
REVIEW ARTICLE

The paediatric burden of rotavirus disease in Europe

The Pediatric ROTavirus European CommitTee (PROTECT)*†

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SUMMARY

Rotaviruses are a major cause of hospitalizations for acute gastroenteritis in developed countries. This review shows the burden of rotavirus disease in <5-year-old children in Europe. An estimated 72 000–77 000 hospitalizations for community-acquired rotavirus disease occur annually in the 23 million under-fives living in the European Union (EU-25), with a median cost of €1417 per case. Annual hospitalization incidence rates range from 0·3 to 11·9/1000 children <5 years old (median 3/1000). The median proportion of hospital-acquired rotavirus disease among all cases of hospitalization for rotavirus disease is estimated to be 21%. Countries of the EU-25 require information on the burden of rotavirus disease to support introduction of rotavirus vaccines. Data on cases treated at home, medical visits, and emergency wards as well as rotavirus-associated deaths are limited. To fully evaluate the impact and effectiveness of rotavirus vaccination programmes in Europe, additional epidemiological studies will be critical and desirable.

INTRODUCTION

Rotaviruses are members of the Reoviridae [1, 2]. They are a major cause of acute gastroenteritis in infants and young children worldwide, are transmitted faecal-orally and are highly infectious. Diarrhoea and vomiting may lead to serious dehydration and death if untreated. Treatment is mainly by oral or intravenous rehydration [3]. Repeated natural rotavirus infections build up protection against disease [4]. The epidemiology is complex with co-circulation of unpredictable changes of different rotaviruses types in different regions at different times of the year [1, 2]. Rotavirus disease peaks between 6 and 24 months of age, and most clinically significant gastroenteritis episodes,

including those requiring hospital admission, occur before the age of 5 years.

A recent update of the global burden of rotavirus disease estimated 111 million episodes at home, 25 million outpatient visits, 2 million in-patient visits and over 600 000 deaths [5, 6]. Most of this disease burden is in developing countries, reflecting the large number of children aged <5 years old, as well as a higher case-fatality rate due to underlying risk factors such as malnutrition, concomitant infections and limited access to health-care. Nevertheless the relative burden of rotavirus disease (measured as incidence rates) is comparable in both developing and developed countries [5]. This indicates that hygienic measures alone are not enough. Therefore there is a need for effective prevention strategies to reduce rotavirus morbidity.

Severe rotavirus disease is largely preventable by vaccination with live attenuated oral vaccines [7]. This was demonstrated with the use of a rhesus rotavirus-based tetravalent human reassortant vaccine

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(RRV-TV) [8–10], and two new rotavirus vaccines being studied [11, 12] are likely to be introduced soon. Rotavirus vaccination will be of interest to developed countries for a number of reasons of which a major one is to achieve a reduction of the large, and costly, burden of hospitalizations for severe rotavirus disease. Policy makers require information on the burden of rotavirus disease and cost-effectiveness of the vaccine to help in their decision-making processes.

This review summarizes the available data for Europe on the burden of rotavirus disease in children <5 years old on hospitals, emergency-room visits, and primary care. Gaps in the information on the burden of rotavirus disease and mortality in Europe, as well as associated costs, were identified.

METHODS

The references selected for this review were identified by Medline searches. To identify papers on the burden of rotavirus disease the following broad search strategy was defined: ‘rotavirus’ (text word) combined with ‘country name’ (text word or in author’s affiliation) and combined with ‘epidemiology’ (medical subheading). The search was limited to the period 1994–2005 and to studies in humans. This search was performed for every European country of the WHO European region separately (North, West, South, Central and East European countries including all former USSR countries and Turkey) and yielded 161 papers. Further inclusion criteria were the languages Dutch, English, French, German, Italian and Spanish; studies containing data for children <5 years old; the observation period being a whole year(s) period (except for data on nosocomial infection); and limited to group A rotavirus infections. Finally, 59 papers containing data relevant to the objectives of this paper were identified. Some additional studies mentioned in the references of the papers retrieved by the initial search were considered for inclusion, including key papers published before 1994.

Although the Medline search strategy was performed for all countries of the WHO European region, data were mostly available for the European Union (EU-25) countries. Therefore, estimates for the absolute disease burden were limited to the EU-25 region. The rates for medical visits and hospitalizations are population-based.

RESULTS

The impact of rotavirus disease at a country level was split in six categories: (1) cases treated at home (without a visit to physician), (2) disease treated at the level of primary health care (medical visits), (3) disease seen and treated in hospital emergency wards, (4) community-acquired disease requiring hospitalization with (5) hospital-acquired (nosocomial) infections regarded as a separate entity and (6) mortality.

