Iranian J Publ Health, Vol. 43, No.10, Oct 2014, pp.1356-1363

Original Article

Rota Viral Infection: A Significant Disease Burden to Libya

Salem ALKOSHI [1], Kacey ERNST [2], Namaitijiang MAIMAITI [3], Maznah DAHLUI [1]

1. *Dept. of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*
2. *Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, the University of Arizona, Tucson, Arizona State, USA*
3. *International Institute for Global Health, United Nations University, Kuala Lumpur, Malaysia*

***Corresponding Author:** Email: alkushis@yahoo.com

(Received 10 May 2014; accepted 10 Aug 2014)

Abstract

Background: Rotavirus is a common infection causing 450,000 deaths annually primarily in children 5 years and below. Despite the high burden of disease, little is known about the epidemiology of rotavirus in Libya. The aim of this study was to estimate the rotavirus disease burden among Libyan children.

Methods: A cross-sectional study was carried out prospectively among children 5 years old and below between August 2012 and April 2013. Stool samples of children with diarrhea attending the outpatient department or admitted to the pediatric wards, at three public hospitals within the northwestern region of Libya were tested for rotavirus. The seasonality, symptomology demographics and outcomes of rotavirus cases were determined and compared to other diarrhea illnesses. An estimated incidence rate per 100,000 children aged 5 years and below was determined.

Results: A total of 545 children with diarrhea were identified for participation. Results of rotavirus immunoassays determined 57% of cases were caused by rotavirus. Inpatients were more likely to be rotavirus positive than outpatients (58% vs. 53%, $P<0.05$), Most rotavirus positive cases (86%) were found among children below 2 years of age. Rotaviral cases peaked in the winter, constituting 76% of diarrheal illness in February and very few rotavirus cases in the summer months. The incidence rate of rotavirus diarrhea was estimated at 640/100,000 children aged 5 years and below.

Conclusion: Rotavirus infection poses a significant disease burden in Libya. Preventive measures such as proper hygiene should be emphasized. Introduction of vaccination against rotavirus into the national immunization program should be examined, as it would likely be a cost-effective investment.

Keywords: Rotavirus, Diarrhea, Burden, Libya, Children, Incidence

Introduction

Rotavirus infection is a major cause of severe diarrhea in infants and young children globally, and can be fatal (1-3). The global burden of rotavirus is estimated at 110 million cases and 520,000 deaths among young children each year. Overall diarrhea is the second leading cause of death in children under age five and approximately 80% of diarrheal deaths in poor regions are caused by rotavirus (4-6). Children under two-years old are the most vulnerable to rotavirus and have higher case-fatality rates (7, 8). Contrary to many bacterial diarrhea infections, rotavirus peaks during cool or humid weather (9). Dehydration is the primary driver of fatality due to rotavirus and breast-

feeding and oral rehydration therapy can reduce the case-fatality rates (2, 10). Two primary prevention strategies are used for rotavirus, improved hygiene, sanitation, and vaccination. The rotavirus vaccine is highly effective; approximately 86% yet many countries, which have the highest burden of rotavirus vaccine, have still not introduced it into their childhood immunization schedule (11). Rotaviral infection is still increasing, accounting for 39% of childhood hospitalizations for diarrhea up from 22% 20 years ago (12). In developing countries, rotavirus leads to a high number of deaths and causes a significant economic burden on the heath sector (13). In Libya, most health service sectors are publicly owned and provide preventive, curative and rehabilitation services to all citizens free of charge. The Ministry of Health is responsible for all health programs including planning, evaluation, health education, medical equipment, medical services, drugs and administration and finance. Historically national surveillance data demonstrated that rotavirus cases accounted for 24%-45% of diarrheal cases between 1980 and 2009 (14, 15). Accurate data became unavailable, however, after the revolution in 2011 disrupted routine surveillance.

To determine current estimates of the burden of rotavirus this study collected information on rotaviral infection in children aged 5 years and below in a northwestern region of Libya.

