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Population-based epidemiology of rotavirus hospitalisations in Switzerland

Barbara Bucher[a], *Christoph Aebi*[a,b]

[a] Department of Paediatrics, University of Bern, Bern, Switzerland
[b] Institute for Infectious Diseases, University of Bern, Bern, Switzerland

Summary

Background: Rotaviruses (RV) are the most common cause of dehydrating gastroenteritis requiring hospitalisation in children <5 years of age. A new generation of safe and effective RV vaccines is available. Accurate data describing the current burden of RV disease in the community are needed to devise appropriate strategies for vaccine usage.

Methods: Retrospective, population-based analysis of RV hospitalisations in children <5 years of age during a 5-year period (1999–2003) in a both urban and rural area inhabited by 12% of the Swiss population.

Results: Of 406 evaluable cases, 328 were community-acquired RV infections in children <5 years of age. RV accounted for 38% of all hospitalisations for gastroenteritis. The overall hospitalisation incidence in the <5-year-old was 1.5/1000 child-years (peak incidence, 2.6/1000 child-years in children aged 13–24 months). The incidence of community-acquired RV hospitalisations was significantly greater in children of non-Swiss origin (3.0 vs. 1.1/1000 child-years, relative risk 2.7; 95% CI 2.2–3.4), who were younger, but tended to be less severely dehydrated on admission than Swiss children. In comparison with children from urban areas, RV hospitalisation incidence was significantly lower among those residing in the remote mountain area (0.71 vs. 1.71/1000 child-years, relative risk 2.2, 95% CI 1.6–3.1).

Conclusion: Population-based RV hospitalisation incidence was low in comparison with other European countries. Significantly greater hospitalisation rates among children living in urban areas and those from non-Swiss families indicate that factors other than the severity of RV-induced dehydration are important driving forces of hospital admission.

Key words: rotavirus; gastroenteritis; incidence; hospitalisation; vaccine

Introduction

In temperate climates, rotaviruses (RV) cause annual winter epidemics of acute gastroenteritis in children under five [1] and are the single most common cause of dehydrating diarrhoea requiring hospital admission [2–4]. It has been estimated that one in seven European children receive medical attention for RV disease during the first 5 years of life, and one in 54 require hospitalisation for RV gastroenteritis [4]. RV is responsible for one fourth to one half of all hospitalisations for gastroenteritis in children under 5 years of age [5–7]. Severe dehydration primarily occurs in young children aged between 6 and 24 months and may necessitate intensive care unit (ICU) admission [8]. Though RV are estimated to cause at least 500,000 deaths annually in developing countries [9], in developed countries the case fatality rate is very low [4]. RV are shed in the faeces in extremely high concentrations, are effectively transmitted from person to person, and are one of the most common causes of nosocomial infections in paediatric inpatient services [10].

Acute gastroenteritis caused by RV is now considered a vaccine-preventable disease. Recently completed field trials have established that two oral live RV vaccines – a live-attenuated human G1P [8] vaccine [11] and a pentavalent live human-bovine reassortant G1, G2, G3, G4 and P [8] vaccine [12] – are effective and safe and do not cause intussusception, which was rarely, but significantly, associated with a first-generation RV vaccine marketed in the USA in the late 1990s [13]. Two or 3 doses of RV vaccine administered to infants under 6 months of age were shown to prevent 70 to 80% of all RV disease and 90–100% of severe disease during the first two years of life [11, 12].

Abbreviations

RV	Rotavirus
ICU	Intensive care unit
CI	Confidence interval
RSV	Respiratory syncytial virus

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This new generation of RV vaccines will be licensed in Europe in the near future. National immunisation advisory committees will then be called to issue recommendations for their use. National and regional epidemiological data on RV infections will be important in providing a rationale for RV vaccine recommendations. In the absence of both substantial mortality and long term sequelae attributable to RV, the burden of disease in developed countries will be measured by the incidence of severe infections, for which the need for hospitalisation is a useful surrogate, the use of hospital resources, the incidence of nosocomial RV infections, and cost-effectiveness analyses of RV vaccines.

