

Rotavirus gastroenteritis and strain diversity in Saudi Arabia

Current status and future prospects

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ABSTRACT

الأهداف: عمل دراسة وبائية للمرض، والتعرف على السلالات الأكثر انتشاراً على ضوء الدراسات المنشورة لإعطاء صورة واضحة و حديثة لأهمية أثر هذا الفيروس في المملكة العربية السعودية.

الطريقة: أجريت دراسة وبائية للفيروس و السلالات الأكثر انتشاراً في المملكة العربية السعودية من خلال مراجعة الدراسات المنشورة في المملكة و عددها 22 خلال الفترة من 1982 حتى 2005م، إضافة إلى الدراسات المنشورة حديثاً في 2008م. أجريت الدراسة في مستشفى الملك فهد - المدينة - المملكة العربية السعودية.

النتائج: أشارت دراستنا المنشورة في العام 2006م أن نسبة حالات التهابات المعوية المسببة بفيروس الروتا تتراوح بين 10-46% بمعدل 30% من حالات التهابات المعوية. كما أشارت الدراسات الحديثة في المملكة العربية السعودية انخفاض معدل اكتشاف المرض بنسبة (18% و 12%). أوضحت هاتين الدراستين انتشار أنواع P و G لفيروس الروتا المنتشر في المملكة العربية السعودية، و أوضحت وجود النمط المصلي G1-G4، و G9، و G12، و P[6]، و P[4]، و P[8].

خاتمة: لهذه النتائج أهمية خاصة لدراسة الخطط المستقبلية لإمكانية التطعيم لفيروس الروتا في المملكة العربية السعودية، و التأكيد على أهمية عمل دراسات مستمرة لفيروس الروتا للأنواع P و G قبل بداية لقاح فيروس الروتا.

Objectives: To determine the epidemiological profile and strain diversity in the light of recent published studies to provide an updated comprehensive picture of the significance of the effect of this virus in Saudi Arabia.

Methods: The epidemiology, disease burden, and strain diversity of rotavirus in Saudi Arabia were reviewed using 22 studies of rotavirus and the etiology of diarrhea. We reviewed the studies conducted between 1982 and 2005 as well as the 2 recently published studies in 2008. This study took place in King Fahd Hospital, Maddina, Kingdom of Saudi Arabia.

Results: In Saudi Arabia, a review published in 2006 showed that rotavirus prevalence ranged from 10-46%, with a median prevalence of 30% of cases of gastroenteritis. Recent studies in the country however showed a lower detection rates (18% and 12%). These 2 studies described the distribution of G and P types of rotavirus circulating in Saudi Arabia and demonstrated the presence of serotype G1-G4, G9, G12, P[4], P[6], and P[8].

Conclusion: These results have importance regarding a future rotavirus immunization strategies in Saudi Arabia, and underscore the need for a countrywide monitoring a rotavirus G- and P-types before the introduction of a rotavirus vaccine.

Saudi Med J 2010; Vol. 31 (3): 276-279

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Received 9th December 2009. Accepted 27th January 2010.

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Diarrheal disease remains a major cause of childhood mortality, annually accounting for more than 1.8 million deaths among children less than 5 years of age.¹ Of the ≥ 50 pathogens capable of causing gastroenteritis, rotavirus is the most important cause of severe, dehydrating gastroenteritis in infants and young children worldwide.² Mostly, all children experience rotavirus infection by the age 5 years³ and an estimated 527,000 rotavirus-associated deaths occur in developing countries.^{4,5} Therefore, control of rotavirus infection would potentially not only lead to a significant reduction of fatalities in developing countries but also considerable healthcare cost savings.^{6,7} Presently, 2, live, and orally-administrable rotavirus vaccines are currently licensed in many countries after they had gone through

