

EPIDEMIOLOGICAL, CLINICAL AND LABORATORY FEATURES OF ROTAVIRUS GASTROENTERITIS AMONG HOSPITALIZED CHILDREN LESS THAN FIVE YEARS OLD IN SELECTED HOSPITALS IN JORDAN, 2007-2008

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ABSTRACT

Background: Acute gastroenteritis continues to be a significant cause of morbidity and mortality worldwide. Rotavirus causes more than 130 million episodes of severe diarrhea in children less than five years throughout the world and is considered as main problem in many countries. Few data are available about gastroenteritis attributable to rotavirus in Jordan.

Objectives: The primary purpose of this study is to determine epidemiological, clinical and laboratory characteristics of hospitalized cases attributable to rotavirus gastroenteritis in children less than five years old in selected hospitals during the period May 2007-April 2008 to provide Ministry of Health with evidence upon which to base its futuristic decision in regard to development of more suitable preventive measures. This study will improve the existing diarrhea surveillance system in MoH, facilitate and support the decision of introducing rotavirus vaccine in national immunization programme.

Methods: Descriptive Cross-sectional study was performed on the hospitalized children less than five years old with acute gastroenteritis in three selected hospitals in three governorates (north, middle and south regions) with population about 45.3% of Jordan population for the period May 2007 to April 2008. Standard case definition was adopted. Analysis was performed using SPSS and Epi Info statistical packages.

Results: 377 cases were enrolled with 171 positive for rotavirus. Results showed that Incidence rate of rotavirus disease is 5.2/ 10000 children less than five years old per year; male: female ratio is 1.8:1 with largest proportion of cases among children 6-11 months old. Southern region has the highest incidence rate. Vomiting is an outstanding symptom for rotavirus cases ($P < 0.01$) in addition to diarrhea and fever which require admission to hospital for fluid replacement. Majority of rotavirus cases were with some dehydration (30%). Mean stay duration is 3 days. Predominant genotypes are G1P8.G2P4 and G9P untypeable.

Conclusions: Although mortality of gastroenteritis is no longer a problem in Jordan due to accessibility to health services, morbidity is still high and rotavirus is a relevant cause for gastroenteritis in children less than five years old; which require hospitalization most of the time (45.4% of admitted gastroenteritis).

INTRODUCTION

Acute gastroenteritis continues to be a significant cause of morbidity and mortality worldwide. ^[1] Despite improved treatment of gastroenteritis, the disease has not been controlled; this raises questions regarding the need for national intervention programmes based on reliable epidemiological data. A major concern is raised based on international literature and experience regarding rotavirus gastroenteritis. Each year, rotavirus causes approximately 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations, and 352,000–592,000 deaths (median, 440,000 deaths) in children <5 years of age. By age 5, nearly every child will have an

episode of rotavirus gastroenteritis, 1 in 5 will visit a clinic, 1 in 60 will be hospitalized, and approximately 1 in 293 will die. Children in the poorest countries account for 82% of rotavirus deaths. ^[2] Approximately 1 in 15 children will require hospitalization due to rotavirus diarrhea by their fifth year of life, resulting in a direct medical cost of millions US dollars. ^[3]

In Jordan there are many health care providers including:

- **Public sector:**
 - *Ministry of health: (which cover 80% of health services)*
 - *Royal medical services*
 - *University hospitals.*
- **Private sector.**
- **UNRWA.**

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The surveillance system for diarrheal diseases is clinical and laboratory based surveillance for bacterial and parasite agents. There is no such system available for viral causes of diarrhea. Diarrhea diseases (watery and bloody) are a compulsory notifiable disease. It is passive surveillance system based on weekly and monthly reporting system from all reporting sites using special reporting form. According to the Ministry of Health (MoH) annual epidemiological report, total admissions of diarrhea cases in MoH hospitals in one year is 7722 and the average hospitalization days is 4 days, the cost per day is estimated to be \$ 150. The annual cost would be about \$ 5 million, which constitutes an economic burden for health services besides its emotional stress for parents and community. Additionally, the rapid progress towards the development of rotavirus vaccines has prompted a reassessment of the disease burden of rotavirus gastroenteritis in developed and developing countries and the possible impact of these vaccines in reducing gastroenteritis morbidity and mortality among infants and young children.

Study Rationale

The current study is carried out with the following rationale in mind:

- Few data and limited information in addition to lack of awareness of importance of gastroenteritis attributable to rotavirus in Jordan.
- To improve the existing diarrhea disease surveillance system by providing information regarding characteristics of gastroenteritis attributable to rotavirus in children less than five years old in Jordan.
- To define strategies for management and prevention and clarify the benefits of potential preventive measures for gastroenteritis attributable to rotavirus (vaccine).

