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ORIGINAL PAPER

Disease burden of rotavirus gastroenteritis in children up to 5 years of age in two Swiss cantons: paediatrician- and hospital-based surveillance

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Abstract Rotavirus gastroenteritis (RV GE) is a leading cause of diarrhoea in young children. The purpose of this epidemiological surveillance was to measure the disease burden of RV GE among children <5 years of age in two regions of Switzerland, Geneva and Lucerne. One hospital and four paediatricians participated per region. The surveillance lasted from December 2006 to June 2007. The population denominator for calculation of the RV GE incidence rate was the average of the overall study population <5 years of age under surveillance during the surveillance period. At the study sites, 513 children with GE were presented. Stool sample was collected and examined in 341 cases, of which 130 were RV positive (38.1%). Informed consent to participate in the study was obtained for 113 RV positive subjects. The overall RV GE incidence rate was 0.97% in Lucerne [lower incidence interval (LCI), 0.71%; upper incidence interval (UCI), 1.2%] compared with 0.65 and in Geneva (LCI, 0.50%; UCI, 0.81%). Disease severity assessments using the Vescari score showed that the RV GE episodes were more severe in Lucerne than in Geneva (14.05±3.05 vs 12.85±2.87), which was confirmed by a higher hospitalisation rate in Lucerne at the study visit (82.9% vs 23.6%). More children had fever in Geneva than in Lucerne (42.9% vs 26.8%), and more children were hospitalised during the follow-up period in Geneva than in Lucerne (14.5% vs 2.5%). Genotyping of RV positive stool samples revealed that both G1 and P8 were the most prevalent types in both regions. There was a statistically significant difference in the distribution frequency of G1 between the two regions (p=0.039). Assessment of health economic data confirmed the economic burden of RV GE episodes. In conclusion, RV GE episodes are a health burden as well as an economic burden also for the children in a developed country such as Switzerland.

Keywords Rotavirus gastroenteritis · Disease burden · Epidemiological study · Switzerland

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Introduction

Rotavirus (RV) is the most common cause of severe, dehydrating gastroenteritis (GE) in infants and young children in developed and developing countries [5, 17]. By the age of 3–5 years, 95% of children worldwide have been infected [20]. RV causes approximately 140 million cases of diarrhoea annually accounting for 20% of outpatient or clinic visits for diarrhoea, 26% of hospitalisations for diarrhoea and a total of 452,000 deaths in children under 5 years of age. However, in industrial countries, mortality due to RV is low [21].

RV is a double-stranded RNA virus with three protein layers (capsids) surrounding the genome [6]. Variability in the two outer layer proteins VP7 and VP4 results in different G, respectively, P geno- and serotypes. Both VP7 and VP4 proteins induce neutralising antibodies and are therefore important targets for vaccine development [10]. The prevalence of the four major RV strains (G1P [10], G2P [5], G3P [10] and G4P [10]) can vary considerably from year to year and from one geographic area to another [24]. Although RV is detected year-round [1], the disease has a winter seasonal pattern in developed countries with a temperate climate.

The primary burden of RV GE is on child health. However, RV as a cause of severe vomiting and diarrhoea, leading to dehydration and hospitalisation, also places significant economic burden on health care systems and society [4, 12, 26]. This health and economic burden might be reduced by RV vaccination. In the USA, it was found that vaccination delayed RV activity during current season in onset by 2–4 months and diminished its magnitude by >50% when compared with 15 previous seasons [25]. After the introduction of RV vaccination programmes, a reduction in the number of hospitalisations and child deaths would be expected in developing countries, while a reduction in the number of clinic visits, hospitalisations and lost work days would be expected in developed countries [13]. Recently, the cost-effectiveness of RV vaccination has been assessed in several countries. The outcomes of RV vaccination evaluation in England and Wales showed that while immunisation could reduce morbidity burden, the cost-effectiveness seems not to be attractive enough [15, 16]. Similar findings were obtained in the USA [28] and Australia [19]. So far, in Switzerland one licensed RV vaccine exists, but RV vaccination is listed as vaccine without recommendation in the official Swiss vaccination plan 2009 [3].