Epidemiological data from Switzerland are incomplete and date from the 1980s and 1990s [5, 6, 14]. The purpose of the present study is to report current population-based RV hospitalisation rates in children, taking advantage of the fact that the University Children's Hospital in Bern is the sole provider of paediatric in-patient care for a precisely defined paediatric population and serves both urban and rural areas.

Methods

Study design: We conducted a retrospective, population-based study of RV hospitalisations in children <16 years of age between January 1, 1999 to December 31, 2003 at the University Children's Hospital in Bern, Switzerland. This institution is the sole provider of paediatric inpatient services for a defined geographical area of the Canton (i.e., State) of Bern (Figure 4) and 4 districts of the Canton of Solothurn with a general population of ~800,000 and an annual birth cohort of ~8700. RV hospitalisations and, for 2002 and 2003, gastroenteritis hospitalisations from all causes were recorded. Nosocomial RV infections were identified.

Definitions: Gastroenteritis hospitalisation was defined as admission to the hospital for >12 hours with one of the following primary ICD-10 discharge diagnoses: A01-A09. RV hospitalisation was defined as gastroenteritis hospitalisation with ≥1 stool specimen positive for RV. Nosocomial RV infection was defined as an episode of gastroenteritis with RV detected in a stool sample obtained >72 hours after hospital admission for a diagnosis other than gastroenteritis.

Identification of cases

Hospital guidelines at this institution require that all patients admitted with the diagnosis of acute gastroenteritis are evaluated in the emergency department and are tested for RV infection by examination of a stool sample using a commercial antigen detection kit (RIDA® Quick Rotavirus/Adenovirus Combi, R-Biopharm, Darmstadt, Germany). The electronic microbiology database identified all patients hospitalised with RV infection except those with a false negative test result. The electronic ICD-10 discharge diagnosis database, which was implemented in 2001, was used to identify the total number of gastroenteritis hospitalisations for the years 2002 and 2003. A defined set of clinical data was extracted from the medical record of each patient.

Demographic data and incidences

RV hospitalisation incidence was defined as the number of community-acquired RV hospitalisations per 1000 child-years in a given age group. The total number of child-years per age group was defined as equal to the corresponding annual number of live births. Infant mortality, currently <5/1000 live births, and migration were disregarded. Annual live birth data for each district of the referral area were obtained from the Swiss Federal Office of Statistics. The patient's origin (Swiss vs. non-Swiss) was defined according to the parents' nationality.

Statistical analysis

Relative risk, odds ratios and 95% CI were calculated as described [15]. For proportions, exact binomial 95% CI were obtained. The two-tailed Student's t-test or Mann-Whitney U-test were used for comparison of continuous variables. *P* values <0.05 were considered significant. VassarStats software was used for analysis (http://faculty.vassar.edu/lowry/VassarStats.html).

Results

Characteristics of RV hospitalisations

449 cases were identified. Of these, 39 and 4 were excluded due to outpatient management and lost charts respectively. There were 406 evaluable cases. Of these, 348 (86%) and 58 (14%) were community-acquired and nosocomial cases respectively. Figure 1 demonstrates the age distribution of both community-acquired and nosocomial RV infections. Table 1 summarises RV hospitalisation data. In 8 cases (2%), co-infection with another intestinal pathogen was detected (adenovirus in 3 cases, *Salmonella spp.* and *Clostridium difficile* in 2 each, *Giardia lamblia* in 1). Two patients died. In neither case was death caused by RV. 136 patients (39%) with community-acquired RV disease were of non-Swiss origin. This finding contrasts with a mean non-Swiss proportion of the annual birth cohort of 19.5% (range 1995–2003, 17.2–21.2%) and prompted additional investigation of these cases. Analysis was limited to those 328 patients who were under 5 years of age (i.e., 94% of all cases of community-acquired RV cases). Table 2 compares clinical and laboratory data of RV cases in children of non-Swiss vs. Swiss origin. Children of non-Swiss origin were significantly more likely to be hospitalised for RV, but not more likely to be hypo- or hypernatraemic on admission. There was no difference in the median duration of hospitalisation in the two groups.