Methods and Materials

Study Design and Study Population

A prospective cross-sectional study was conducted from August 2012 to April 2013 (9 months) in all three public hospitals in northwestern Libya; Zliten, Khoms and Mslata public hospitals. These hospitals serve approximately 57,180 children aged 5 years and below, being 8% of total children (705,190) aged 5 years and below in Libya. There are no private hospitals in this region while private and public clinics do not provide treatment services as intravenous fluid (IVF) for diarrhea. Children 5 years old and below who presented with diarrhea at the outpatient clinics or who were admitted to the pediatric wards were eligible for inclusion. Demographic, risk factor and symptomology data were collected.

Case Definition

Patients described in this study were children aged 5 years and below with diarrhea, with or without other symptoms such as fever, vomiting or dehydration (16, 17), both outpatient and hospitalized cases were included. The standard definition of diarrhea was used; three or more instances of liquid stool in a day (18).

Data Collection

Laboratory, clinical and risk factor data were collected.

Laboratory data: Stool samples were collected by a nurse. Since rotavirus testing was not done routinely in the three hospitals, the stool samples were tested by the laboratory of the National Center for Diseases Control (NCDC) located in Tripoli and Zliten, the only facility in Libya with this capacity. Stool specimens were stored at approximately -20°C and tested within one week after taking the samples. An enzyme immunoassay (ProSpect Rotavirus Test, Oxoid Ltd, UK) was used to confirm the infection of rotavirus (Group A). "The ProSpecT™ Rotavirus test is a qualitative enzyme immunoassay for the detection of rotavirus (Group A) in human faecal samples as an aid in the diagnosis of acute gastroenteritis. The test utilises a polyclonal antibody to detect group specific proteins, including the major inner capsid protein (VP6), present in Group A rotaviruses" (19).This test was appropriate since human rotavirus serotypes for group A are a main cause of diarrhea among young children worldwide (20, 21). Risk factor and clinical data: Information was collected on the characteristics of diarrhoea and the proportion rotavirus infection among the diarrhea cases was determined. Demographic data were collected on patient status, gender, place of residence, date of visit/ admission. Factors associated with rotavirus infection such as the duration of symptoms, fever, vomiting and severity of dehydration, the type of rehydration treatment, outcome of treatment and mortality were identified from the patient's record.

Statistical Analysis

The data was entered into SPSS version 16. Comparisons were made between characteristics of the rotavirus and non-rotavirus positive cases using the chi-square test, with *P* values <0.05 considered statistically significant. To determine the association between risk factors/ clinical factors and rotavirus infection other tests including the Mann–Whitney test and multiple logistic regression were performed. Seasonality of rotavirus infections was examined by determining the relative percentage of diarrheal cases attributed to rotavirus by month. Approximate yearly incidence of rotavirus diarrhea in the study area was determined per 100,000 children aged five years and below based on the catchment population of 2012 in study districts (57,180 children aged 5 years and below). The missing rotavirus cases from May to July were projected using data from NCDC's reports during the period from 2007 to 2009. We assumed that the seasonal pattern was similar for rotavirus across Libya and applied the relative average percentage of national-level cases detected in May, June and July from the NCDC's reports to the regional data.

Ethics

Oral consent was obtained from patient's parents after informing them on the purpose of the study. This study was approved by the University of Malaya Medical Ethics Committee (IRP - 908.6) in Malaysia, NCDC in Libya and managements of the study hospitals.

Results

Proportion of Diarrhoea accounted for by Rotavirus

A total of 545 diarrheal cases were observed during the study period. Of these, 135 (25%) were outpatients and 410 (75%) were admitted cases. Rotavirus accounted for a significantly higher proportion of diarrheal cases than other infectious agents (311 (57%) vs. 243 (43%), *P*=0.001) Rotavirus positive cases were more common in admitted patients 58% (239/410), than in outpatient, 53% (72/135), *P*=0.313. No difference was seen in diarrhea attributed to rotavirus between males and females (57% (179/315) vs. 57% (132/230); *P*=0.895), or urban and rural areas (56% (70/124) vs. 57% (241/421), *P*=0.876). Rotavirus comprised nearly all diarrheal illnesses in children under two years of age but only a small percentage in children over age 2 (86% (266/311) vs. (14% (45/311), *P*=0.031).

