,223 (19.55%)	3,428 (19.25%)	3,604 (17.81%)	2,289 (15.03%)	1,928 (12.86%)	30,752 (18.25%)
SPECIFIED ETIOLOGY									
Viral: ICD9CM 008.62–008.8 (without RV)	3,055 (11.09%)	3,275 (11.94%)	2,524 (10.69%)	2,235 (10.35%)	1,930 (10.84%)	1,987 (9.82%)	1,455 (9.55%)	1,392 (9.29%)	17,853 (10.59%)
Rotavirus: ICD9CM 008.61	5,824 (21.14%)	5,439 (19.83%)	5,144 (21.78%)	5,324 (24.65%)	4,146 (23.28%)	5,301 (26.2%)	3,753 (24.65%)	4,093 (27.31%)	39,024 (23.16%)
Bacterial: ICD9CM 001–005, 008–008.5	661 (2.4%)	634 (2.31%)	475 (2.1%)	460 (2.13%)	383 (2.15%)	406 (2.01%)	481 (3.16%)	447 (2.98%)	3,947 (2.34%)
Parasitic: ICD9CM 006–007	202 (0.73%)	228 (0.83%)	174 (0.74%)	163 (0.75%)	181 (1.02%)	142 (0.70%)	154 (1.01%)	115 (0.77%)	1,359 (0.81%)
TOTAL	27,555	27,428	23,620	21,596	17,811	20,234	15,227	14,988	168,509

AGE trend-test: β coefficient $= -1{,}939$; $p < 0.001$; Number of RVPD hospitalizations, trend-test: β-coefficient $= -253$; $p < 0.014$.