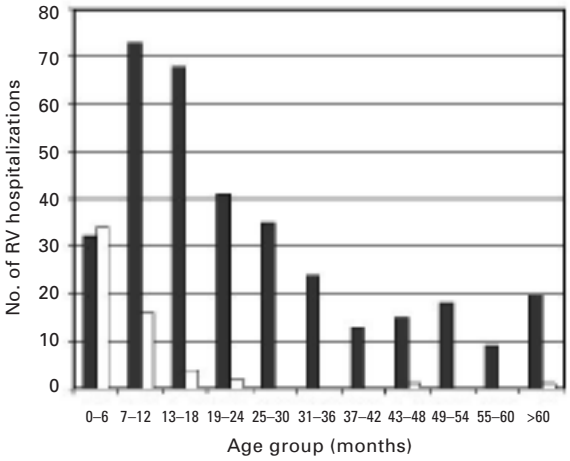

Figure 1

Age distribution of community-acquired (black columns) and nosocomial (white columns) RV infections at the University Children's Hospital, Bern, Switzerland 1999–2003.

Seasonality of RV hospitalisations

In 1999, 2000, 2001, 2002, and 2003 there were 62, 70, 111, 101 and 62 RV hospitalisations respectively. Figure 2 depicts the seasonal distribution of RV cases during the study period. In the years 2002 and 2003 there were 219 and 212 hospitalisations respectively for gastroenteritis from all causes. The monthly proportion of all gastroenteritis cases caused by RV ranged from 0% in summer to a maximum of 60 to 74% in late winter and early spring. Overall, 38% of hospitalisations for gastroenteritis were associated with RV.

Incidence of RV hospitalisations

Population-based hospitalisation incidences were calculated for community-acquired cases (table 3). The number of child-years listed for each age group was derived from the annual live birth rates from 1995 to 2003 (mean, 8755; range, 7774–9613). The cumulative risk of RV hospitalisation by the age of 4 and 5 years was 1:143 and 1:132 respectively. For comparison, hospitalisation incidences for RSV infection, the single most common viral aetiology of hospital admission in young children, are also listed [16]. The overall hospitalisation incidences for RV and RSV in chil-

Table 1

Clinical characteristics of RV hospitalisations.

	RV hospitalisation		Total
	Community-acquired	Nosocomial	
No. of cases	348	58	406
No. of cases <5 years of age	328	57	385
Female gender (%)	159 (46)	28 (48)	187 (46)
Median age (months)	18.5 [10.3–31.8][1]	5.0 [3.2–9.2][1]	15.9 [7.8–29.9][1]
Non-Swiss nationality (%)	136 (39)	15 (26)	151 (37)
Median hospitalisation (days)	4 [3–5][1]	17 [11–31][1]	4 [3–6][1]
Intestinal co-infection (%)	7 (2.0)	1 (1.7)	8 (2.0)
ICU admission (%)	4 (1)	6 (10)	10 (2.5)
related to RV infection (%)	2 (0.6)	0	2 (0.5)
Death	2[2]	0	2 (0.5)
Sequelae at discharge	0	0	0

1 Interquartile range

2 Sudden infant death syndrome (SIDS) without clinically evident dehydration in 1 case, type II glutaric aciduria with sepsis caused by *S. pneumoniae* in 1 case.

Table 2

Comparison between community-acquired RV hospitalisation episodes in non-Swiss and in Swiss children <5 years of age.