Seasonality of Rotavirus Diarrhea

The distribution of cases attributable to rotavirus fluctuated greatly over the course of the study period. Almost all rotavirus cases (n=283, 91%) were diagnosed in the winter months (Dec 2012–Mar 2013).

Table 1: Seasonal distribution of diarrhea aged 5 years and below

Season	Month	n of tested	Positive-Rotavirus	%
Summer				
	Aug 2012	12	1	6
	Sept 2012	30	3	10
	Oct 2012	31	1	0.3
	Nov 2012	21	3	14
Winter				
	Dec 2012	61	34	56
	Jan 2013	87	63	72
	Feb 2013	143	109	76
	Mar 2013	105	77	73
Spring				
	Apr 2013	55	20	36
Total		545	311	57

Significant level is *P*<0.05

Only n=8, 3% were diagnosed in the summer months (Aug 2012 – Nov 2012). The proportion of diarrheal illness attributed to rotavirus was lowest in October 2013 (n=1, 0.3%) and highest in February (n=109, 76%) (Table 1).

Factors Associated with Rotavirus Infection and Mortality

The duration of symptoms in most rotavirus cases (n=255, 82%) was below one week. Fever was found in 65% of rotavirus cases (n=203), and vomiting in 98% of rotavirus cases (n=304). Severe, moderate and non-dehydration were found in 31% (n=97), 66% (n=205) and 3% (n=9) of rotavirus patients, respectively (*P*=0.519). 99% (n=309) of positive rotavirus patients were treated by intravenous fluid (IVF) with only two positive rotavirus cases treated by solely with oral rehydration therapy (ORT) (n=2, 1%) (Table 2). Death related to diarrhea or rotavirus infection was not observed during the period of the study. Predictors of rotavirus diarrhea vs. other causes of diarrhea included presentation during cool months (OR=; *P*=4.383), presence of vomiting (OR=; *P*=8.420) and patient with severe dehydration (OR=; *P*=5.389) (Table 3).

Table 2: Factors associated with diarrhea among patients

Demographic Profiles and Characteristics		Rotavirus Positive (n = 311)		Rotavirus Negative (n = 234)	
		n	%	n	%
Duration of Symptoms					
	< 1 Week	255	82	185	79
	8 Days and Above	56	18	49	21
Fever		203	65	163	70
Vomiting		304	98	196	84
Dehydration		302	97	204	87
Dehydration Degree					
	Severe	97	31	60	26
	Moderate	205	66	144	62
	None	9	3	30	13
Rehydration Treatment					
	ORT	2	1	17	7
	IVF	309	99	217	93
Outcome of Treatment					
	Improved	196	63	74	32
	Complicated	3	1	4	2
	Unknown	112	36	156	67

Table 3: Factors associated with rotavirus diarrhoea in the study

Variable		Crude OR[a] (95%Cl)	Adjusted OR[b] (95%Cl)	Wald statistics[b] (df)	*P*-value[b]
Season					
	Summer	0.163 (0.066–0.404)	0.186 (0.073–0.471)	12.851 (1)	0.000
	Winter	4.383 (2.427–7.915)	4.282 (2.335–7.853)	22.094 (1)	0.000
	Spring	1	1		
Vomiting					
	Yes	8.420 (3.687–19.230)	6.041 (2.407–15.162)	14.678 (1)	0.000
	No	1	1		
Dehydration					
	Severe	5.389 (2.394–12.132)	3.860 (1.496–9.959)	7.801 (1)	0.005
	Moderate	4.745 (2.187–10.298)	2.713 (1.103–6.675)	4.725 (1)	0.030
	None	1	1		

[a]Simple logistic regression, [b]Multiple logistic regression

Incidence of Rotavirus Diarrhea in the Study Area

The unadjusted incidence of rotavirus requiring treatment was 544 per 100,000 per nine months. The projected annual number of rotavirus was 366 cases. Applying this adjusted number of rotavirus diarrhea cases for 12 months requiring treatment in this study, the incidence rate of rotavirus diarrhea for children 5 years old and under the catchment population of 2012 in the studied hospitals (57,180 children aged 5 years and below) was estimated to be 640 per 100,000 per year among children aged 5 years and below (range: 589–696 per 100,000 children aged 5 years and below).