Cases treated at home

It has been estimated that by the age of 5 years nearly every child will have had one or more rotavirus infections [5], but information on the proportion of symptomatic disease is limited. In a prospective cohort of 336 Finnish infants followed from birth to 2.5 years of age 1 in 7 infants had a symptomatic episode of rotavirus disease [13]. In another cohort of Finnish infants followed prospectively in a vaccine clinical trial (the placebo group of a RRV-TV trial) [9], 188 symptomatic cases of rotavirus infection occurred among 1145 infants followed for 1 year. This corresponds to about one symptomatic case in six infants [9]. Of these, only 28% were treated at home. To our knowledge, no other reports on rotavirus cases treated at home are available.

Primary health care: general practitioner, family paediatrician, and outpatient clinic

In the Finnish vaccine trial 86 of 1145 infants in the placebo group of the RRV-TV vaccine trial visited a physician for rotavirus disease [14], corresponding to 7.5/100 infants per year. Prospective observational studies in paediatricians’ offices in Austria, Switzerland, and Germany gave annual incidence rates of 0.84, 1.8, and 4.1/100 children aged <5 years old respectively [15–18]. In The Netherlands, 0.76/100 children aged <1 year old and 0.46/100 children aged 1–4 years old visited the GP for rotavirus disease each year, telephone consultations were excluded [19, 20].

Emergency wards

In the Paris area (France) rotavirus infections accounted for 2–2.4% of all paediatric consultations at the emergency department [21]. In the Basque country (Spain), the incidence rate of rotavirus disease treated at the emergency ward was 2.2 cases/100 children aged <4 years old [22]. A similar incidence

rate (2.6/100) was found in infants in the placebo group of the Finnish RRV-TV vaccine trial [9]. In this trial 1.8 visits were made to the emergency department for every hospitalization for rotavirus disease [9]. This ratio is likely to be lower when the emergency wards are equipped with facilities to provide 24-h intravenous fluid replacement. A study in Italy showed that 10 cases could be treated in the emergency ward for every case admitted to hospital (C. Giaquinto, unpublished observations).

Hospitalizations

In the EU-25 region 6–11% of all hospitalizations of children aged <5 years old are caused by acute gastroenteritis [23–27], and a median of 40% (range 14–54%) of acute gastroenteritis hospitalizations is attributable to rotavirus infection [17, 25, 26, 28–40]. The reported percentage of rotavirus disease in acute gastroenteritis hospitalizations clearly depends on study design, coverage and representativeness of laboratory surveillance systems, as well as the year(s) and geographical area(s) included in the study.

An overview of the incidence rates of hospitalization of children aged <5 years old due to community-acquired rotavirus disease in Europe (Table 1 estimates a median incidence rate of 3/1000 children per year (range 0.3–11.9/1000), median cumulative incidence rate of 1 in 67 children hospitalized because of rotavirus gastroenteritis before the age of 5 years, and 72 000–77 000 hospitalizations per annum of <5-year-old children for rotavirus disease in the EU-25 region.

In the Finnish RRV-TV vaccine trial 13 children were hospitalised for rotavirus disease among 1145 infants [9] in the placebo group, corresponding to 11.4/1000 infants per year – comparable to the high end rate seen in the British Isles (Ireland) [25].

The average length of hospital-stay ranged from 2 to 9.5 days (median 4.8 days) [17, 23, 27–29, 33, 34, 36, 41–43]. The longest durations were found in Central Europe with 8.3 days for infants in Hungary, and 9.5 days for children <5 years old in Poland.

Depending on the studies and countries the hospitalization incidence peaked in children aged 6–11 or 12–23 months [22, 23, 28, 31, 41, 42]. Around 50–60% of the cases occurred in children <1 year old [26, 34, 44], and 60–80% in children <2 years old [28, 30, 34, 36, 41]. In Europe, as in the rest of the world, the risk of being hospitalized for rotavirus disease was highest among children aged <2 years old.

The related direct medical costs per hospitalized case of community-acquired rotavirus disease ranged from €691 in Poland to €1773 in Spain (median: €1417 per case of rotavirus disease, Austria excluded) (Table 2).