The purpose of this pilot epidemiological study was to estimate the disease burden of RV GE among children <5 years of age in two regions of Switzerland, Lucerne and Geneva, using paediatrician- and hospital-based surveillance. The primary objective was to estimate the RV GE incidence rate in a defined area. The secondary objectives were to determine (1) the age distribution of RV positive patients, (2) the disease severity and (3) the prevalence of RV genotypes. Furthermore, (4) the socioeconomic impact of the RV GE episode was analysed.

Materials and methods

Study design

We conducted an observational, prospective, paediatrician- and hospital-based, multi-centre, epidemiological study in primary but no nosocomial RV GE positive children <5 years of age in the cantons of Geneva and Lucerne between December 2006 and June 2007. The study was approved by the Ethic Committee of Geneva and Lucerne, respectively.

There were one hospital and four paediatric offices participating per region. Sites were considered an appropriate selection of possible study sites per region.

All children <5 years of age presenting at the selected study sites with acute GE, defined as the production of three or more watery or looser than normal stool or forceful vomiting within a 24-h period, were proposed to participate in the study. When oral consent of parents/guardians was given, a stool sample was collected from the children with acute GE and tested for RV using Vikia rapid test kit (Vikia® Rota-Adeno, bioMérieux, S.A.).

Only children with positive RV rapid test and whose parents gave written informed consent, who were attainable by telephone and communicate in a local language, were included in the study. Children suffering from an underlying chronic gastrointestinal tract disease and children who had been hospitalised within the last 14 days prior to the visit were excluded from the study. During the study visit, the disease severity was assessed using the 20-point-scale method by Vesikari [23].[1] Demographics, medical history, risk factors and additional costs were collected by means of a case report form. Based on the outcome of the study visit, patients were classified into several subgroups termed “sent home”, “sent to a specialist”, “sent to the emergency room”, “hospitalised” and “scheduled for a further visit”. All patients seen at the two hospital sites were emergency contacts and considered as having had at least a “hospital visit”.

A follow-up phone call to the parents/guardians of the enrolled child 14 days after the study visit completed the study for the enrolled patient. During the follow-up telephone call, the health status of the child was assessed, and data on further economic costs were collected. Variables such as full recovery, necessity to contact a medical facility after the study visit and hospitalisation due to the same episode of RV GE were also recorded.

Stool samples

Genotyping was performed by RT-PCR on RV-positive stool specimens. Briefly, nucleic acids were extracted using an automated system based on magnetic beads (easyMAG, bioMérieux, Boxtel, The Netherlands) and then reverse transcribed using random hexamers. G-types were determined by amplification of the VP7 gene with

[1] The score assesses the duration of diarrhoea, the maximal number of episodes of diarrhoea per day, duration of vomiting, maximal number of episodes of vomiting per day, maximal rectal temperature, the degree of dehydration and treatment (oral rehydration or hospitalisation).

one consensus (End9) and six type-specific primers as described previously [14]. In cases of uncertain assignment, the amplicon obtained with consensus primers Beg9/End9 was sequenced. P-typing included amplification of the VP4 gene with two consensus primers (con2/con3 [10]) followed by sequence analysis and comparison to sequences deposited in GeneBank.

Demographic data

Children were grouped in age groups of 1 year and by Swiss or non-Swiss nationality. Non-Swiss children were defined as children living in the canton of Geneva or Lucerne but having no Swiss passport.

Estimation of medical and societal costs

Data on medical costs related to the episodes of RV GE were assessed by collecting the anonymised invoices (according to TarMed system), which included costs for laboratory test and drugs dispensed in the centre. Extra expenses such as for medication, nutritional products, transportation and others covered by parents were assessed at the study visit and at the follow-up call. Societal costs such as loss of working days, necessity to organise day nurse and missed nursery or playschool hours were also assessed at the follow-up call.