Discussion

This study aimed to determine the burden of rotavirus infection posed to the north-western region of Libya. Results indicate that rotavirus infection among children under 5 years is high, constituting over half of diarrheal illnesses and poses a significant disease burden to the northwestern region of Libya. The rate of diarrhea cases attributed to rotavirus infection determined in the current study was comparable to reports at national and local levels. Official reports of Libya from 2007 to 2009 (15, 22, 23) reported that on average rotavirus accounted for 44% of diarrheal illnesses similar to reports from 1980 to 2009 which indicated rotavirus accounted for 24% to 45% of all diarrhea illness in children under 5 years. (10, 14, 24-26). Also, in Tripoli, the capital of Libya, rotavirus also constituted a lower amount (33%) from September 2008 to May 2009 (9 months) (26).

Given the severe nature of dehydration that often occurs in rotavirus patients, it was not surprising that rotavirus accounted for a higher percentage of diarrheal illness in admitted vs. outpatient cases. This has been found in other studies of rotavirus in Libya (24, 26). As severe illness from rotavirus is most common in children under two, it was not surprising that our study also demonstrated this trend (15, 22-24, 26). As the hospitals in the study site are located in more rural populations, most of the cases were from rural areas (77%).

Global estimates of rotavirus incidence prior to the implementation of wide-scale vaccination programs varied widely and were not necessarily correlated with level of development (27). In Australia rates were higher than in Libya (750 cases per 100,000 children under 5 (28), but in Europe rates were lower (29, 30). Prior to adoption of vaccination programs for rotavirus, about 45% of countries in the world had the incidence of rotavirus of about more than 200 cases per 100,000 children aged 5 years and below (31). Compared to other countries in the Middle East and North Africa region, most countries, with the exception of Oman and Iran, had a lower incidence of rotavirus than what was found in northwestern Libya (14). Libya, therefore, is considered a high rotavirus incidence country. It is difficult to make direct comparisons to other countries as part of the high disease incidence in Libya may be attributed to easy access to health services and thus capture of a higher proportion of rotavirus infections than in countries with less available health care.

No deaths were attributed to rotavirus infection in the study population; however, WHO estimated the mortality rate in Libya was 14 per 100,000 in children under five from 1999 to 2009. This is lower than some countries in the region where mortality due to rotavirus ranges from 0 to 112 per 100,000 children aged 5 years and below (14). Comparisons that are more global indicate that mortality due to rotavirus infection in Libya is low compared to some African and South American countries (32). It is likely that Libya's free and accessible health care facilitates effective treatment for diarrhea in children with diarrhea. Indeed, mortality due to rotavirus is very low in other countries where health care access is high, including the United States and Europe (27).

Globally, the rotavirus infection increased from 22% to 39% for the period of 1986 to 2004, which was similar to the increase of the rotavirus detection in this study (13, 33). Since that time, rotavirus has declined in countries, which have introduced the vaccine (34, 35). Based on the rate of rotavirus infection during the study period, the incidence rate of rotavirus diarrhea was 640/100,000 of children aged 5 years and below.

This incidence is higher than the reported national incidence from 2009 published by the NCDC in Libya of 449 cases per 100,000 of children aged 5 years and below. The NCDC's report indicated that rotavirus infection was rising steadily and study results suggest this may be the case. However, there may also be geographic differences in rotavirus transmission that could be an alternative explanation for the higher incidence reported out of the hospitals in northwestern Libya.

