Rotavirus infection in Saudi Arabia

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BACKGROUND: Human rotavirus, an important causative agent of severe gastroenteritis in infants and young children worldwide, leads to high morbidity in both developing and developed countries, including Saudi Arabia, and high mortality in developing countries. Effective control depends upon an accurate understanding of disease burden and the relative importance of circulating serotypes.

METHODS: We examined the epidemiology and disease burden of rotavirus in Saudi Arabia through a review of 22 published studies of rotavirus and the aetiology of diarrhoea carried out from 1982 to 2003.

RESULTS: The prevalence of rotavirus infection ranged between 10% to 46% with a median of 30%. Most cases were among children less than 2 years of age, and particularly in the first year of life. There were significant differences in seasonality within Saudi Arabia, with increased infection during winter in some cities and during summer in others. G1 was the predominant serotype followed by G4, G3 and G2, in 4 studies where strains had been G-typed. The prevalence of nontypeable strains ranged from 11.0% to 31.3%. No data were available on P types. Results of electropherotyping in 4 studies revealed that the long electropherotype was predominant.

CONCLUSION: Rotavirus is an important cause of severe diarrhoea in Saudi children. However, the available data on rotavirus strains in circulation are limited and there is an urgent need for up-to-date and comprehensive studies to evaluate rotavirus strains in circulation and identify unusual types that could be incorporated into future vaccines.

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Human rotavirus (HRV) is a member of the Reoviridae family and is recognised as the most important causative agent of severe gastroenteritis in infants and young children worldwide.[1-3] It has also been implicated as an aetiological agent of diarrhoea in older children and adults.[4,5] Rotavirus infects every child by the age of 5 years, resulting annually in an estimated 138 million episodes of diarrhoea leading to 2 million hospitalisations.[6] Furthermore, between 418 000 and 870 000 deaths each year are attributed to rotavirus diarrhoea,[7,8] accounting for 20% to 26% of all deaths due to diarrhoea and 6% of all deaths in children under 5 years of age. Most of these occur in developing countries.[9,10] The disease burden is the same in both developing and developed countries and rotavirus infection is responsible for one-third to one-half of hospital admissions for paediatric gastroenteritis.[11] Moreover, approximately 1 in 295 children die of the disease before the age of 5 years.[6]

Although rotavirus leads to high morbidity in both developing and developed countries, it is accompanied by particularly high mortality in developing countries. It has been estimated that more than 85% of rotavirus deaths occur in Asia, Latin America and Africa. In Africa, Asia

and Latin America, 744 million to 1 billion cases of diarrhoeal disease and 2.4 to 3.3 million deaths occur annually among children less than 5 years of age, corresponding to 6600 to 9000 deaths daily.[12] In contrast, the mortality rates caused by diarrhoea in developed countries are significantly lower. However, developed countries experience a substantial economic burden from diarrhoeal diseases as a consequence of the direct and indirect costs to each community. The costs of treating rotavirus infection have been estimated to be in excess of £6.3 million annually in the United Kingdom[13] and $352 million in the United States.[14] These figures may increase significantly if societal effects are added. In the United States, for instance, rotavirus infection costs the economy a total of $1 billion annually.[15] Therefore, control of rotavirus infection would potentially not only lead to a significant reduction in fatalities in developing countries but also considerable healthcare cost savings in developed countries. It has been shown that in the United States alone, a national rotavirus vaccination programme would result in 227 000 fewer physician visits, 95 000 fewer emergency department visits, 34 000 fewer hospitalisations and 13 fewer deaths each year.[15]

Rotaviruses are triple-layered icosahedral particles, and their genomes consist of 11 segments of double-stranded RNA. Rotaviruses are classified according to the genetic and antigenic diversity of the two outer capsid proteins, VP4 and VP7. These proteins independently induce type-specific neutralizing antibodies and form the basis of the present dual classification of group A rotaviruses into P (protease sensitive) and G (glycoprotein) serotypes, respectively.[16]

Rotaviruses express an extensive antigenic and genomic diversity. To date, 14 G serotypes and 20 P types have been defined,[16,17] but a 15th G serotype and a 21st P genotype based on nucleotide sequence characterizations of a bovine rotavirus strain have been proposed.[18] Reassortment of genes can occur upon dual infection of a single cell with two different strains in vivo as well as in vitro. As the segregations of VP4 genes and VP7 genes occur independently, various G and P combinations have been observed in natural infections.[19] Effective control of rotaviral disease in any community depends upon an accurate understanding of disease burden and knowledge of the relative importance of circulating serotypes. Based on such data a variety of candidate rotavirus vaccines have been developed.