The present study aimed to determine

epidemiological, clinical and laboratory characteristics of hospitalized cases attributable to rotavirus gastroenteritis in children less than five years old in selected hospitals during the period May 2007-April 2008 to provide MoH with evidence upon which to base its futuristic decision in regard to development of more suitable preventive measures. Specifically, the study was planned to attain the following objectives:

- I. To estimate the annual incidence of gastroenteritis attributable to rotavirus in children less than five years old.***
- II. To determine the different potential epidemiological factors in rotavirus infection.***
- III. To identify the main clinical symptoms of rotavirus cases in hospitalized children less than five years old.***
- IV. To identify the prevalent strains (genotype) of rotavirus in hospitalized cases in children less than five years old.***
- V. To estimate duration of hospital stay of rotavirus cases among children less than five years old***

PATIENTS AND METHODS

This study is a Descriptive Cross sectional hospital-based study.

Data Sources and Characteristics:

Population in Jordan in the year 2007 is 5744473, of which 732604(12.7%) were under the age of five years.

The study is carried out at three governorates, which are representative of different geographical areas of Jordan (Irbid in the north, Amman in the middle and Karak in the south). The three governorates cover 45.3% of Jordan population. Amman has 31.0%, Irbid 11.0% and Karak city 3.3% of Jordan population.^[4]

Table 1. Number of children less than five years in the study governorates in Jordan.

Governorate	Population in Selected Governorates	Percentage from Jordan Population	Population Less than 5 years in Selected Governorates
Amman	1781547	31.0%	227204
Irbid	629679	11.0%	80304
Karak	190756	3.3%	24328
Total	2601982	45.3%	331836

In each governorate there is only one governmental hospital, which is considered as major pediatric hospital:

The three hospitals had the highest rate of admitted cases with gastroenteritis, which constitutes approximately 32% of all reported admissions with gastroenteritis in children less than five years old in MoH hospitals during last five years. [5]

Sample Size

All children under 5 years of age (less than 60 months of age) presenting to the three selected hospitals with acute gastroenteritis and requiring hospitalization for treatment of gastroenteritis and fit the adopted case definition, between May 2007 and April 2008, were included in the study. Informed consent was obtained from the parents of all children enrolled in the hospital-based study. The study was approved by National Rotavirus Surveillance Committee in Ministry of Health. World Health Organization provided the financial and logistic support.

Inclusion criteria:

1. Child less five years of age (< 60 months).
2. Presence of gastroenteritis of less or equal to 7 days.
3. Admitted for treatment of gastroenteritis as a primary illness.

Exclusion Criteria:

1. Child with bloody diarrhoea.
2. Patients acquired gastroenteritis during their hospitalization for treatment of other diseases (hospital acquired gastroenteritis).

Case Definition

Suspected case: A child under 5 years of age (<60 months of age) and admitted to a designated sentinel hospital for treatment of gastroenteritis.

Confirmed case: A suspected case in whose stool the presence of rotavirus is demonstrated by means of an enzyme immunoassay EIA.

No **probable case** definition was adopted in this study.

Data Collection Methods:

1. Questionnaire:

For this study special questionnaire was designed based on data obtained through rotavirus surveillance system. The questionnaire includes:

Patient information: ID, name, age (by months), sex and address.

Clinical information: duration of symptoms, symptoms (fever, diarrhea, No. of episodes of diarrhea, vomiting, No. of episodes of vomiting), dehydration status, treatment, duration of hospitalization, outcome.

Laboratory information: EIA rotavirus identification in stool, genotype G and P.

2. Rotavirus Screening:

A sufficient amount of bulk stool, approximately 5 ml, was obtained from each suspected case during the acute illness, on the day of presentation to hospital. Attempts were made to obtain a stool specimen from all possible cases within 48 hours of hospital admission so as to avoid the detection of nosocomial infection.

Stool samples were collected and divided into aliquots to be tested by hospital laboratory on weekly basis for group A rotavirus by an enzyme-linked immunosorbent assay (Rota DakoCytomation Ltd, United Kingdom) to detect VP6 antigen. All positive stool samples for rotavirus were subject for quality control while only 25% of negative samples were sent to central laboratory for the same purpose every two weeks and were retested by expert personnel. The positive samples were stored for strain characterization and genotyped at NAMRU-3 as referral laboratory.

Statistical analysis: To ensure standardization of data entry an electronic investigation form was developed for data entry and code checking using Epi Info for windows programme and SPSS software. Data were analyzed using Epi Info programme and SPSS software.