Several limitations were encountered during data collection. The incidence of rotavirus infection was obtained by estimating the rate of rotavirus among children aged 5 years and below who presented with diarrhea at all hospitals which serve of the north-western region of Libya. Ideally, incidence rates should be calculated for a period of one year, covering all twelve months in a year. However, due to insecurity after the revolution, data collection was lapsed in the months of May to July. These three months were not included since the study had to be discontinued due to expired rotavirus kit in the laboratory after only nine months' of data collection. Because of the complex and time-consuming procedures needed to import new kits under the auspices of the Ministry of Health as well as instability after the revolution. Therefore, we applied the average proportion of reported cases occurring in May, June and July from the NCDC report to obtain an estimate of annual incidence. Given the seasonality of rotavirus (36) is likely a better approximation of yearly incidence than either averaging the nine months of available data to create an estimated incidence or assuming that there were no cases detected during May, June and July. However, the resulting rate was higher than that in previous reports from NCDC and may be an over-estimate.

This study has indicated that rotavirus is a significant cause of diarrhea or diarrhea and is still in widespread, indicating that preventive program should be taken up or straightened. The introduction of rotavirus vaccine with a high coverage rate into the national immunization program could reduce the transmission of rotavirus infection among infants and young children as has been successfully in many countries. The cost-effectiveness of implementation should be conducted carefully as it has been shown that incorporating routine vaccination is more cost-effective in high mortality countries. Given the low mortality rate in Libya, the cost-benefit must be determined before broad-scale implementation is recommended (37).

Conclusion

The significant burden of rotavirus diarrhea was estimated among children aged 5 years and below in Libya. The study demonstrated that the incidence of rotavirus diarrhea was high among children 5 years old and below. The disease burden could be reduced by enhancing health education such as proper hygiene care. Further exploration of the cost-benefit of vaccination implementation is warranted given the high burden of rotavirus infection present in Libya.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

Acknowledgements

We would like to thank NCDC in Libya and medical staff at the study hospitals. Patients and their parents were appreciated to the participation in the study. The authors declare that there is no conflict of interests.

References

1. Payne J,Elliott E (2009). Gastroenteritis in children. *Clin Evidence*, 2009:0314.
2. WHO (2005). *Guidelines for estimating the economic burden of diarrhoeal disease with focus on assessing the costs of rotavirus diarrhoeal.* Dept. of Immunization, Vaccines and Biologicals.