Hospital-acquired rotavirus infections

The burden of hospital acquired (nosocomial) rotavirus infections is summarized in Table 3 and described as attack rates (percentage of hospitalized children developing rotavirus disease) and incidence densities (rotavirus disease cases/1000 bed days), respectively. Data were available for seven countries. Of the children aged <5 years old 2.5–11.8% developed rotavirus disease [50–59] during hospitalization (including two studies using onsets at 48 and 72 h after admission). The median proportion of nosocomial rotavirus infection among all rotavirus-associated hospitalizations (community- and hospital-acquired) was estimated to be 21% (range 5–51%) in European countries [21, 22, 27, 30, 33, 36, 47, 60]. About half of all nosocomial rotavirus infections prolonged the length of stay [15, 36] by a number of *excess* hospital days ranging from 2 to 7 days (median 4.3 days) [15, 36, 48, 50–53, 58].

Mortality

Estimates on mortality from rotavirus infection could only be made for a few North and West European countries. In Finland one death from rotavirus disease was reported every 2–5 years [28], corresponding to an annual mortality rate of 0.7–1.8 rotavirus deaths per million children aged <5 years old. In France, an estimated 2–6 children aged <5 years old die from rotavirus disease each year [23], equivalent to an annual mortality rate of 0.5–1.6 rotavirus deaths per million children aged <5 years old. In a German children's hospital a mortality rate of 1/1000 rotavirus hospitalizations was found [27]. Using the hospitalization incidence for rotavirus disease for Germany of 3/1000 children aged <5 years old [15], an annual mortality rate of 3 per million children aged <5 years old is estimated. In Ireland, 1 rotavirus death occurred in 11 907 hospitalizations for diarrhoea. The hospitalization-incidence rate for diarrhoea for children aged <5 years old was 24/1000 [25], leading to an estimate of 1.9 rotavirus deaths per million children <5 years old per annum. In England and Wales, 18 deaths from infectious intestinal disease

Table 1. Population-based hospitalization incidence rates for community-acquired rotavirus (RV) disease in European countries

Country (reference)	Age group (yr)	Population <5 yr old (×1000)*	Observation period	Annual RV hospitalization incidence rate per 1000 children <5 yr old	Absolute number of annual RV hospitalizations of children <5 yr old†	Cumulative incidence rate by age 5 yr	Method‡
UK (Ireland) [25]	<5	285	1997–1998	11.9	3392	1 in 17	A
Hungary [33]	<5	433	1993–1996	8.4	3637	1 in 24	B
Finland [28]	<5	280	1985–1995	6	1680	1 in 33	A
UK (England) [29]	<5	3242	1993–1994	5.2	16 858	1 in 38	B
Sweden [26]	<4	457	1981/1993–1996	3.7	1691	1 in 54	B
Poland [36]	<5	1825	1990–1996	3.1	5658	1 in 65	C
Germany [15, 17]	<5	3630	1997–1998	3	10 890	1 in 67	D
Denmark [35]	<5	316	1995–1999	2.8	885	1 in 71	C
The Netherlands [30]	<5	973	1996–1998	2.7	2627	1 in 74	A
Spain [32, 41, 42]	<5	1894	1999–2000	1	1894	1 in 200	A
			1989–1995	2.5	4735	1 in 80	A
			1993–1996	3.1	5871	1 in 65	B
France [23]	<5	3832	1997	2.1	8047	1 in 95	E
Switzerland [15]	<4	396	1997–1998	2.1	831	1 in 95	D
Austria [15]	<4	351	1997–1998	0.3	105	1 in 667	D
EU-25 countries mentioned in table		17 518			55 613–61 341§	1 in 63 to 1 in 57§	
EU-25 countries not mentioned in table		5351			16053¶	1 in 67	
Total EU-25		22 869			71 666–77 394	1 in 64 to 1 in 59	

* Estimates for 2005. UN Department of Economic and Social Affairs. Population Division. World Population Prospects: The 2002 Revision Population Database. United Nations, New York, 2004 (<http://esa.un.org/unpp/index.asp?panel=1>).

† Data for children <4 years old have been applied to the population of children <5 years old.

‡ A, direct or indirect estimate (logistic regression) based on *national* hospital admission data for acute gastroenteritis and laboratory data for rotavirus infection; B, same method as A, but based on *regional* data; C, hospital-based studies testing all or a sample of acute gastroenteritis admissions; D, prospective study among representative sample of paediatric offices and subsequent hospital admissions (laboratory-confirmed cases); E, direct estimate based on the International Classification of Diseases and Causes of Death (9th revision) code for rotavirus disease in national hospital discharge data.

§ The absolute numbers of the individual EU-25 countries in the table (thus excluding Switzerland) have been summed. A range is given, because for some countries more than one estimate of the absolute number of RV cases was available. The cumulative incidence is based on the estimated absolute number of cases and the population size.