Study Limitations:

-Advantages of this study:

1. It is mainly laboratory based surveillance system
2. Diagnosis is based on one standard technique with high specificity
3. Reporting system is standardized in three selected hospitals
4. Quality of collected data is highly monitored.

-Disadvantages:

1. This study reflects occurrence of rotavirus gastroenteritis in severely ill children as it is a hospital based study
2. It could be affected by factors associated with users of health care services; type of the hospital (*main referral versus general pediatric hospital*)
3. Population base incidence rate is not precise because the catchment area is not defined and this study counts diarrhea episodes rather than sick children with diarrhea (person).

RESULTS

Data of 377 children were included in respect to rotavirus case definition adopted for this study, and stool samples were obtained for all cases. One hundred seventy one (45.4%) were laboratory confirmed positive for rotavirus and two hundred six (54.6%) were rotavirus negative. The age range of children presenting with gastroenteritis was 0 to 60 months with mean age of 11.3, median 8.0, mode 6.0 months.

(Table-1), shows that the estimated annual incidence rate of rotavirus gastroenteritis among hospitalized children less than five years old in selected governorates in respect to hospitals is 5.2 per 1000 children per year.

There is regional difference in annual incidence rate of rotavirus gastroenteritis. The highest rate is in the southern region (Karak city).

Table 1. Estimated annual incidence rate of Rotavirus in hospitalized children less than five years old in selected governorates during May 2007- April 2008.

Hospital	Population < 5 years old	Rota +ve	Incidence rate/10000	Expected rotavirus cases
Amman	227204	62	2.7	930
Irbid	80304	51	6.4	510
Karak	24328	58	23.8	480
Total	331836	171	5.2	1920

(Table-2), shows that the largest proportion of rotavirus gastroenteritis is among children in 6-11 month age group with mean age 8 months; while the smallest proportion is noted in those more than 25 month age group (P<0.01). 88.4% of cases are under the 18 month age group. Regarding gender it shows that 58% of gastroenteritis cases are among males, out of which 29.2% are positive for rotavirus, while females constitute 39.5 % with 16.2% rotavirus

positive cases. (P<0.02). According to rotavirus cases Male: Female ratio is 1.8:1. Regarding hospital it shows percent of gastroenteritis tested for rotavirus in hospitals in Middle (35.3%), Northern (23.9) and Southern regions (40.9) with percent of rotavirus positive cases 16.44%, 13.53% and 15.38% respectively. Incidence rates by age and gender are shown in (Table-3).

Table 2. Percent of rotavirus gastroenteritis cases in hospitalized children by age group, gender and hospital during May 2007-April 2008.

Epidemiological feature	Rota +ve		Rota -ve		Total	
	No.	%	No.	%	No.	%
Age Group(months)						
0-5						
6-11	47	12.5	55	14.6	102	27.1
12-17	71	18.8	78	20.7	149	39.5
18-24	33	8.75	33	8.75	66	17.5
≥25	14	3.7	11	2.9	25	6.6
	6	1.6	29	7.7	35	9.3
Gender						
Male	110	29.2	110	29.17	220	58.4
Female	61	16.2	96	25.46	157	39.5
Hospital						
Al-Basheer	62	16.44	71	18.83	133	35.28
Princess Rahma	51	13.53	39	10.34	90	23.87
Al-Karak	58	15.38	96	25.46	154	40.85
Total	171	45.4	206	54.6	377	100

Table 3. Incidence rate of rotavirus cases in hospitalized children less than five years old in selected governorates by age group and gender.

Epidemiological feature	Population < 5 years old	Rota +ve	%	Incidence rate/10000
Age group				
0-5	32857	47	12.5	14.3
6-11	36957	71	18.8	19.2
12-17	38655	33	8.75	8.5
18-24	43862	14	3.7	3.2
≥25	179505	6	1.6	0.3
Gender				
Male	168336	110	29.2	6.5
Female	163500	61	16.2	3.7
Total	331836	171	45.4	5.2

(Table-4), exhibits that rotavirus gastroenteritis significantly different from gastroenteritis patients associated with other enteric pathogens in respect to vomiting ($P<0.01$), while no such difference observed in respect to diarrhea ($P<0.97$) or fever ($P<0.87$). Severe and some dehydration constitute 69.5%. No statistical

significance in respect to dehydration status in rotavirus positive cases with gastroenteritis patients associated with other enteric pathogens ($P<0.86$). The mean stay duration for positive rotavirus cases was 3 days with no difference between positive rotavirus cases and other gastroenteritis patients ($P<0.1$).