3. WHO (2009). *Diarrhoeal Diseases. Initiative for Vaccine Research (IVR).* Dept. of Immunization, Vaccines and Biologicals.
4. Cortese MM, Parashar UD, Centers for Disease C,Prevention (2009). *Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP).* ed. Dept. of Health & Human Services, Centers for Disease Control and Prevention.
5. Patel MM, Steele D, Gentsch JR, Wecker J, Glass RI,Parashar UD (2011). Real-world impact of rotavirus vaccination. *Pediatr Infect Dis J,* 30:S1.
6. WHO (2008). *Generic protocol for monitoring impact of rotavirus vaccination on gastroenteritis disease burden and viral strains.* Dept. of Immunization, Vaccines and Biologicals.
7. WHO (2009). Rotavirus Bulletin. *Western Pacific Region,* 1.
8. WHO (2009) Rotavirus. *Weekly Epidemiological Record.* 51-52: 533-540
9. DAS S, Begum D, Ahmed S, Ferdous F, Farzana F, Chisti M, Latham J, Talukder K, Rahman M, Begum Y (2014). Geographical diversity in seasonality of major diarrhoeal pathogens in Bangladesh observed between 2010 and 2012. *Epidemiology and Infection*:1-12.
10. Ghenghesh KS, Franka EA, Tawil KA, Abeid S, Ali MB, Taher IA,Tobgi R (2008). Infectious acute diarrhea in Libyan children: causative agents, clinical features, treatment and prevention. *Libyan J Infect Dis,* 2:10Ã 9.
11. Yen C, Tate JE, Hyde TB, Cortese MM, Lopman BA, Jiang B, Glass RI,Parashar UD (2014). Rotavirus vaccines: Current status and future considerations. *Human Vaccines & Immunotherapeutics,* 10:0-1.
12. Gray J, Vesikari T,Damme V (2008). Economic Burden of Rotavirus Disease. *Centre for Infections, Health Protection Agency, London, UK, Journal of Pediatric Gastroenterology and Nutrition.*
13. Parashar UD, Alexander JP,Glass RI (2006). Prevention of rotavirus gastroenteritis among infants and children. *Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR Recomm Rep,* 55:1-13.
14. Hanane K, Isla O, El Khoury Antoine DY,Mireille G (2009). Burden of rotavirus gastroenteritis in the Middle Eastern and North African pediatric population. *BMC Infect Dis,* 11:9.
15. NCDC (2009). *Annual report for infectious disease in Libya.* Surveillance Department at NCDC.
16. WHO (2002). *Generic protocols for (i) hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children and (ii) a community-based survey on utilization of health care services for gastroenteritis in children.* Vaccines and Biologicals, World Health Organization.
17. Neale J (2009). Research methods for health and social care. *Palgrave Macmillan,* 10:137-148.
18. Masters J (2007) Gastroenteritis and the rotavirus vaccine. Health University of Bristol.
19. ProSpect Rotavirus Test (2013). Remel - Diagnostic Tests. *Oxoid Ltd, UK.*
20. Steinhoff MC (1980). Rotavirus: the first five years. *J Pediatr,* 96:611-622.
21. Blacklow NR,Cukor C (1981). Viral gastroenteritis. *J Occup Environ Med,* 23:862.
22. NCDC (2007). *Annual report for infectious disease in Libya.* Surveillance Department at NCDC.
23. NCDC (2008). *Annual report for infectious disease in Libya.* Surveillance Department at NCDC.
24. Abugalia M, Cuevas L, Kirby A, Dove W, Nakagomi O, Nakagomi T, Kara M, Gweder R, Smeo M,Cunliffe N (2011). Clinical features and molecular epidemiology of rotavirus and norovirus infections in Libyan children. *J Med Virol,* 83:1849-1856.
25. Ghenghesh KS, Kreasta M, El-Bakoush M,Tobgi R (2002). ROTAVIRUSES-ASSOCIATED GASTROENTERITIS. *Med J,* 2: 12-17.
26. Kalaf RN, Elahmer OR, Zorgani AA,Ghenghesh KS (2011). Rotavirus in children with diarrhea in Tripoli, Libya. *Libyan J Med,* 6.
27. Parashar UD, Hummelman EG, Bresee JS, Miller MA,Glass RI (2003). Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis,* 9:565.
28. Carlin JB, Chondros P, Masendycz P, Bugg H, Bishop RF,Barnes GL (1998). Rotavirus infection and rates of hospitalisation for acute gastroenteritis in young children in Australia, 1993-1996. *Med J Australia,* 169:252-256.
29. De Wit M, Koopmans M, Van der Blij J,Van Duynhoven Y (2000). Hospital admissions for rotavirus infection in the Netherlands. *Clin Infect Dis,* 31:698-704.
30. Ryan M, Ramsay M, Brown D, Gay N, Farrington C,Wall P (1996). Hospital admissions attributable to rotavirus infection in England and Wales. *J Infec Dis,* 174:S12-S18.

31. Kim SY, Sweet S, Slichter D,Goldie S (2010). Health and economic impact of rotavirus vaccination in GAVI-eligible countries. *BMC Public Health,* 10:253.
32. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J,Parashar UD (2012). 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis,* 12:136-141.
33. CDC (2008). Rotavirus Surveillance --- Worldwide, 2001—2008. *Dept. of Health and Human Services,* 57(46):1255-1257.
34. Lepage P,Vergison A (2012). Impact of rotavirus vaccines on rotavirus disease. Expert Rev Anti Infect Ther. 2012 May;10(5):547-61.
35. Lopman BA, Payne DC, Tate JE, Patel MM, Cortese MM,Parashar UD (2012). Post-licensure experience with rotavirus vaccination in high and middle income countries; 2006 to 2011. *Current Opinion in Virology,* 2:434-442.
36. Levy K, Hubbard AE,Eisenberg JN (2009). Seasonality of rotavirus disease in the tropics: a systematic review and meta-analysis. *Int J Epidemiol,* 38:1487-1496.
37. Atherly DE, Lewis KD, Tate J, Parashar UD,Rheingans RD (2012). Projected health and economic impact of rotavirus vaccination in GAVI-eligible countries: 2011–2030. *Vaccine,* 30:A7-A14.