Rotavirus infection is a major cause of childhood morbidity in Saudi Arabia.[20-37,42,49-51] Although many studies have documented the high prevalence of rotavirus among Saudi children, these have never been analysed together to provide a comprehensive picture of the significance of the effect of this virus in the country. In anticipation of introduction of rotavirus vaccine in Saudi Arabia, the aims of this review were:

- To estimate the disease burden and assess the prevalence of rotavirus infection to inform the need for a rotavirus immunisation programme;
- To examine the age distribution of severe cases in order to help determine an optimal schedule for immunisation;
- To evaluate the rotavirus strains in circulation and identify unusual types that might be incorporated into a vaccine; and
- To determine the seasonal pattern of rotavirus infections and their links with possible routes of transmission or regional trends relevant to immunisation strategies.

Methods

Published articles were identified from a multilingual MEDLINE search for publications from 1975 to 2005 using the keywords 'rotavirus', 'viral gastroenteritis' and 'Saudi Arabia'. In addition, the *Annals of Saudi Medicine* and *Saudi Medical Journal* were handsearched for articles on rotavirus.

For each study, the prevalence of rotavirus infection was examined initially. Seasonality, age profile, and gender were also examined where data were available. Climate information was provided by either the article when provided or by reviewing the information available for each city from meteorological records. The seasonality of rotavirus for each study was determined by plotting the monthly detection rates and comparing them with the median monthly value for rotavirus detection for that period of study. Finally, we reviewed studies in which molecular characterisation, serotype, sub-grouping and electropherotyping were available to examine the distribution of rotavirus strains in circulation.

Results

Description of Studies

Using the above keywords and handsearching revealed a total of 17 articles published between 1985 and 2005. Another 5 articles were found in reviewing

the references in these publications. The prevalence of rotavirus infection was addressed by 19 articles.[20-24,26-36,42,49-50] In addition, 5 articles studied the molecular characterisation of the virus.[21,22,30,37,51] Furthermore, one study compared viral gastroenteritis at large medical centres in Saudi Arabia and the United Kingdom.[32] Finally, another article studied the viral contamination of environmental surfaces on general paediatric wards and playrooms in major referral centres in Riyadh.[25] In all, these studies were from six different cities in the Kingdom of Saudi Arabia, namely Jeddah,[20,22,28,30,37,51] Taif,[21,28] Riyadh,[23,31-35,42] Jizan,[24] Dammam,[26-27,36] and Makkah.[29] These studies were conducted in hospitals (Table 1) in the four major regions of Saudi Arabia (Table 2, Figure 1). Diarrhoeal cases were targeted in 17 studies. Eleven studies were designed to select inpatient cases only whereas inpatient and outpatients were included in another seven studies and one study targeted outpatients only.[26] In addition, only one study was prospective.[49] Infants in the nursery were included[27] in one study and hospitalised infants and their mothers (with or without diarrhoeal symptoms) in another.[34]

In most studies faecal specimens were screened by an enzyme-linked immunosorbent assay (ELISA). Other techniques, such as latex agglutination (LAT), electron microscopy (EM), were also used in some studies.

As shown in Table 1, study duration was highly variable, ranging from a few weeks[26,27] to several years.[23] Two studies lasted less than a month, and eight others lasted a year or longer. The median study duration was 12.0 months.

Of the 21 studies, 17 surveyed infants and children. Of these, infants and children under 5 years old were targeted in nine studies; those less than 3 years old in one;[24] less than 14 days in one;[27] and adults and adolescents were included in three studies.[22,26,28] For the remaining studies, the age group was not reported although the stated target populations were infants and young children.

Prevalence

The prevalence of rotavirus infection ranged from 10%[29] to 46%[20] with a median of 30%. There was no apparent relationship or trend between the geographic location within Saudi Arabia and prevalence. The prevalence of rotavirus differed depending on the targeted population. Inpatient studies showed significantly higher prevalences than those where outpatients were included. The range, median and standard deviation of inpatient prevalence studies