Sample size

The population under surveillance was expected to be between 5,000 and 10,000 children <5 years served by the sites selected for the study. It was calculated that this would allow detection of an adequate number of RV GE cases among these children (e.g., assuming an expected RV GE incidence rate for cases leading to physician consultation of two cases per 100 children-years, one would expect to see between 100 and 200 RV GE cases for a population under surveillance of 5,000–10,000 children <5 years of age)

Statistical analysis

The data of the intent to treat (ITT) population are presented. The ITT population comprised all study subjects including children where follow-up period exceeded 20 days

The incidence of RV GE leading to a physician or hospital (study site) visit among children <5 years of age overall and by 1 year age groups was calculated with 95% CI. The population denominator for the incidence was the average of the overall study population <5 years of age per region under surveillance during the surveillance period. This analysis was performed for all RV GE episodes with positive results on a rapid stool test and confirmed at the central laboratory. The used statistical test procedures were the chi-square test to compare several incidence proportions and the z test for comparing proportions.

Quantitative parameters were analysed using t test for comparing the means of two groups and ANOVA for comparing the means of several groups. p values <0.05 were considered statistically significant.

Results

Study population

The per protocol analysis population consisted of 87 patients, and the ITT population consisted of 113 patients. Only results of ITT population are presented and discussed below.

Overall, 513 children suffering from acute GE were seen at the sites. After obtaining oral consent from parents, stool samples of 341 children were collected of which 130 were tested positive for RV. Ensuing 113 patients of these RV positive patients were enrolled in the study. Further details are given in Table 1.

Demographic characteristics

The age distribution of children enrolled in the study was analysed for the regions Geneva and Lucerne in subpopulation of 1-year age groups. The majority of children enrolled in the study were between 0 and 1 year (overall 41.6%, n=47) and 1–2 years (overall 44.2%, n=50). Eight per cent (n=9) of all children were between 2 and 3 years, 5.3% (n=6) between 3 and 4 years and 0.9% (n=1) between 4 and 5 years old. No statistically significant differences in the distribution of age groups were observed between the two regions.

In Geneva, 50% of the children enrolled were of Swiss nationality, and 50% were of non-Swiss nationality. In

Table 1 Overview of the screened population at the centres in Geneva and Lucerne

Number of children	Geneva	Lucerne	Overall
With acute GE	127	386	513
Where an oral consent was given	127	231	358
Where a stool sample was collected	114	227	341
Positive for RV	73	57	130
Where written consent was given	72	43	115
Enrolled in the study	72	41	113

In some children, it was not possible to obtain a stool sample. In two patients, the consent was withdrawn

Lucerne, 75.6% of children enrolled were of Swiss nationality, and 24.4% were of non-Swiss nationality. There was a significant difference in the distribution (p=0.008).

Incidence rate of RV GE

The incidence rates of GE are shown in Fig. 1a. The GE incidence rate in Lucerne [6.6%; lower incidence interval (LCI), 5.9%; upper incidence interval (UCI), 7.2%] was higher than in Geneva (1.1%; LCI, 0.94%; UCI, 1.3%) based on the study population of children under 5 years. The overall incidence rate was 3.0%±0.26%. In both cantons, children under 2 years were markedly more susceptible for GE compared to the older children. The incidence rates were highest in these age classes (3.5–3.9%).

The incidence rates of RV GE are shown in Fig. 1b. The RV GE incidence rate was higher in Lucerne (0.97%; LCI, 0.71%; UCI, 1.2%) than in Geneva (0.65%; LCI, 0.50%; UCI, 0.81%). The overall incidence rate was.0.76% (LCI, 0.63%; UCI, 0.90%). The incidence rates for children under 2 years were higher compared to the children 2–5 years old.

RV GE accounted for 36.3% of GE cases among the study population. This percentage was markedly higher in Geneva than in Lucerne (57.5% vs 24.7%). See also Table 1.

To evaluate whether the children of certain age groups were more prone to RV GE, the age distribution in the study sites