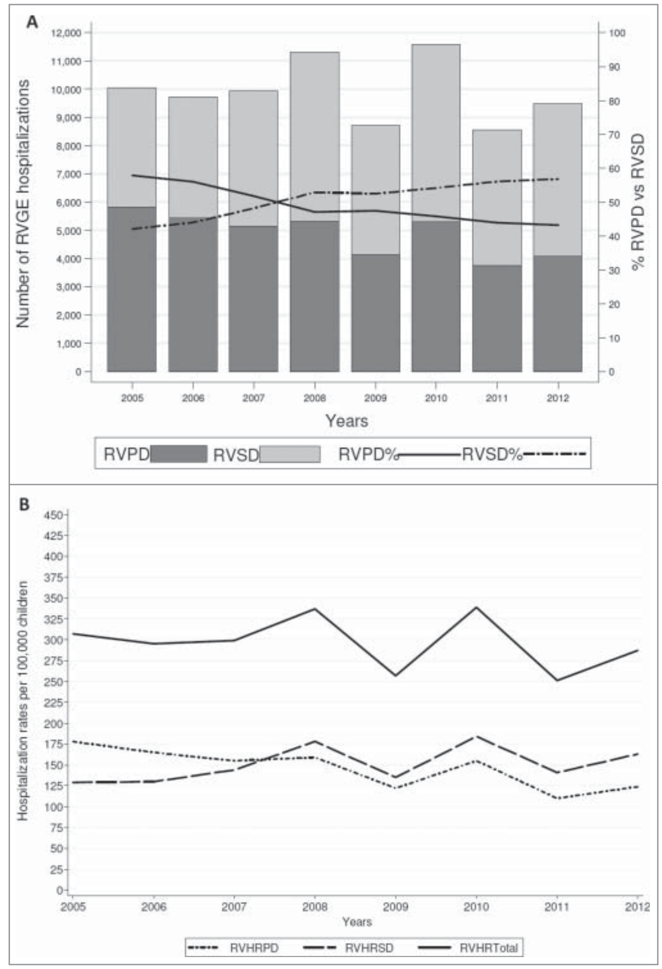


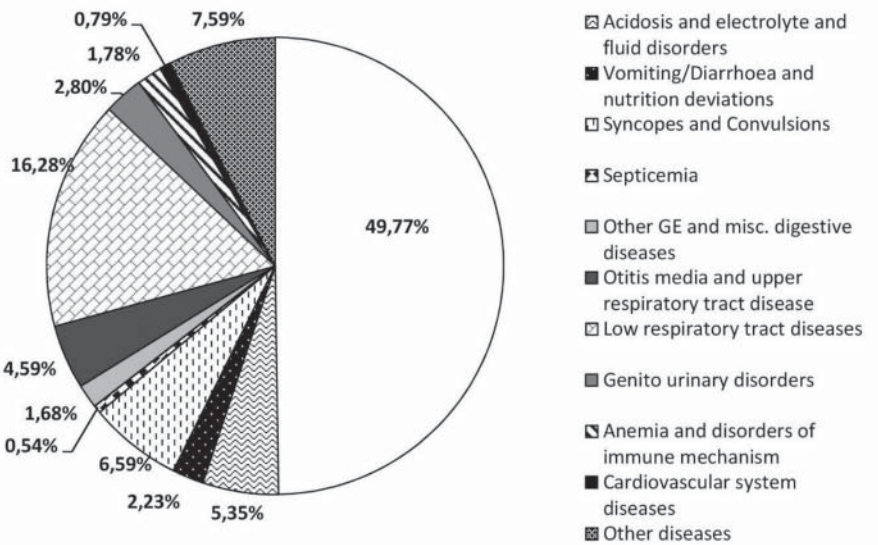
Figure 1. (**A**) Number of RVGE hospitalizations (code ICD9CM 008.61) in primary (PD) and secondary diagnosis (SD) among children <6 y of age in 2005–2012. Number of RVPD hospitalizations trend-test: β-coefficient $= -253$; $p<0.014$; number of RVSD hospitalizations trend-test: β-coefficient $=163$; $p = 0.184$; total number of RV hospitalizations trend-test: β-coefficient $=-89$; $p = 0.630$. RVPD: RVGE hospitalizations in primary diagnosis; RVSD: RVGE hospitalizations in secondary diagnosis; % RVPD: percentage of RVGE hospitalizations in primary diagnosis; % RVSD: percentage of RVGE hopistalizations in secondary diagnosis. (**B**) Hospitalization rates per 100,000 of RVGE PD and SD among children <6 y of age in 2005-2012. Hospitalization rates per 100,000 of RVGE PD trend-test: β-coefficient=-8.21; p=0.010; hospitalization rates per 100,000 of RVGE SD trend-test: β-coefficient=4 .40; p=0.209. Total HRRV trend-test: β coefficient $= -3.80$; $p = 0.487$. RVHRPD: hospitalization rates for RVGE gastroenteritis in primary diagnosis; RVHRSD: hospitalization rates for RVGE gastroenteritis in secondary diagnosis; RVHRTotal: hospitalization rates for RVGE gastroenteritis in any diagnosis (PD and SD).

an average of 14,000 hospitalizations per year by using the RVGE hospital rates collected within the REVEAL study;[19] in our study, an average of 9,918 hospitalizations per year for RV in any diagnosis was found out. Whereas an underestimation of hospitalizations through the HDD by around 40–50% was reported, even if calculated from a different setting, our findings are consistent with those reported. RV HRs variations were in line with the switch of PD with SD. Our findings support the need of including both PD and SD, which also includes

Table 2. Temporal distribution of rotavirus infections in Italy. Distribution (absolute and relative) by age groups of the hospitalizations for rotavirus gastroenteritis (code ICD-9 CM 008.61) in PD in children aged <6 y over the 2005–2012 period

	Age groups												
	<1 y of age 0–11 months		1 year 12–23 months		2 years 24–35 months		3 years 36–47 months		4 years 48–59 months		5 years 60–71 months		
	N	%	N	%	N	%	N	%	N	%	N	%	Total
2005	1,599	27.46	1,957	33.60	1,057	18.15	622	10.68	367	6.30	222	3.81	5,824
2006	1,499	27.56	1,898	34.90	994	18.28	559	10.28	294	5.41	195	3.59	5,439
2007	1,498	29.12	1,694	32.93	939	18.25	524	10.19	291	5.66	198	3.85	5,144
2008	1,514	28.44	1,733	32.55	1,011	18.99	562	10.56	302	5.67	202	3.79	5,324
2009	1,246	30.05	1,375	33.16	812	19.59	393	9.48	203	4.90	117	2.82	4,146
2010	1,557	29.37	1,845	34.80	933	17.60	487	9.19	290	5.47	189	3.57	5,301
2011	1,119	29.82	1,252	33.36	670	17.85	371	9.89	207	5.52	134	3.57	3,753
2012	1,156	28.24	1,386	33.86	784	19.15	385	9.41	212	5.18	170	4.15	4,093
2005–2012	11,188	28.67	13,140	33.67	7,200	18.45	3,903	10.00	2,166	5.55	1,427	3.66	39,024

N/% = number/percentage of all hospitalizations in the given year for the specified age group.