Figure 1. Map of Saudi Arabia and neighbouring countries showing major cities

were 10% to 46.0%, 41.5% and 12.2%, respectively, whereas the range, median and standard deviation of combined inpatient and outpatient studies were 10.6% to 37.5%, 16% and 10.5%, respectively. For example, in Jeddah City, rotavirus prevalence was investigated in four studies.[20,22,28,30] Three of them targeted inpatients only and showed higher prevalences, ranging between 42% and 46%.[20,28,30] However, when outpatient cases were included in the fourth study,[22] the overall prevalence decreased to 16.6% (inpatients 45.6%, outpatients 5.9%). The only prospective study carried out in Saudi Arabia reported an overall rotavirus prevalence of 11.5%.[49] However, this study included all age groups presenting at any one of the participating hospitals with a history of acute diarrhoea, acute cases of diarrhoea detected by purpose-trained staff during home visits in a designated community, and controls matched for age and sex, who were patients that presented at King Fahd Hospital University (KFHU) with conditions other than diarrhoea or abdominal disease.

As expected, rotavirus infection was more common in children younger than 2 years of age. Data from 13 studies showed the age group distribution of rotavirus in patients less than 2 years of age, the age group with the highest morbidity. Moreover, in 4 other studies, data indicated that children in the first year of life were at highest risk of infection.

Table 1. Rotavirus detection rates of paediatric gastroenteritis in Saudi Arabia

	Dates	Duration	Detection assay	Number	Age	Setting	Prevalence	Seasonality	Age	Ref
Jeddah	12/05 - 10/96	11 mo	ELISA	576	<5 yr	H(I&O)	16.6%	Winter	83% <2 yr	(22)
Taif	04/92 - 02/93	11 mo	ELISA	349	**	H(I)	43.0%	Warmer	87% <2 yr	(21)
Jeddah	03/88 - 12/92	4 yr	ELISA	1367	<5 yr	H(I)	42.6%	Winter	Mean age 20 mo	(28)
Taif	04/92 - 06/93	14 mo	ELISA	359	<5 yr	H(I)	42.1%	Warmer	Mean age 20 mo	(28)
Jeddah	03/88 - 12/92	4 yr	ELISA	1242	<5 yr	H(I)	42.2%	Winter	NR	(30)
Riyadh	01/85 - 12/86	2 yr	ELISA	688	<5 yr	H(I)	44.3%	Winter Feb-Mar Dry July-Sep	NR	(33)
Dammam	04/87	2 wk	ELISA	150	<5 yr	(O)	30.0%	NR	7-12 mo	(26)
Riyadh	90-93	3 yr	ELISA	7439	**	H(I&O)	14.1%	NV	70% <5 yr	(31)
Jeddah	03/88 - 03/89	13 mo	ELISA	363	<5 yr	H(I)	46.0%	Winter	3-15 mo	(20)
Gizan	10/83 - 02/84	5 mo	ELISA	203	<3 yr	H(I&O)	16%	NR	< 12 mo	(24)
Riyadh	01/85 - 08/89	4.5 yr	EM & ELISA	1729	***	H(I&O)	31.6%	NV	50% <2 yr	(23)
Makkah	01 - 12/03	12 mo	LAT& ELISA	479	<5 yr	H(I)	10.0%	NR	<2 yr	(29)
Riyadh	05/83 - 10/83	6 mo	EIA	52	*	H(I)	27%	NR	NR	(42)
Eastern Region	12/87 - 07/89	19 mo	EM & ELISA	83	<2 yr	H(I&O)	11.5%	NR	<2 yr	(49)
Riyadh	06/90 - 06/93	3 yr	EIA	2227	<16 yr	H(I&O)	10.6%	NV	<1 yr	(32)
Dammam	87-88	12 mo	ELISA	240	<2 yr	H(I&O)	37.5%	NR	<2 yr	(36)
Dammam	04/84	3 wk	EIA	75	<14 d	H(I)	12.0%	NR		(27)
Riyadh	1985	12 mo	ELISA & EM	435	<10 d mothers	H(I)	35% 15%	Early spring & early fall		(34)
Riyadh	03 - 07/82	5 mo	ELISA	184		H(I)	19.0%	July & April	<2 yr	(35)
Dammam	09/86 - 05/87	6 mo	ELISA	76	<2 yr	H(I)	41.0%			(50)
Median		12 mo		359			30.0%			
(range)	1982- 2003	3 wk - 4.5 yr		52-2227			10.0% - 46.0%			

NR: not reported. NV: no variation. NA: not available. H: Hospital based *Infant **Infant & young children ***Children & adult I: Inpatient. O: Outpatient

Table 2. Prevalence of rotavirus infection in Saudi Arabia by region.