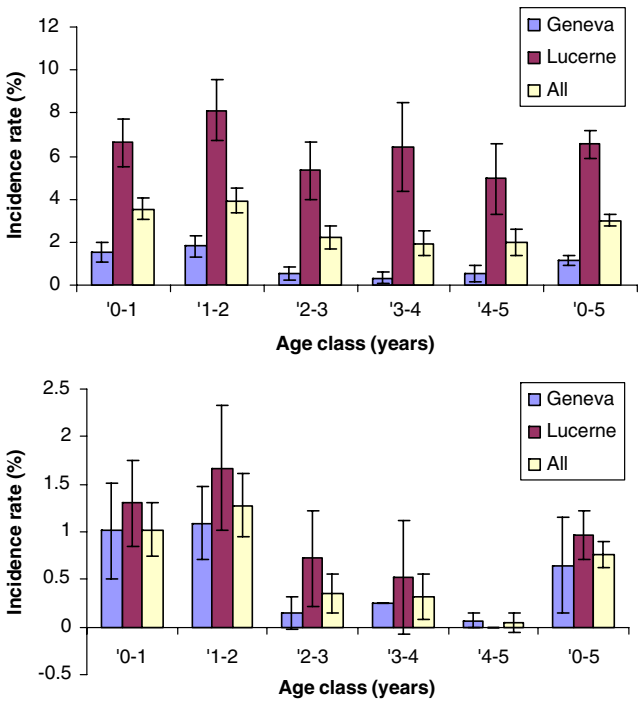

Fig. 1 **a** Incidence rates (IR) by site region and age for acute gastroenteritis (GE) calculated with 95% CI and based on the overall study population by age group. **b** Incidence rates (IR) by site region and age for acute rotavirus gastroenteritis (RV GE) calculated with 95% CI and based on sthe overall study population by age group

population (n=17,042, e.g., all children seen at all study sites regardless of indication) and the population of children enrolled in the study (n=113, "RV GE sample") were compared. There were statistically significant differences in the age distribution between these populations (p<0.001). The proportion of children younger than 2 years was higher in the "RV GE sample" (85.8%) compared to the all study sites population (57.0%).

To evaluate whether the incidence rates (IR) varied among children that were initially seen at a hospital (with and without hospitalisation during the study period) or at a paediatrician practice, the incidence rates were calculated separately for these subpopulations. The highest RV GE IR was found in children seen at hospital (overall, 0.61%; LCI, 0.49%; UCI, 0.73%), then in children seen at the hospital and hospitalised at visit or during the follow-up period (overall, 0.38%; LCI, 0.29%; UCI, 0.48%). The RV GE IR was lowest in children seen at the paediatrician only (overall, 0.15%; LCI, 0.09%; UCI, 0.21%). For the subpopulations "hospital visit" and "hospital visit and hospitalised", the incidence rates were higher in Lucerne compared to Geneva.

Severity of RV GE

The relative abundance of RV GE clinical symptoms such as fever, vomiting and diarrhoea was checked. No statistically significant differences were found for the distribution of the vomiting and diarrhoea between the regions Geneva and Lucerne. However, there was a higher proportion of the children having fever at the study visit in Geneva in comparison with Lucerne (42.9% vs 26.8%; p=0.091).

To estimate the disease severity, the Vesikari score was recorded and the data analysed. A higher mean Vesikari score was reached in the region Lucerne than in Geneva (14.05±3.05 vs 12.85±2.87; p=0.039).

Outcome

The analysis of the data revealed a significant difference between the two regions in outcome variables assessed at the study visit (p<0.001). A higher proportion of children were hospitalised in Lucerne at the study visit when compared with Geneva (82.9% vs 23.6%; p<0.001); accordingly, 60.4% of children seen in Geneva were sent home vs 11.8% of children seen in Lucerne (p<0.001). More children were scheduled for a follow-up visit in Geneva than in Lucerne (11.3% vs 2.9%; p<0.001). However, more children had to be hospitalised during the follow-up period in Geneva than in Lucerne (14.5% vs 2.5%; p=0.045). The median duration of clinical symptoms was 8.3 days; the median duration of hospitalisation was 3 days. No statistical differences were found between the regions Geneva and Lucerne regarding the full recovery of

the patients and regarding the necessity to contact a medical facility or a paediatrician.

Distribution of RV genotypes

Genotyping was performed on 113 RV positive stool samples using VP7 primers and VP4 primers. The distribution of the G-types among the regions was statistically significantly different (p=0.039), with the G1-type being the most prevalent one in both regions (74.1% in Geneva and 51.5% in Lucerne; Table 2). Among the P types, P[8] was dominating in both regions (89.6% in Geneva and 57.1% in Lucerne, Table 2). The distribution of P types did not differ significantly between the two regions.