	Origin of family		Statistical test
	Non-Swiss (n = 136)	Swiss (n = 212)	
No. of cases	132	196	2.7 [2.2–3.4][1]
No. of child-years	43524	176258	
Incidence per 1000 child-years	3.0	1.1	
Median age (months)	15.4 [9.4–26.3][2]	19.6 [10.4–31.6][2]	P = 0.034[3]
Median hospitalisation (days)	4 [3–5][2]	4 [3–5][2]	P = 0.093[3]
Admission laboratory			
Na <130 or >150 mmol/l (%)	3 / 113 (3)	13 / 167 (8)	0.3 [0.1–1.2][4]
Na <132 or >145 mmol/l (%)	8 / 113 (7)	27 / 167 (16)	0.4 [0.2–0.9][4]
pH <7.30 (%)	17 / 107 (16)	23 / 168 (14)	1.2 [0.6–2.4][4]
Base excess <-10 mmol/l (%)	21 / 102 (21)	41 / 168 (24)	0.8 [0.4–1.5][4]
Mean haemoglobin (g/l) (SD)	119.8 (14.1)	124.7 (13.4)	P = 0.0065[5]

1 Relative risk [95% confidence interval]

2 Interquartile range

3 Mann-Whitney U test

4 Odds ratio [95% confidence interval]

5 Two-tailed Student's t-test

dren under 5 during the 5-year study period were 1.5 and 3.0/1000 child-years respectively.

Regional variation of RV hospitalisation incidences

We next investigated whether there were regional differences in RV hospitalisation incidences. Figure 3 shows hospitalisation incidences for each district of the primary referral area in the Canton of Bern for children under 5. Overall, the incidence in the 11 districts of the lowland area ("Mittelland") was significantly greater (1.71/1000 child-years) than in the 7 mountain districts ("Oberland") (0.71/1000 child-years; relative risk 2.2, 95% CI 1.6–3.1). Analysis of RV hospitalisations revealed that patients from these two areas did not differ significantly in age, duration of hospitalisation and admission laboratory parameters (data not shown).

Discussion

This study provides data on the current burden of RV hospitalisations in both an urban and rural area of Switzerland. The strengths of the study setting consist of a nearly complete catchment of virologically confirmed RV cases which did not rely on ICD-10 codes, the availability of precise demographic data, the distinction between community-acquired and nosocomial infections and the inclusion of both urban and rural referral areas. Limitations of the study design include its retrospective character, the lack of predefined clinical criteria for the decision to hospitalise, and the relatively small population size and number of hospitalisations, which resulted in relatively large confidence intervals for point estimates. Also, the study setting did not allow identification of patients with nosocomial infections occurring after hospital discharge. Diagnosis of RV infections by stool antigen detection assay inevitably misclassifies 5 to 10% of cases because of the performance characteristics of these tests [17]. This limitation, however, does not introduce a major error and does not preclude comparison with other studies, since most investigators relied on similar tests for identifying RV cases.

The clinical features of RV infections requir-

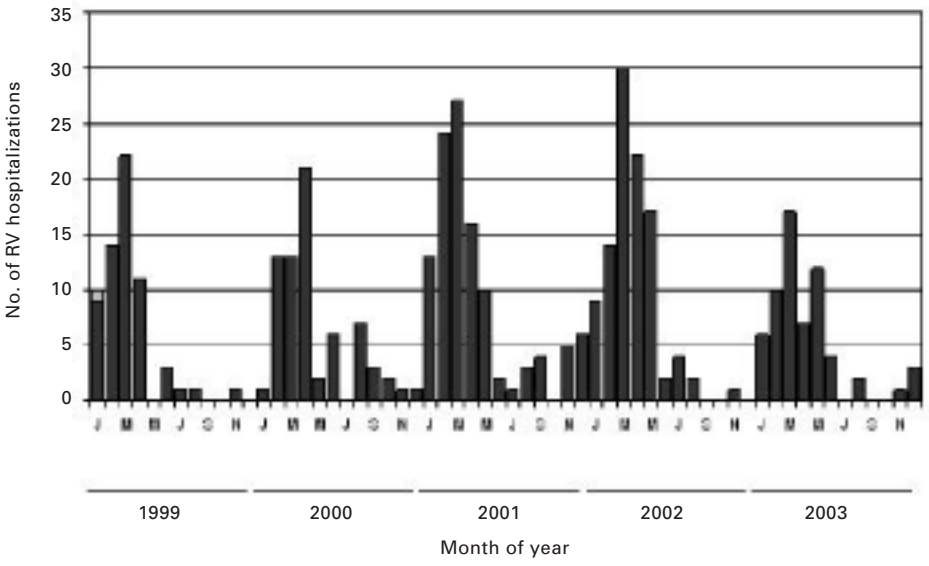

Figure 2

Time course of RV hospitalisation epidemiology at the University Children's Hospital, Bern, Switzerland 1999–2003. Capital letters on the x-axis represent calendar months.