Description of complicating diagnoses	N	%
Dehydration	20,066	49.77
Acidosis and electrolyte and fluid disorders	2,158	5.35
Vomiting/Diarrhoea and nutrition deviations	900	2.23
Syncopes and Convulsions	2,656	6.59
Septicemia	218	0.54
Other GE and misc. digestive diseases	677	1.68
Otitis media and upper respiratory tract disease	1,852	4.59
Low respiratory tract diseases	6,566	16.28
Genito urinary disorders	1,129	2.80
Anemia and disorders of immune mechanism	717	1.78
Cardiovascular system diseases	320	0.79
Other diseases	2,971	7.59
Total	40,320	100,00

Figure 2. Number (N) and frequency (%) of other diseases in PD in RVGE SD cases.

nosocomial infection forms and the incidence of which was estimated in Italy by 5.3% in children under 30 months, in RV hospitalizations analysis.[18-33]

The most frequent PD in cases of SD RVGE were: dehydration, acidosis and vomiting (54%), infections of the upper and lower respiratory tract (respectively 11% and 13%), seizures or other neurological symptoms (7%) and urinary tract infection (6%), in agreement with previous reports.[34] Although further studies would be needed to confirm the hypothesis, a consistent part of admissions such as dehydration, gastrointestinal disorders, febrile seizures and electrolyte abnormalities reported in main diagnosis could be associated with the RV etiology; this would also partially justify the under estimation of RVGE hospitalization figures. It can be assumed that variations in coding RV hospitalizations in the studied years might be related to the introduction of strategies of containment of the sanitary expense, being some ICD9-CM codes leading to a more specialized management and reimbursement.[20]

Even though the study was not intended as an economic analysis of RVGE hospitalizations, some calculations of RVGE costs were derived from the codes available in the database. However, figures obtained were just a rough indicator of real healthcare costs when compared to more accurate calculations.[35]

Limitations of the Study. The data shown are not linked to RV uptakes that

are not searched. Indeed, regional data are not detailed even if the regional differences in the payment of RVGE hopitalizations may influence the coverage of RV vaccines and the AGE hospitalizations.

In conclusion, RVGE hospitalization figures in Italy are still relevant and generate significant costs to the NHS. As observed in other Countries, the introduction of RV UMV in Italy might consistently reduce morbidity and associated medical costs.

Materials and Methods

This is a retrospective population-based study, conducted among all pediatric patients aged <6 y hospitalized for AGE in Italy, between January 1st 2005 and December 31st 2012.

The data source was the Italian HDD obtained from Ministry of Health (Processing National HDD, Ministry of Health, General Directorate for Health Planning, VI Office). This database contains administrative and health data regarding hospital admissions, that all public and privately-owned hospitals in Italy are legally required to report. For each admission, a PD is reported; this represents the clinical condition which took up the greatest amount of resources and therefore involved the greatest cost for the hospital. Up to 5 additional SD may be listed.

The clinical information is coded by the international ICD9-CM system (International Classification of Diseases, 9th revision, Clinical Modification), currently used in Italy. Gastroenteritis codes include the following:

- unspecified etiology gastroenteritis of presumed infectious etiology (009–009.3) and presumed noninfectious etiology (558.9);
- gastroenteritis with specified etiology: VGE (008.61–69), bacterial gastroenteritis (001–005 and 008–008.5) and parasitic gastroenteritis (006–007). RVGE discharges were identified by the code 008.61.

In this study we included all admissions with at least one gastroenteritis related main or secondary discharge diagnosis. For each of these hospitalizations, we obtained the following data: age, month of admission, costs related to admissions.

Each hospitalization cost, on average, has been estimated, according to the theoretical remuneration of admission reported in each HDR provided by Diagnosis Related Group (DRG) system. Even if a specific DRG rates for RVGE is not available, the 3 possible DRG codes to which the disease can be referred to (184: esophagitis, gastroenteritis etc., € 785; 298: symptoms concerning nutrition and metabolism <18 years, € 1,190; 422: diseases of viral origin and fever of unknown origin, € 1,660) were considered.[36,37]

Data provided by the Ministry of the Health did not contain any patient identifiers and was therefore completely anonymous. Hence notification of the study to Ethics Committees was not applicable, nor was informed consent of patients required.

The frequency of hospitalization with a PD of gastroenteritis was calculated as the ratio between patients with any AGE code in PD over the total aggregate observed in the database. As the RVGEs are the only vaccine-preventable, for these frequencies and hospitalization rates also in SD were analyzed, to obtain their overall epidemiological picture.

HRs were calculated for every year as the ratio between the number of hospital discharges and the resident populations aged <6 y per 100,000. Population data for 2005–2012 period was obtained from Italian Institute of Statistics (ISTAT), which registers the National population, by age group, as of the January 1st for each year.[38]

The statistical significance of temporal trend of HRs was determined using the analysis of the slope of the regression line between HRs and years of observation. $p < 0.05$ was the criterion for statistical significance. Data analysis was performed using STATA/IC 12.1.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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