Health economics data: cost identification analysis

The total sum of 109,800 Swiss francs (CHF)/72,638 EUR (37,254 CHF/24,645 EUR in Geneva and 72,546 CHF/47,993 EUR in Lucerne) was invoiced by hospitals and paediatricians for acute RV GE episodes (currency rate CHF/EUR=1/1.5116). The mean direct costs were 998±1,034 CHF/660±684 EUR overall, 540±734 CHF/357±486 EUR for Geneva and 1,769±1,001 CHF/1,170±662 EUR for Lucerne. Mean costs were calculated for the following groups: (1) patients seen at the hospitals (direct costs of 1,242±1,046 CHF/1,170±662 EUR overall, 672±814 CHF/1,170±662 EUR for Geneva and 2,114 ±705/822±466 EUR for Lucerne); (2) patients seen at the hospital and hospitalised at the study visit or during the study follow-up (direct costs of 1,927±861 CHF/1,275±570 EUR overall, 1,501±1,045 CHF/993±691 EUR for Geneva and 2,114±705/1,399±466 EUR for Lucerne); and (3) patients seen at a paediatrician and no hospitalisation (direct costs of 126±67 CHF/83±67 EUR overall, 135±74 CHF/89±49 EUR for Geneva and 100±37/66±24 EUR for Lucerne).

The indirect medical costs paid by parents/guardians, such as extra expenses for medication, nutritional products, and transportation and others, were relatively small.

At follow up, it was assessed that 2.9±2.36 working days were lost overall, 3.30±2.84 in Geneva and 2.35±1.31 in Lucerne. Overall, 21.58±15.36 day nurse hours were needed at the overall costs of 160.60±325.70 CHF/106±215 EUR. Overall, 47.7±74.4 kindergarten hours were missed, 52.2±80.0 in Geneva and 25.2±32.5 in Lucerne.

Discussion

This study provides data on the burden of RV GE among children <5 years of age in two regions of Switzerland, Geneva and Lucerne, a more urban and a more rural region, respectively. The incidence rate of RV GE episode in a defined area was determined. Furthermore, demographic parameters, data on the severity of the RV GE episode, the prevalence of RV genotypes and socioeconomic data were assessed. Since in countries with moderate climate, the majority of RV GE cases occur in winter [1], the period from December to June was chosen to perform the study.

During the study period, the incidence rate of GE was higher in Lucerne than in Geneva, possibly reflecting the difference in obtaining the consent between the two

Table 2 Cross-table PCR genotyping for rotavirus strains by site region

	G-type[a]	P-type[b]				Percentage (%)			
		4	8	other	total	4	8	other	total
Geneva	1	0	43	0	43	0.0	89.6	0.0	74.1
	2	3	2	0	5	60.0	4.2	0.0	8.6
	3	0	1	0	1	0.0	2.1	0.0	1.7
	4	1	1	0	2	20.0	2.1	0.0	3.4
	9	0	1	0	1	0.0	2.1	0.0	1.7
	Other	1	0	5	6	20.0	0.0	0.0	10.3
	Total	5	48	5	58	100.0	100.0	0.0	100.0
	Unknown				14				
Lucerne	1	0	16	1	17	0.0	57.1	25.0	51.5
	2	1	2	0	3	100.0	7.1	0.0	9.1
	3	0	3	0	3	0.0	10.7	0.0	9.1
	4	0	3	0	3	0.0	10.7	0.0	9.1
	9	0	4	0	4	0.0	14.3	0.0	12.1
	Other	0	0	3	3	0.0	0.0	75.0	9.1
	Total	1	28	4	33	100.0	100.0	100.0	100.0
	Unknown				8				

[a] Statistically significant difference in distribution of G-types between the two regions (p=0.039)