Table 3

Age-specific community-acquired rotavirus (RV) and respiratory syncytial virus (RSV) hospitalisation incidences in the area of Bern, Switzerland, 1999–2003.

Age (years)	Cases	Child-years	Rotavirus (RV)		Respiratory syncytial virus (RSV)	
			Incidence per 1000 child-years [95% CI]	Cumulative incidence per 1000 children	Incidence per 1000 child-years [95% CI]	Cumulative incidence per 1000 children
0–1	105	41 424	2.5 [2.1–3.1]	2.5	12.6 [11.5–13.7]	12.6
1–2	109	42 581	2.6 [2.1–3.1]	5.1	1.9 [1.5–2.4]	14.5
2–3	59	43 887	1.3 [1.0–1.7]	6.4	0.9 [0.7–1.2]	15.4
3–4	28	45 480	0.62 [0.40–0.89]	7.0[1]	0.3 [0.1–0.6]	15.7
4–5	27	46 410	0.58 [0.38–0.85]	7.6[2]	0.2 [0.1–0.4]	15.9
0–4	301	173 372	1.7 [1.5–1.9]		3.8 [3.5–4.2]	
0–5	328	219 782	1.5 [1.3–1.7]		3.0 [2.8–3.3]	

[1] Cumulative RV hospitalisation risk is 1:143
[2] Cumulative RV hospitalisation risk is 1:132

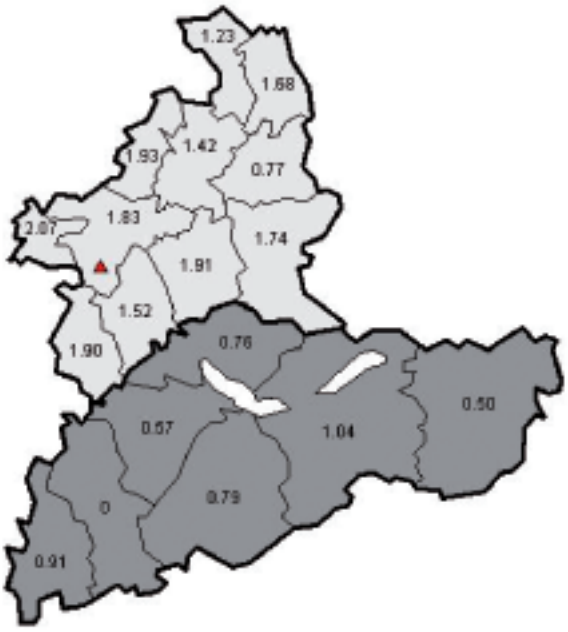

Figure 3

Incidences of community-acquired RV hospitalisations per 1000 child-years in children <5 years of age in districts of the primary referral area in the Canton of Bern. Light grey, districts in the lowland ("Mittelland"); dark grey, districts in the mountain area ("Oberland"); triangle, location of the study hospital.

ing hospitalisation in our population did not differ from other studies. The proportion of gastroenteritis hospitalisations in which a positive RV test result was obtained was 38% and was consistent with other Swiss [5, 6, 18] and international studies [7, 19]. The median duration of hospitalisation was in accordance with some studies [20–22], but somewhat longer than in others [19, 23]. The proportion of nosocomial infections was in the range of other reports, although varying definitions demand caution in interpreting such data [10, 21]. Taken together, these clinical findings confirm that RV hospitalisation episodes in our population and comparator studies are similar in character, severity and duration. Comparison of hospitalisation incidences thus appears valid.