large scale safety and efficacy trials.^{8,9} Rotaviruses are triple-layered icosahedral particles and their genomes consist of 11 segments of double-stranded RNA. Based on epitopes on the inner capsid, rotaviruses are subdivided into 7 groups (A-G), but most human infections are due to group A rotaviruses. Rotaviruses are further classified according to the genetic and antigenic diversity of the 2 outer capsid proteins, VP4 (P serotype) and VP7 (G serotype).¹⁰ In addition, as G and P type-specific immunity is believed to play a role in protection against disease, the epidemiology of G and P serotypes (and genotypes) of circulating strains, forms a critical knowledge base for the development and implementation of rotavirus vaccines.¹¹ To date, 19 G serotypes and 27 P types have been defined. However, only a few P-, G-, and P/G combinations have been found in human. The G1-G4, G9, P[4], P[6] and P[8] are the major rotavirus types found in global collections of strains.¹² The proportion of active gastroenteritis cases in Saudi Arabia that were rotavirus positive ranged from 32-46% among hospitalized children with variation by month and season.¹³ Although 2 recent studies have documented the prevalence of rotavirus among Saudi children conducted in 2 Saudi cities namely Maddina and Gizan,¹⁴⁻¹⁶ these have never been analyzed together to provide an updated comprehensive data of the significance of the effect of this virus in the country. In anticipation of introduction of rotavirus vaccine in Saudi Arabia and its recent introduction in Bahrain and Kuwait,¹⁷ we aim to estimate the disease burden with regards to the recent published studies and assess the prevalence of rotavirus infection to inform the need for a rotavirus immunization program.

Methods. We identified a multilingual MEDLINE search for publications from 1975 to 2005 using the keywords of 'rotavirus', 'viral gastroenteritis', and 'Saudi Arabia' to review the literature of rotavirus studies. All papers published using the mentioned keywords were included. Any uncompleted or unpublished studies were excluded. In addition, the *Annals of Saudi Medicine* and the *Saudi Medical Journal* were hand searched for papers on rotavirus. In 2008, 2 studies from Maddina and Gizan were reported. The subject enrolment and specimen collection in these studies was conducted as described previously.^{14,15} This study took place in King Fahd Hospital, Maddina, Kingdom of Saudi Arabia.

The data was entered in MS Excel software. Descriptive statistics (median, standard deviation and percentage) were applied to summarize quantitative and qualitative variables.

Results. Twenty-two studies addressing rotavirus infection in Saudi Arabia revealed a prevalence ranging

from 10%¹⁸ to 46%¹⁹ with a median of 30%. In-patient studies showed significantly higher prevalence compared with those where outpatients were included. The range of inpatient prevalence was 10-46%, median 41.5%, and standard deviation 12.2%, whereas the range of combined inpatient and outpatient studies were 10.6-37.5%, median 16%, and standard deviation 10.5%. The highest infection rates were seen among children <2 years of age.¹³ Summary of the 2 recent studies investigating rotavirus infections among children conducted in 2 Saudi cities namely Maddina and Gizan are shown in **Tables 1-3**. Of 1049 specimens collected from children <6 years of age with acute diarrhea in Maddina, rotavirus was detected in 189 (18%) specimens by enzyme-linked immunosorbent assay,¹⁵ whereas in Gizan, a total of 54/454 (12%) specimens were positive for group A rotavirus, which was detected throughout the 5 months study period.¹⁴ Thus, the 24 studies addressing rotavirus infection conducted in Saudi Arabia between 1982 and 2008 revealed a range from 10%¹⁹ to 46%²⁰ with a median of 27%. With regard to G and P typing, the 2 recent studies identified G1P[8] as the most predominant type followed by G2P[4] and G9P[8]. The other types detected are G3P[8], G12P[8], and G2P[6].^{14,15}

Discussion. The characteristics of rotavirus diarrhea among children in Maddina was 12% and Gizan 18%, included relatively lower detection rate.^{14,15} However, the rotavirus detection rate obtained in both studies fell well within the expected range of the previous 22 studies reported in this country showed that the detection rate ranged between 10% and 46%.¹³ Although the Gizan study is limited by a small sample, these 2 studies were the first to describe the distribution of G and P types of rotavirus circulating in Saudi Arabia and have demonstrated the presence of serotype G1-G4, G9, G12, P[4], P[6], and P[8]. The finding of serotype G12 strains (comprising 4% of all G-types) was both highly significant and surprising, since this serotype had rarely been identified in humans 4 years ago. In addition, this is the first report^{14,15} of combination of G12 with P[8] in human and the first detection of G12 from the Middle East,²⁰ which suggests that G12 is following in the footsteps of G9. The presence of this serotype has recently been documented in many countries throughout the world. The emergence of G12 strains in humans has an important implications for the vaccines that are currently recommended internationally by the World Health Organization.²¹ As neither vaccine contains a G12 strain,¹² the ability of either vaccine to protect against G12 strains may prove to be important once they are introduced into national vaccine programs. Although the GlaxoSmithKline (Brentford,