[b] No statistically significant difference in distribution of P-types between the two regions (p>0.05)

regions. The incidence rate of RV GE was different in children seen at hospital or at the paediatrician. More cases were seen at the two hospital sites than at the paediatricians. Whereas in Geneva, the consent to perform RV GE rapid test was obtained in all GE cases; in Lucerne, the consent was given only by 59.84% parents of the GE positive children. Differences in consenting might reflect differences in mentality between the two regions. On the other side, it can be assumed that the incidence rate of RV GE is similar in the "children without consent" as in the "children with consent" given. In comparison with other studies, the RV GE incidence rate was quite low in our study. However, the surveillance period was only one season. Laubereau et al. [18] described an incidence rate of RV GE in the season 1997/1998 of 1.6%. In Germany, based on federal statistics from years 2001–2004, the incidence rate of RV GE in children below 4 years was 1.2% [8], and the incidence rate of RV GE was higher in children younger than 2 years than in the older age groups, as it was found in several studies [7, 18, 22, 29]. Similarly, the percentage of <2 years children was also substantially higher in our study population than in the overall site population, suggesting that children <2 years are more prone to RV GE compared to older children. A recent Swiss study investigating RV infections in children <5 years of age indicated the peak incidence of RV GE for children aged 13–24 months [2]. The higher incidence rate for RV GE (1.5%) in this study compared with the current data was probably due to the longer observation period (5 years).

In comparison with other studies, the RV GE incidence rate was low in our study, which might be attributed to several reasons. The 6-month period in our study may not be representative for the seasonal distribution and temporal variability of RVGE incidence during a whole year. In addition, the fact that cases were not selected from all hospitals in the canton Lucerne may constitute reasons for the lower incidence rates in this study compared to other European investigations. Selection bias, especially related to those who did not provide informed consent, may also have contributed to the low estimates compared to other studies.

To estimate the disease severity, the Vesikari score was recorded. Higher mean Vesikari score was reached in Lucerne than in Geneva. Nevertheless, there were no differences in full recovery of the patients between both sites. Overall hospitalisation varied from 37.7% in Geneva and 82.4% in Lucerne. This striking difference in hospitalisation rate and in the mean Vesikari scores (which includes the need for hospitalisation) discussed above can be explained by the possibility to keep patients in the emergency unit for less than 24 h on an outpatient basis in Geneva, whereas children needing supportive care in Lucerne had to be hospitalised, even for a short period of time. Differences in outcome and hospitalisation rates between cantons most probably rather reflect differences in mentality and admission policy rather than true differences of disease severity, as the criteria for admission were not standardised. The incidence of RV hospitalisation has been investigated in several studies. In the REVEAL study performed in the several countries, the estimated percentage of children with RV GE admitted to a hospital was 10.4–36.0%. These hospitalisation rates are slightly lower than the overall hospitalisation rate in our study at the study visit (45.9%). Furthermore, the relative risk of hospitalisation was significantly higher for children with RV positive GE than for those with RV negative GE [11]. Another study performed in Italy in children <5 years and analysing data from the period of January 2001 to December 2005 showed that 36% of GE-related hospitalisations were attributed to RV GE [9].

Since the prevalence of the distinct RV strains can vary considerably from year to year and from one geographic area to another [24], genotyping was performed to compare the distribution of different RV strains in the regions Geneva and Lucerne. Indeed, regional differences in the distribution of distinct G-type strains were observed. However, the G1-type was the most prevalent one in both regions. Laubereau et al. [18] identified G4 and G1 as the most prominent strains during the study period 1998/1999. Differences in the RV genotypes distribution were also observed in the REVEAL study performed in the RV GE season 2004–2005. G1 was identified in Spain, Sweden and UK, G9 in Italy, France and Belgium and G4 in Germany. Only the G4 and G9 genotypes were identified in all study areas [27].

In addition to the health burden, it is obvious that RV GE places also economic burden on society. The socioeconomic parameters presented in our study allow only rough estimations since collected data were limited. More appropriate socioeconomic data from seven European countries have been published recently [12]. A well sampled, truly multi-centre, nationwide and multi-season study with clearly defined outcome variables and a standardised methodology would be highly valuable and add to the current bulk of evidence. Appropriate collection of health economic data including modelling shall also be done for Switzerland.

Conclusions

The incidence rates of RV GE were similar in both study regions with the peak incidence rate in the group of children under 2 years. Overall, the incidence rate was very low (0.32%) compared with other studies. In both regions, G1 was the most prevalent RV genotype. However, there were

regional differences in relative distribution of distinct genotypes. RV GE was also associated with considerable socioeconomic costs. Suitable health economic model calculations will help to estimate real socioeconomic burden of RV GE episode in Switzerland.

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Conflict of interest The authors declare that they have no conflict of interest.

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