Region	Cities	No. of Studies	Prevalence median	Prevalence range
Central	Riyadh	6	23%	10.6% - 44.3%
Eastern	Dammam	4	24.5%	12.0% - 41.4%
Western	Al-Taif, Jeddah	6	42.4%	16.6% - 46.0%
Southern	Gizan	1	16%	16%

Seasonality

The seasonality of rotavirus was determined by examining the seasonality patterns provided in each of the 11 studies, which demonstrated significant differences in seasonality. In Jeddah city, which has high temperatures and high humidity, rotavirus infection was present throughout the year with a maximum level during the cooler months of the year, November to January.[20,22,30] This is significantly different from the results from Al-Taif city, where the prevalence of rotavirus infection increased during the warmer months, July to September.[21,28] Al-Taif is located in a valley where the climate is moderate to relatively cool throughout the year. In Riyadh, a hot and dry desert city where most data came from, the seasonality was not clearly defined. In the six studies that assess the seasonality in this city, three of these showed no seasonal variation[23,31,32] and the rest showed two peaks at different times of the year.[33-35] No seasonality data were reported from Makkah,[29] Dammam,[10,26,27,36] and Gizan.[24] The latter two are coastal areas of the Kingdom with high temperatures and humidity.

Rotavirus strain characterisation

The rotavirus serotypes identified in Saudi Arabia are shown in Table 3. Serotyping was performed in 4 studies by enzyme-linked immunosorbent assay (ELISA) by using monoclonal antibodies specific for serotypes G1, G2, G3 and G4. Serotype G1 was the most common type identified. It was the dominant strain in all studies. Serotype G4 was the second most common nationally. In addition, a high proportion of samples were nontypeable. The prevalence of nontypeable strains ranged from 11.0% to 31.3%. To our knowledge, no data are available on P types.

Rotaviruses were characterised by electropherotyping in 4 studies. Data obtained from these studies revealed that the long electropherotype was the predominant type. In addition, variability in migration patterns showed 5 to 6 long electropherotypes and 4 to 6 patterns among short electropherotypes. Interestingly, some unusual patterns were also reported such as long electropherotypes with G2 serotypes suggestive of rotavirus reassortment.[21,37]

Discussion

Significant differences were observed in the prevalence of rotavirus infection, which ranged between 10%[29] and 46%[20] in the 22 studies covered in this review. Inpatient studies showed significantly higher prevalences than those where outpatients were included. The only prospective study carried out in Saudi Arabia showed a significant low prevalence with 11.5%. Interestingly, the prevalence differed even in one city. In Riyadh for instance, the prevalence varied from 10.6%[32] to 44.3%.[33] This is contrary to what might have been anticipated if the variation were due only to methodological differences as electron microscopy was only used in the studies with a low rotavirus infection rate; however, this was combined with enzyme immunoassay in all studies. These data might suggest that non-viral or other viral causes are more common in those cities, which showed low prevalences. The finding that most rotaviral infection occurs among children aged less than 2 years is consistent in most studies and is comparable with most reports from other parts of the world.

In temperate countries, rotavirus exhibits marked seasonal variation with peaks of infections in cooler months.[38-40] This pattern does not coincide with data gathered from countries with tropical and subtropical climates, where the virus is present throughout the year with winter and summer peaks.[2,41] Seasonality in Saudi Arabia, however, shows both patterns in some cities and no seasonal variation in others. For example there is no defined seasonality in the hot dry city of Riyadh. Some studies show seasonality during some times of the year,[33-35] other studies reported no seasonal variation.[23,31,32] In contrast, there appears to be a peak of infection in the warmer seasons in the cooler areas,[21,28] and a peak of infection in the cooler season in the warmer areas.[20,22,28,30]

For the most part, the serotypes of rotavirus in

Table 3. Serotypes, sub-groups and electropherotypes of rotavirus in Saudi Arabia.

G- Serotype					Subgroup				Electropherotype			Ref
1	2	3	4	Non typeable	Mix types	I	II	None I, II	I and II	Short	Long	
39.6%	4.2%	6.3%	15.6%	31.3%	3.1%	-	-	-	-	33.8% 4 patterns	66.0% 6 patterns	(22)
43.0%	5.0%	11.0%	10.0%	27.0%	3.0%	17%	59%	24%		22% 6 Patterns	78.0% 5 Patterns	(21)
53.0%	6.8%	5.9%	22.8%	11.0 %		26%	61%	5%	7%			(30)
52.6%	10.6%	6.5%	15.5%	13.06%	1.6%	14.3%	82.1%			Subgroup 1 58.3%	Subgroup 2 4.3%	Subgroup 1 41.7%	Subgroup 2 95.7%	(37)
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	13% 6 patterns		87% 12 patterns		(51)