Table 1 - Rotavirus detection rate by month in Maddina and Gizan.^{14,15}

Month	Maddina				Gizan			
	Sample (monthly distribution)		Positive (detection rate)		Sample (monthly distribution)		Positive (detection rate)	
April	129	(12)	16	(12)	-	-	-	-
May	88	(8)	9	(10)	-	-	-	-
June	62	(6)	5	(8)	-	-	-	-
July	71	(7)	9	(13)	-	-	-	-
August	51	(5)	9	(18)	-	-	-	-
September	81	(8)	8	(10)	-	-	-	-
October	82	(8)	9	(11)	28	(6)	3.0	(11)
November	67	(6)	19	(28)	33	(7)	5	(15)
December	121	(12)	28	(23)	160	(35)	20	(13)
January	90	(9)	35	(39)	116	(26)	15	(13)
February	101	(10)	28	(28)	115	(25)	11	(10)
March	106	(10)	14	(13)	2	(0)	0	(0)
Total	1049		189	(18)	454		54	(12)

Data are expressed as number and percentage (%)

Table 2 - Rotavirus detection rate by age in Maddina and Gizan.^{14,15}

Age (month)	Maddina		Gizan			
	Sample (monthly distribution)	Positive (detection rate)	Sample (monthly distribution)	Positive (detection rate)	Sample (monthly distribution)	Positive (detection rate)
0-5	120 (11)	28 (23)	25 (6)	2 (4)		
6-11	201 (19)	75 (37)	27 (6)	4 (7)		
12-17	121 (12)	38 (31)	40 (9)	8 (8)		
18-23	106 (10)	22 (20)	33 (7)	18 (18)		
24-35	206 (20)	12 (6)	60 (13)	9 (15)		
36-47	149 (14)	8 (5)	64 (14)	8 (13)		
48-59	81 (8)	4 (5)	29 (6)	7 (24)		
60-72	65 (6)	2 (3)	176 (39)	15 (9)		
Total	1049	189 (18)	454	54 (12)		

Data are expressed as number and percentage (%)

Table 3 - Rotavirus G and P combinations in Maddina and Gizan.^{14,15}

Combination	Maddina n (%)	Gizan n (%)
P[8]G1	84 (44)	48 (89)
P[4]G2	38 (20)	1 (2)
P[8]G9	20 (11)	(1) (2)
P[8]G12	7 (4)	-
P[8]G3	7 (4)	-
PNTGNT	6 (3)	1 (2)
P[8]G4	3 (2)	-
Mix	16 (8)	-
Other	8 (4)	3 (4)

Middlesex, TW8 9GS, United Kingdom) vaccine is based on a single, attenuated serotype G1 strain, it has demonstrated efficacy against other G serotypes such as G9 strains, on the basis of preliminary efficacy data from Brazil.²² In addition, the Merck (Merck & Co., Inc. Whitehouse Station, New Jersey, USA) vaccine is composed of 5 bovine-human reassortants intended to induce serotype-specific protection against the 4 main G types (G1-G4) plus the common P[8] antigens. In Saudi Arabia, these G9 and G12 strains had a P[8] antigen which is included in both vaccines, thus disease caused by G9 and G12 rotavirus strains that have either of the 2 common P-antigens may well be prevented by this vaccine, otherwise manufacturers will need to consider providing specific protection against rotavirus by additional reassortments that may be required to increase the efficacy of the vaccine.

As the decision for the vaccine evaluation depends on the outcomes of combined clinical and epidemiological studies, laboratory-based research undertaken with the purpose of generating data is needed to facilitate the introduction of rotavirus vaccine in Saudi Arabia. These data will also assist with the estimation of the cost-effectiveness of such vaccines as well as facilitate the detection of the emergence of new serotypes. It is anticipated that the major question facing policy makers will be; what is the impact (in terms of lives and money saved) of rotavirus vaccines? This enquiry highlights the further need to evaluate information regarding costs and the synergy with (or replacement for) other diarrheal disease treatment interventions. The costs associated with rotavirus diarrhea and the

cost-effectiveness of an available vaccination should be given significant consideration by policy makers. During the last few years, we demonstrated the value of establishing strain surveillance before the introduction of any rotavirus vaccine in order to monitor the strains in circulation. Such activity helps to characterize strains against which vaccines might not be effective and to identify new variant strains that could potentially arise after a program of vaccination begins. In addition, our recent studies on rotavirus genotyping in Maddina have demonstrated a generally high rate of mixed infection and samples that were frequently untypeable. These results showed a complexity of serotypes in Saudi children and thus have importance regarding a future rotavirus immunization strategy in Saudi Arabia. The results also underscore the need for countrywide monitoring of rotavirus G- and P-types prior to the introduction of a rotavirus vaccine.

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