

Burden of hospitalizations due to Rotavirus infection in Emilia Romagna, Italy

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Abstract. The aim of this study was to collect data on hospitalizations due to gastrointestinal diseases, in particular Rotavirus gastroenteritis (RVGE), in the Region of Emilia Romagna, Italy. The national hospital discharge database was used to evaluate the epidemiology of RV infections in the 2000–2003 period, analyzing only the principal diagnosis. The available age groups were 0–14 years, 15–64 years and, >64 years. Hospitalization related costs were estimated through Diagnosis Related Group (DRG) rates even though a specific DRG for RVGE does not exist. In the 0–14yr. old subjects, RV were responsible for an average of 310 GE-related hospitalizations per year and globally represented 17% of admissions for enteritis and 84% of hospitalized viral GE. Fifty-six percent of the enteritis was of undefined origin. Considering the three possible DRG codes to which the disease can be referred (184, 298, 422) and the classification of hospitals in two categories, the cost of each admission for RVGE ranged between 1,293.83 € and 2,263.79 €. RV seems to play an important role as a cause of severe viral gastroenteritis, although RV infections are certainly underestimated for several reasons, one of them being the low sensitivity of hospital discharge forms. Today we have safe and effective vaccines that can be used in order to protect from moderate/severe forms of RV-related diarrhea. The extensive use of these vaccines could reduce hospitalizations and related costs in industrialized countries. (www.actabiomedica.it)

Key words: Rotavirus, hospitalizations, epidemiology, costs

Background and aim of the work

Rotaviruses (RV) represent the main cause of gastroenteritis in children worldwide (1). It is estimated that they are responsible for a large number of diarrhea associated hospitalizations in childhood each year (2).

These infective agents are ubiquitous and about 95% of children worldwide are infected before 3–5 years of age (3). The highest incidence occurs between 6 and 24 months (4); during the first 12 months of life the risk of severe forms, which require hospitalization, is particularly high, due to the high risk of dehy-

dration in infants and the difficulty in restoring their electrolyte balance.

RV infections can affect adults, often in sub-clinical forms, and occasionally determine clinically evident cases in parents of children with diarrhoea, in immunodeficient patients, in the elderly, and in travellers who visit developing countries (5).

RV are transmitted from person to person, mainly through the fecal-oral route, even though a possible transmission through respiratory secretions and contaminated surfaces has been hypothesized (6, 7).

RV are very contagious and it is estimated that 10 plaque forming units (PFU) are sufficient to transmit

the infection. Furthermore the viral concentration in feces is particularly high ($>10^{10}$ - 10^{11} particles/gram) and especially in children the excretion is prolonged. RV are resistant on hands, surfaces, in water, and to common disinfectants (8). Microbiologically, they are RNA viruses, characterized by a triple-layered structure, with a broad host spectrum (9).

Most children are infected more than once in the first years of life and the first infection is usually the most severe. Repeated infections are rarely caused by the same strain. The primary infection attenuates the severity of the subsequent ones. Two infections virtually confer 100% protection from moderate/severe forms of RV-associated diarrhoea, independently from the serotype (10).

The immune response in infants and children is mainly composed of neutralizing antibodies against the G serotype of the infecting virus. It is a homotypic response which develops after the primary infection. Repeated infections determine both a homotypic and heterotypic (against G serotypes which are different from the infecting type) response. Currently a correlation of protection against RV infections has not been identified and the protective role of antibodies has not been completely defined. Presumably the immune response determines fast recovery but does not protect from reinfections or from mild forms of disease (11).

The possibilities of an effective prevention against pathogens like RV, through improvement of hygienic-sanitary conditions are limited. Epidemiologically, it is estimated that RV worldwide are responsible for over 135 million cases of childhood gastroenteritis, of which 114 million episodes are treated at home, 24 million require outpatient visits, and 2.4 million require hospitalization. They cause about 600,000 deaths/year (12, 13).

In Europe it is estimated that every year among the 23.6 million children <5 years old, 3.6 million RV infections are found, of which about 2.8 million require assistance at home, 700,000 require outpatient visits, and 87,000 require hospitalization. Two hundred and thirty one yearly deaths are estimated (14).

All these data bring to the conclusion that RV represent an important problem for public health care with a significant economic impact for families and society.

The aim of the present study is to describe the burden of RV-associated hospitalizations in the Emilia Romagna region in children aged between 0 and 14 years, in order to obtain updated epidemiological data and estimate the economic impact of these infections.

Methods

The study was carried out by examining the database of the hospital discharge forms (SDO) of the Emilia Romagna region available on the website of the Italian Ministry of Health (15). The main discharge diagnoses in the period 2000-2003 were analyzed.

The SDO is an official instrument of the Ministry of Health, introduced to obtain information about clinical and organizational aspects of hospital admissions. The clinical information is coded by the international ICD9CM system (International Classification of Diseases, 9th revision, Clinical Modification), currently used in Italy. The national SDO database was created in 1994 and since then it has been progressively expanded and improved: currently it includes about 13 million individual records relative to every year of activity, and covers over 95% of the information flow (16).