¶ For EU-25 countries for which no data were available from the literature, the absolute number of cases has been estimated from the median hospitalization incidence rate for EU-25 countries in the table (median 3.0/1000). The cumulative incidence is based on the estimated absolute number of cases and the population size.

occurred among children aged <5 years old. Laboratory data showed that 39% of the infectious intestinal diseases were caused by rotavirus infection, leading to seven rotavirus deaths in young children per year [61] and an annual mortality rate of 2.3 deaths per million children aged <5 years old. In summary, the mortality rate in North and West

European countries ranged from 0.5 to 3 deaths per million children aged <5 years old per year.

DISCUSSION

This review shows that in the EU-25 region 40% (median) of the hospitalizations for acute

Table 2. *Direct medical costs per case hospitalized with community-acquired rotavirus disease in European countries*

Country (reference)	Age group (yr)	Year in study	Costs per case (€, 2004)*
Austria [45]	<4	1997	109†
France [23]	<5	1997	1281
Finland [28]	≤1	1993	1562
Germany [46]	<5	2002	1730
Hungary [33]	<5	1998	1553
Poland [36]	<5	1996	691‡
Spain [41]	<5	2000	1773
Sweden [26]	<4	1996	1102
UK (England) [47]	<2	1992	1710
UK (Ireland) [48]	<15	2000	843§
UK (Ireland) [49]	<7	1997	1265

* Cost estimate for 2004. Price levels in study corrected for inflation. Cost calculations differ for countries using the cost of bed-days alone (Ireland [49]) or including diagnostics and medication (Austria, France, Hungary, Poland, England, Ireland [48], Spain (?)), as well as doctor's wages (Finland, Germany (?)) or using the reimbursement fee the hospital obtains per case (irrespective of length of stay) (Sweden). (?) Cost calculation not completely clear from the paper.

† Calculation based on two cases only.

‡ Prices are considered as 'severely underestimated', and 'expected to rise steeply to EU levels' [36].

§ Calculation based on median bed-days and median investigations, interventions and medication. When the calculation was based on actual costs, the mean cost per case was €1409.

gastroenteritis in children aged <5 years old were attributable to rotavirus disease, comparable to Asia (45%) [62], and close to the upper limit of 26–49% recently estimated for the United States [63]. Based on the country-specific hospitalization incidence rates for rotavirus disease, this review estimates a minimum of 72 000–77 000 hospitalizations per annum among children aged <5 years old with community-acquired rotavirus disease in the EU-25 region (Table 1). Nosocomial rotavirus disease adds to the hospital burden of disease. An estimated median of 21% of all (community-acquired and nosocomial) rotavirus-associated hospital cases in the EU were nosocomial, adding about 20 000 nosocomial cases of rotavirus disease to the burden of hospitals. This estimate is in line with another recent study which estimated a median of 27% of all rotavirus-associated hospital cases in developed countries to be hospital-acquired [64].

The differences in hospitalization rates may reflect genuine geographical differences with a different

epidemiological pattern of disease in North and East Europe compared to West and Central Europe. While the available data do not allow for a proper comparison of the incidence rates between different European countries, they nevertheless suggest that true regional differences exist within Europe. The differences may also reflect genuine differences in disease severity between countries. The prospective studies in Austria, Germany and Switzerland, however, did not reveal an association between disease severity measured with the Vesikari score [65] and hospitalization rate or primary-care visits [15], suggesting that factors other than disease severity affect the differences in hospitalization rates as well. The differences in burden of rotavirus disease between countries may also be due to differences in study design, sample size, age groups included in the studies, differences in health-seeking behaviour, access to health care, and case-disease management.

The Finnish clinical trial data [14] showed fairly high incidence of rotavirus disease in primary and hospital care compared to most observational studies from other countries. The study design of observational studies and clinical trials is very different. Clinical trials have a strictly controlled study design with a very stringent follow-up of cases. Thus, the experimental setting of a trial is likely to lead to higher estimates than the non-experimental setting of the studies based on hospital data as described in Table 1.

In the observational studies a high hospitalization incidence rate was found for Ireland and a low rate for Austria. The authors of the Irish study suggested that the quality of their data sources might be better than in other countries, or there might be a greater tendency to hospitalize children with diarrhoea than to treat them in the emergency room or as outpatients, but there are no data to support this hypothesis [25]. A low incidence rate for Austria was estimated from a population-based prospective study with about 3500 children-years under observation, comparable to the size of the Swiss cohort in the same study [15]. The number of outpatient rotavirus cases was low in Austria, and especially the percentage of outpatient cases that needed hospitalization was very low (4%) in Austria compared to Switzerland (12%), leading to a very low hospitalization incidence rate [15]. However, the differences between Austria and Switzerland were not significantly different [15].