NV: No seasonal Variation
NR: Not reported.

circulation in Saudi Arabia appear to be similar to those common in the rest of the world. Data collected from Saudi Arabia revealed G1 to be the dominant serotype followed by G4, G3 and G2, respectively. It is important to note that some recently emerged serotypes such as G9 have not been investigated in Saudi Arabia. This may explain the high number of nontypeable strains. To our knowledge, P typing was not investigated in any study carried out in the country. The shortage of information on P types and high portion of nontypeable strains have widened the gap in knowledge of rotavirus serotypes in Saudi Arabia.

Rotavirus infection is common in both developed and developing countries. Overall, it is responsible for approximately 25% to 50% of all hospitalisations of children with diarrhoea in both worlds. However, rotavirus infection produces the highest rates of morbidity and mortality in the latter, since 5% of all deaths under 5 years of age in developing countries are due to rotavirus.[38] In comparison to populations living in developing countries, residents of Saudi Arabia generally benefit from a higher expenditure per capita on health care. Nevertheless, young children are at higher risk of diarrhoeal disease because of impaired host defences and are exposed to suboptimal hygienic conditions. A national survey reported a diarrhoeal disease prevalence of 14.5% in children between 6-18 months.[53] Furthermore, in 2001, diarrhoeal disease caused 267 277 to 439 411 health centre visits resulting in 8185 hospitalisations.[54] However, to our knowledge, no data were reported on the disease burden of rotavirus in Saudi Arabia.

Comprehensive knowledge of rotavirus infection prevalence in Saudi Arabia is limited by the nature of the previous studies in this area. Several factors have contributed to this overall limitation, the most prominent of which are discussed here. The limited sample size was a major limiting factor, as these varied between 52[42] and 7439[31] subjects. The scale of this range makes it difficult to carry out meaningful comparisons or draw definitive conclusions at a national scale from these studies.

Furthermore, the variability in study duration limited the value of the results. While the majority of the studies lasted several months, several studies were of less than a month in duration, whereas some were several years in duration. As such, meaningful comparisons and trends cannot easily be determined from the reported results due to a lack of consistency between their durations. Any study less than

Table 4. Prevalence of rotavirus in neighbouring countries.

Country	Prevalence	Period	Method	Reference
Bahrain	14%	1998-2000	LAT	(46)
	20.9%	1984-1986	LAT	(52)
Kuwait	15.3%	1980	ELISA	(43)
	24.5%	1982		(44)
	40.2%	1984		(45)
Oman	11.5%	1996-1999	ELISA	
	31%	1990-1992		(47)
Jordan	40.0%	1999-2001		(48)

12 months in duration is considered inadequate for investigating seasonal variation, and the prevalence results may not be entirely representative of even that season in question. Few of the available studies are recent enough to have a meaningful bearing on the current situation in Saudi Arabia, as most studies cover the 14-year period from 1982 to 1996 and only one was done in 2001 and one in 2003.

It is notable that the prevalence findings are inconsistent with the findings from neighbouring countries such as Kuwait,[43-45] Bahrain,[46] Oman[47] and Jordan[48] (Table 4) taken from studies during a similar period. These figures cannot be relied on totally as there is again no sound and justifiable basis for comparison. Although seasonal climate variations are generally similar between countries neighbouring the different regions of Saudi Arabia, and as the health care standards are generally very similar, the inconsistency of the figures suggests there is a need for further investigation.

The studies each recruited different age groups. Although almost half the studies concentrated on the under 5-year age group, there were several studies that concentrated on newborn babies and others on adolescents. The conclusions drawn from each of these studies will naturally be inconsistent and difficult to compare.

The findings of this review reveal the limitations of the available data regarding rotavirus infection in Saudi Arabia. It also emphasises the urgent need for up-to-date and comprehensive studies. The results obtained by this review confirm the complexity and diversity of rotavirus genotypes.

For future studies, we recommend that the period of study be at least 12 months in order to be able to detect any seasonal variation. Implementing this recommendation should also resolve the problem caused by the large variations in sample sizes. Furthermore, future studies should focus only on those children in the age group <5 years, as this is consistent with the findings of previous studies in the region and elsewhere. And wherever possible, molecular techniques should be used for typing rotavirus in order to provide valuable information about all circulating G and P type strains in the region.

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