In the regional database, the SDO are ordered by solar year and three age groups are studied: 0-14 years, 15-64 years and >64 years. Unfortunately, further subdivision of these age groups is not available.

RV associated gastroenteritis (RVGE) in subjects of 0-14 years of age was searched in the database by using the ICD code 00861, which belongs to enteritis due to specified viruses (ICD 0086). In the same class we also searched for enteritis due to other viruses: adenovirus (ICD 00862), Norwalk virus (ICD 00863), other Small Round viruses (ICD 00864), Calicivirus (ICD 00865), Astrovirus (ICD 00866), Enterovirus NEC (Not Elsewhere Classified) (ICD 00867), and other viral enteritis (ICD 00869). Further inquiries were carried out for the following pathogens: cholera (ICD 001), typhoid and paratyphoid fever (ICD 002), other salmonella infections (ICD 003), shigellosis (ICD 004), other bacterial toxi-infections (ICD 005), amebiasis (ICD 006), other protozoal intestinal disea-

Table 1. Hospitalizations for enteritis in Emilia Romagna stratified by pathogen and year, 2000-2003

Age 0-14yrs	Total	NI	Viruses	Salmonella	Other bacteria	Protozoa	Other pathogens
2000	1955	1009	455	228	62	29	172
2001	1823	1065	318	175	62	16	187
2002	1834	1061	373	158	50	9	183
2003	1627	885	333	208	51	4	146
Total	7239	4020	1479	769	225	58	688

Legend: NI= not identified

ses (ICD 007), *Escherichia coli* (ICD 0080), Arizona group of paracolon bacilli (ICD 0081), *Aerobacter aerogenes* (ICD 0082), and *Proteus* (ICD 0083). Finally ill-defined intestinal infections (ICD 009), other specified bacterial intestinal infections (ICD 0085), and those due to other organisms not elsewhere classified (ICD 0088) were considered.

The costs associated to RVGE hospitalizations were estimated through DRG (Diagnosis Related Group) reimbursement rates. Currently a specific DRG for RVGE does not exist and, according to the Emilia Romagna regional DRG reimbursement system (HCFA-DRG, 19th version, 2005), this disease can be referred to three DRG codes (184, 298, 422). Since hospitals are classified into two groups (A, highly specialized structures, and B, traditional structures), the estimated cost for each RVGE hospitalization varies from a minimum of 1293.83 € to a maximum of 2263.79 €. In case of outliers, patients that require a longer or shorter hospitalization compared to that established for each DRG, a daily DRG-specific increase or decrease in cost is used.

Results

In the 2000-2003 period in Emilia Romagna 7,239 children aged 0-14 years were hospitalized for gastrointestinal infections (Table 1), with an annual average of 1,810 hospitalizations.

Ill-defined intestinal infections were 56% of hospital admissions, while specified viral infections were reported in 20%. The RVGE represented 84% of specified viral infections and were uniformly distributed between years. The results are described in figures 1 and 2.

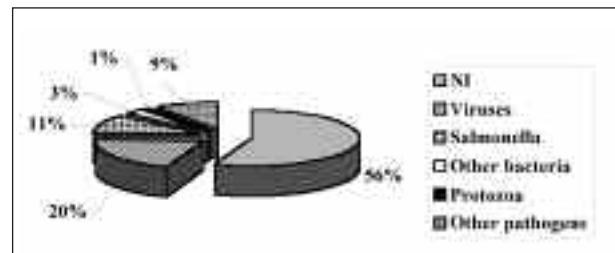


Figure 1. Agents responsible for hospitalizations due to enteritis in Emilia Romagna in 0-14 year old subjects, 2000-2003

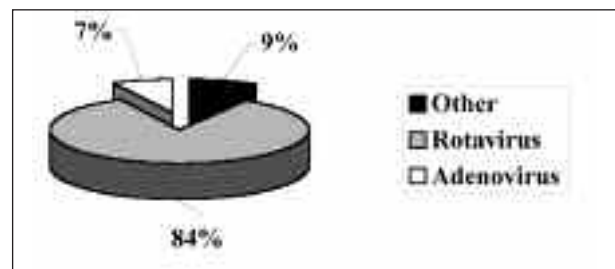


Figure 2. Hospitalizations for viral enteritis in Emilia Romagna in 0-14 year old subjects, 2000-2003

Therefore, RV were responsible for 17% of all the reported intestinal infections and for 1,239 hospitalizations (average 310 cases per year). A slight increased prevalence in males (56%) was observed with an average length of hospital-stay of 3.83 days.

The annual rate of hospitalization in the 2000-2003 period, referred to the resident population between 0 and 14 years in Emilia Romagna in 2004 (17), was 377.92/100,000 for all intestinal infections and 64.7/100,000 for RV.

When only the ordinary hospitalizations were considered the economic impact of RVGE for the Regional public health system varied between 400,000 and more than 700,000 € per year.