Most studies estimated the incidence rates from either national or regional hospital discharge data on acute gastroenteritis and from the detection rate of

Table 3. Nosocomial attack rates and incidence density rates for rotavirus (RV) disease in European countries

Country	Age group (yr)	Attack rate (% of hospitalized children developing RV disease)	Incidence density (RV cases per 1000 bed-days)	Study period*	References
Austria	<4	n.a.	1.6–2.6	A	[15, 45]
			2.3–2.6	B	
France	0.25–3	11.1	n.a.	B	[58]
	<2	6.6	16	B	[51]
	<3	6.7	n.a.	B	[55]
	<3	4.3	n.a.	B	[56]
	<3	2.9–3.7	n.a.	B	[57]
	<5	3.6	8.1	B	[50]
Germany	<4	n.a.	1.6	A	[15]
			2.3	B	
Italy	<1.5	11.8	n.a.	B	[53]
Spain	<2	5.1	10	A	[52]
Sweden	<2	2.5–2.9	7–10	A	[54]
Switzerland	<4	n.a.	0.7	A	[15]
			1.0	B	

* A, whole year(s) period; B, rotavirus season.
n.a., Not available.

rotavirus infection confirmed by laboratory data. It has been shown that this method, preferably using a combination of routine laboratory data and a systematic surveillance programme, yields accurate estimates of rotavirus hospitalizations [63]. Studies based on national hospital discharge data using the specific ICD-9 code for rotavirus disease only (e.g. France [23]) grossly underestimate the real disease burden [63, 66].

For nosocomial rotavirus disease different case definitions were used in published studies, ranging from infection occurring 48–72 h after admission, and the studies were often performed during the rotavirus season only.

The use of Medline as a source of information might have been a limitation as studies in local languages and contexts were not reported. Therefore, little data on Central and East European countries could be presented.

The median cost of €1417 for a hospital stay for community-acquired rotavirus disease is a rough estimate for countries of the EU-25. The figures presented are based on different cost calculations using the cost of bed-days alone or including diagnostics and medication, or using the reimbursement fee the

hospital obtains per case (irrespective of length of stay). European data on the cost structure of rotavirus disease show that hospital stay is a main cost driver, but that non-medical costs are not negligible. In the Finnish vaccine trial, hospitalizations accounted for 75% of the medical costs [14, 28]. The total medical costs accounted for 88% and the non-medical costs (including travel and production loss of caregivers) 12% of the total costs of rotavirus disease. For Germany, it was estimated that hospital stay accounted for 51% of the costs associated with rotavirus disease (including nosocomial cases), outpatient visits for 27% and days of work lost by the mother for another 21% [46]. In Austria the productivity loss of the caregiver was estimated to be only 6.6% of the total costs [45]. The costs and cost structure associated with rotavirus disease differ between European countries, depending on the structure of health services and social system (e.g. the period of maternity leave, participation of mothers in employment, etc.) in the country.

There is a need for effective prevention strategies to reduce rotavirus morbidity. Hygienic measures alone do not seem to be enough as incidences of severe disease in developing and developed countries are

comparable. In addition, nosocomial transmission is difficult to control with preventive methods of hygiene and isolation due to the resistance of the virus to the environment, and other possible routes of transmission beside the faecal–oral route [57, 64]. During the rotavirus season, the epidemic peak of rotavirus disease leads to a substantial disruption of the hospital care system. The hospitalization rate can increase 1.8- to 2.5-fold compared to a whole year's period [28, 34, 41]. Vaccination could overcome the shortcomings of other prevention strategies. The most tangible primary impact of a rotavirus vaccination programme in Europe would be a reduction of severe rotavirus disease requiring hospitalization as well as nosocomial rotavirus infection. New rotavirus vaccines are likely to become widely available in the near future. In order to evaluate the impact and effectiveness of a vaccination programme, data on the burden of rotavirus disease and its associated costs are required. The available data on the burden of rotavirus disease show great variability in study design and case definition. Data on cases treated at home, medical visits and emergency wards for rotavirus diarrhoea are limited, as well as on the associated costs, and the true number of rotavirus-associated deaths is not known. Standardized surveillance studies addressing the rotavirus disease burden and its determinants for different settings of health care as well as economic studies on medical and non-medical costs are needed.

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DECLARATION OF INTEREST

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APPENDIX. Writing Committee of PROTECT Advisory Board

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