Table 4. Distribution of gastroenteritis cases according to clinical symptoms and duration of hospitalization.

Symptom	Rota +ve		Rota -ve		Total	
	No.	%	No.	%	No.	%
Diarrhea						
Yes	170	45.1	205	54.4	375	99.5
No	1	0.26	1	0.26	2	0.5
Vomiting						
Yes	159	42.2	174	46.2	333	88.3
No	12	3.2	32	8.5	44	11.7
Fever						
Yes	121	32.1	146	38.7	276	70.8
No	50	13.3	60	15.9	110	29.2
Dehydration						
Severe	9	2.4	12	3.2	21	5.6
Some	112	29.7	129	34.2	241	63.9
No	50	13.3	65	17.2	115	30.5
Duration of hospitalization						
1-2 days	80	21.2	91	24.1	171	45.3
3-4 days	57	15.1	81	21.5	138	36.6
5-7 days	22	5.8	27	7.2	115	13.0
8-17 days	12	3.2	7	1.9	19	5.1
Total	171	45.4	206	54.6	377	100

All of 171 positive rotavirus stool samples collected from the hospitals were available in sufficient quantity for VP7 and VP4 genotyping. G and P typing results could be obtained for 83% of positive samples (134 samples). The results are shown in (Table-5).

In middle region the prevalent genotype is G1, G9 with P4, P8.

In northern region the prevalent genotype is G1, G9 with P8 P untypeable.

In southern region the prevalent genotype is G1, G2 with P4, P untypeable.

Table 5. Prevalent genotype of rotavirus by hospital.

Hospital Name	G/P	P4	P4 P11	P4 P8	P6	P6 P8	P8	P8 P11	UT	Total
Al-Basheer										
	G1	4			1		7	1	5	18
	G1 G2	1								1
	G1 G4								1	1
	G1 G9								1	1
	G2	2								2
	G3						4			4
	G9		1	1			2	1	5	10
Total G/P		7	1	1	1		13	2	12	37/37
Al-Karak										
	G1	5	2		2	1	7		7	24
	G2	22			1					23
	G9						1		7	8
	UT	1								1
Total G/P		28	2		3	1	8		14	56/56
Princess Rahma										
	G1				2		12		6	20
	G1 G2	1								1
	G2								1	1
	G3						4			4
	G3 G9								1	1
	G9			1				3	9	13
Total G/P		1		1	2		16	3	17	40/40
TOTAL G/P		37	3	2	6	1	37	5	43	134/134

The most common G type was G1 (46.9%) followed by G9 (23.8%), G2 (18.5%), and G3 (6.2%). Other G types included mixed G1G2 (1.5%), G1G4 (0.8%), G1G9 (0.8%), G3G9 (0.8%) and 1 untypeable (0.8%). The most common P type was untypeable strains (33.1%)

followed by P8 (27.7%) and P4 (26.2%). Other P types included P6(4.6%), mixed P4P11(2.3%), P4P8(1.5%), P6P8(0.8) and P8P11(3.8%). The prevalent combined genotype is G1P8, followed by G2P4 and G9PUT.

Table 6. Prevalent G and P Type of rotavirus by age group.

Age group	0-5	6-11	12-17	18-24	>25	Total
Type G						
G1	18	20	15	5	3	61
G1G2	2	0	0	0	0	2
G1G4	0	1	0	0	0	1
G1G9	0	1	0	0	0	1
G2	7	10	4	3	0	24
G3	1	5	0	2	0	8
G3G9	0	1	0	0	0	1
G9	8	15	5	2	1	31
UT	1	0	0	0	0	1
Type p						
P4	12	14	4	3	1	34
P4P11	1	1	1	0	0	3
P4P8	1	1	0	0	0	2
P6	5	1	0	0	0	6
P6P8	0	0	1	0	0	1
P8	9	14	6	5	0	36
P8P11	0	4	6	0	0	5
UT	9	18	11	4	1	43
Total	37	53	24	12	4	130

Table 7. Percent of major G-P rotavirus strain combinations in hospitals

Rotavirus strain	No. of strain	Percentage
G1P8	26	19.7
G2P4	23	17.4
G9PUT	21	15.9
G1PUT	18	13.6
G1P4	9	6.8
G3P8	8	6
G1P6	5	3.8
G9P8	3	2.3
G2P6	1	0.8
GUTP4	1	0.8
G2PUT	1	0.8
Mixed G or P strains	14	8.3
Total	130	100