Conclusions

In the European countries RV are the main cause of diarrhoea associated hospitalizations in children under 5 years of age. In that age group about 40% of acute gastroenteritis are due to RV (18). These viruses are responsible for 21-38% of outpatient visits for diarrhoea and for 21-54% of hospitalizations for gastroenteritis.

In Italy it is estimated that RVGE affects over 400,000 children <60 months every year, with 320,000 home visits, 80,000 outpatient visits, and about 10,000 hospitalizations (14).

Nationally, RV represent the main cause of hospitalization for diarrhoea and vomiting in children <5 years and are responsible for 84% of all viral enteritis and for 26% of all diarrhoea associated pediatric hospital admissions (16).

We evaluated the epidemiological impact of RV infection in Emilia Romagna. The analysis of the SDO in the 0-14 year age group also showed that in this region Rotaviruses are responsible for 17% of hospitalizations for intestinal infections and for 84% of hospitalizations for viral infections. This rate is comparable with the one found in a recent study carried out in the Arcispedale Sant'Anna of Ferrara, where such percentage represented 79% (19). We confirm the high number of ill-defined cases (56%) found in the database similar to those reported by Marocco et al (54%).

The completeness of the information found in the SDO has reached a considerable level thanks to the commitment and collaboration which started in 1997 between Independent Provinces/Regions and the Ministry of Health. However, the problem of the underestimation of cases due to the high specificity (98%) and low sensitivity (25-47%) of the SDO persists (20, 21).

The incidence of RVGE is underestimated for several reasons: not all the patients undergo a stool analysis; some laboratories do not have sensitive enough tests for the detection of the virus; not all the data are carefully included in the SDO, and only the main diagnosis is included in the regional database. An effort should be made to improve the diagnostic ability in the 56% of ill-defined infections causing hospital admission.

RV infections are associated to two types of costs: direct and indirect. Direct costs refer to outpatient visits, Emergency Room, and hospitalization costs; the indirect costs are related to workdays missed by parents also for cases treated at home. According to the different health care systems and the specific situations of each country, costs for RVGE may vary. Overall costs related to RVGE are high in industrialized countries, while they are difficult to define precisely in developing countries.

In USA costs for RVGE amount to over 1 billion dollars per year, of which 250 million for direct costs and 750 million for indirect costs (22-24).

In Europe the socio-economic effects have been studied in few countries and the methods used are not always comparable (25-28). The average cost of one case of RVGE in Europe has been calculated as equal to 1,417 € (29).

The studies performed in several countries have tried to analyze the proportion between direct and indirect costs associated with RVGE. The results however are discordant. In fact, while in Germany it is estimated that 51% of costs are referable to hospitalization, 27% to outpatient visits, and 21% to indirect costs (30), in Austria the indirect costs were calculated to be 6.6% of the total (31). An American study estimated that each episode of RVGE treated at home costs the family \$289 (32). In Italy, a multicenter study found that one case of diarrhoea due to any cause costs about 110-116 € (33), which nationally amounts to about 27-68 million euro/year. When only children under 4 years of age were considered, 75% of the indirect costs were due to workdays missed by the parents.

In terms of workdays missed by caregivers a study conducted in seven European countries estimated that they were 2.3-6.4 workdays missed per episode (18). As expected, in order to assist the child mothers were significantly more absent from work than fathers (59% vs 2%) (34).

According to the present study, the average length of hospital-stay in Emilia Romagna is similar to the national data, i.e. about 4 days for 1-4 years old children and 4.31 days <1 year (16), and to the French and Spanish studies which show an average length of 4 days.

The economic impact of cases registered in the Emilia Romagna SDO database varies between 400,000 and 700,000 euro/year; it is important to underline that the hospitalized cases represent only a portion of RVGE in the population.

Another important aspect that must be considered is the incidence of nosocomial RVGE, which complicate hospitalizations for other diseases with a further increase of costs. It has been estimated that 1/5 of all RV infections are hospital-acquired. This prolongs the hospital stay of 5 or more days (25, 35) and increases the economic impact of the disease. In a prospective multicenter study conducted in Austria, Germany, and Switzerland RV was detected respectively in 57%, 69%, and 49% of children <4 years of age with diagnosis of nosocomial gastroenteritis (25). In conclusion, RVGE has a significant impact on public health systems in relation to costs for treatment, competition for scarce resources (hospital beds included) and the overload of health services during winter, and on society because of the loss of productivity and family expenses (babysitters, diapers, etc.). The worldwide epidemiological impact of these pathogens, their microbiological characteristics, and knowledge on the immune response have made the development of safe and effective vaccines against RV a priority. Two live attenuated oral vaccines are available and phase 3 studies have demonstrated that they are able to prevent severe RVGE (36, 37).

The great epidemiological and economical burden on healthcare systems and families indicates the importance of a vaccine program in all newborns in their first weeks of life.

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Accepted: 29th October 2007

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