Comparing hospitalisation incidences from different developed countries indicates that the burden of RV hospitalisations in our study area (1.5/1000 child-years in children <5 years of age) is relatively low. Recent studies from the USA [20], Canada [19], Sweden [24], Denmark [25], England and Wales [26], Japan [22] and Ireland [5] reported RV admission rates between 0.6 and 13/1000 child-years for children under 4 [24, 27] or 5 years of age, respectively [19–22, 25, 26]. A recent study from Europe estimated that one in 54 children are hospitalised for RV disease during the first 5 years of life [4]. The corresponding rate in our population (1:132) is 2.5 times lower and similar to estimates from the USA and Canada [19]. No previous large-scale studies from Switzerland are available. A prospective study performed between December 1997 and April 1998 in Basel reported 11 RV hospitalisations in children <4 years of age followed for a total of 3336 child-years in a winter season [6]. Post hoc analysis results in an RV hospitalisation incidence of 3.3/1000 child-years. For comparison with our study and international ones, this figure needs to be divided by a factor of ~2 since most RV hospitalisations in Switzerland occur between December and May. Thus the estimated incidence of 1.7/1000 child-years is identical to our findings and corroborates their accuracy. In the same small study [6], centres from Germany and Austria reported similar hospitalisation incidences.

Rotavirus gastroenteritis has been termed a "democratic" disease because it similarly affects all children regardless of sanitation, socioeconomics or geography [28]. In the USA RV hospitalisation incidences are either not associated with race and socioeconomic status [20] or are more frequent among white children and those with private medical insurance [27]. We found a significantly higher incidence among children from non-Swiss families despite the fact that, based on their admission laboratory results, they were not more severely dehydrated than children from Swiss families (table 2). This finding suggests that parental concern and language barriers preclude adequate instruction in home management of diarrhoea and thus have a substantial influence on the decision to hospitalise a child with acute gastroenteritis. Similarly, the low hospitalisation rate in children residing in the remote mountain areas (Figure 3) suggests that the absence of a paediatric hospital in close proximity affects the private physicians' referral practice and increases the proportion of children with gastroenteritis managed on an outpatient basis. Age-specific seroprevalence data would be needed to rule out the possibility that in the mountain area RV infections occur at a later age than in urban areas and thus cause less severe disease.

In conclusion, RV hospitalisation incidences among infants and young children in this area of Switzerland are low in comparison with several other European countries, but similar to those reported from North America and in a Swiss study from the late 1990s. Important differences exist in hospitalisation rates according to nationality and place of residence. Considering that the RV-related risks of death or permanent disability are extremely low, there is potential for reducing RV hospitalisation rates by improved outpatient management. Additional studies assessing the outpatient burden of RV disease, genotype distribution of RV isolates and cost-effectiveness will be needed to provide a rationale for RV vaccine recommendations in Switzerland.

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Correspondence:
Christoph Aebi, MD
Department of Paediatrics
University of Bern
Inselspital
CH-3010 Bern
E-Mail: christoph.aebi@insel.ch

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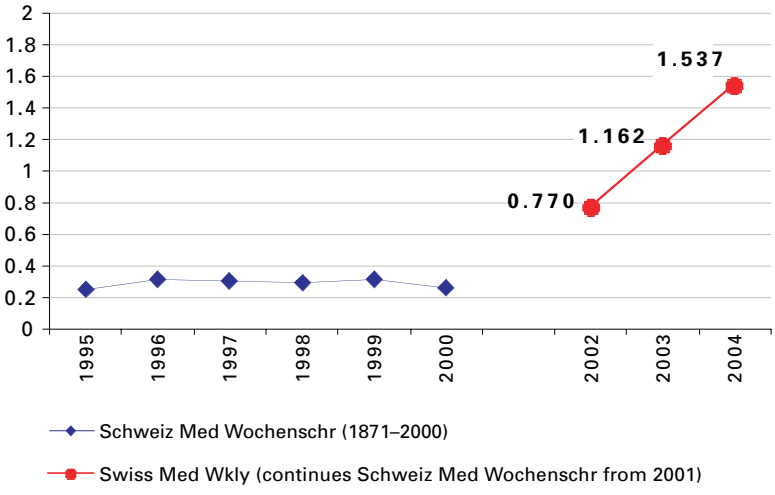

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