DISCUSSION

Overall, rotavirus was detected in 45.4% (171/377) of the children less than 60 months of age who consulted a pediatrician and admitted because of gastroenteritis. The proportion was higher than the percentages observed in Spain (24%), Finland (26%), or England and Wales (29%) and in Mediterranean region Tunisia (22%), Iraq (37%). Meanwhile it is lower than in Saudi Arabia (50%).^[6-11] The incidence of rotavirus gastroenteritis during the study period

is 5.2 per 10000 children per year. The incidence is obtained during a whole year (May 2007-May 2008), which is higher than figures reported in many countries, which carried their hospital based studies in 3-6 months period, for example in Austria the incidence was 1.33 (6 months period study), while in Finland it was 9.1(3 months period study), or in Switzerland it was 1.6 per 100 children per year (3 months period study).^[12] Globally it is known that 80%

of diarrhea cases are self-limited and they don't seek any medical care because gastroenteritis is considered a self limited disease. This was proved by one unpublished household survey done in Jordan in 2003 in respect to food borne diseases with syndromic approach and its burden in Jordan; it revealed that only 20% of gastroenteritis cases seek care for treatment and 50% out of them (10%) seek care in other health sectors (royal medical services, UNRWA and private sector). Taking this study in consideration the expected gastroenteritis due to rotavirus in three selected hospitals will exceed 2000 admissions per year, which constitute burden on health services beside its societal effect on children and their parents. The largest proportion of rotavirus gastroenteritis was noted in the 6-11 month age group with average age 8 months. Ford-Jones *et al*, reported age dependent rates of rotavirus gastroenteritis in children. Peak of occurrence is in the age group under 23 months and declines in older age groups to zero incidence after 3 years old. In contrast to developing countries, rotavirus diarrhea occurs at a higher age in industrialized countries like the USA, where the peak occurs during the second year of life. The highest rate of rotavirus disease occurs between 3 months and 2 years of age, which is similar to findings in this study.^[6-10] There were 64% of positive cases males while 36% females with average for both groups 8 months. Difference in sex ratio (male: female 1.8:1) might be explained by socio-economic and cultural reasons. Similar finding was found in a study carried among Austrian children (69.4% males: 30.6% females).^[13] In addition to age dependence, variations were observed between different regions. The highest apparently was in the south region. This might be caused by nature of living conditions, health care users, access to hospitals and health care providers. The Clinical presentation of patients with rotavirus gastroenteritis didn't differ from that of patients associated with other enteric pathogens. Rotavirus Gastroenteritis was significantly

different from rotavirus negative gastroenteritis only in respect to vomiting ($P < 0.01$), while no such difference observed in respect to diarrhea ($P < 0.97$) and fever ($P < 0.87$). Diarrhea, vomiting and fever were observed with low sensitivity 45.3%, 47.7%, 45.3% respectively. Dehydration status with "severe", "some" and "no" dehydration was observed also with low sensitivity 42.9%, 46.5% 43.5% respectively and no statistical significance among positive rotavirus cases with negatives ($P < 0.86$). Low sensitivity of diarrhea and fever and dehydration status might be explained by population under study, which represent children treated at hospitals, who are the most severely ill: on Vesikari Scale (> 10 score), while vomiting was a dominant symptom for children with rotavirus gastroenteritis, so for further understanding of the spectrum of disease and clinical symptoms a combined community and hospital based studies which investigate both mild and severe disease could be carried out. In similar studies children infected with rotavirus gastroenteritis were more likely to have watery stools, severe vomiting and less severe dehydration.^[12,13] A significant finding in this study was the high percentage of G1P8, G2P4 and G9 with untypeable P type, accounting for 19.7%, 17.4% and 15.9% respectively of rotavirus gastroenteritis. A recent review of global rotavirus genotypes states that G1P8 accounts for 70% of rotavirus infections in North America, Australia and Europe, whereas it represents about 30% of infections in South America and Asia and about 23% in Africa.^[14] Rotavirus serotype G9 is recognized as the most widespread of the emerging genotypes, representing 4.1% of global rotavirus infections and accounting for up to 70% of rotavirus infections in recent reports.^[13] In Jordan the most prevalent genotype in Southern region is G2P4; in Northern and Middle regions is G1P8. Mean stay duration of rotavirus positive cases is 3 days. The mean length of stay in similar studies was 4.0 days.^[16]

CONCLUSIONS

Incidence rate of Rotavirus gastroenteritis in children less than five years old is 5.2 per 10000 children per year. It comprises a relevant cause of severe gastroenteritis and requires admission to hospitals most of the time, with average duration of stay of 3 days. Vomiting is a dominant symptom for rotavirus cases.

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