review

Cryptosporidiosis in Saudi Arabia and neighboring countries

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Ann Saudi Med 2007; 27(5): 325-332

Cryptosporidium is a coccidian protozoan parasite of the intestinal tract that causes severe and sometimes fatal watery diarrhea in immunocompromised patients, and self-limiting but prolonged diarrheal disease in immunocompetent individuals. It exists naturally in animals and can be zoonotic. Although cryptosporidiosis is a significant cause of diarrheal diseases in both developing and developed countries, it is more prevalent in developing countries and in tropical environments. We examined the epidemiology and disease burden of *Cryptosporidium* in Saudi Arabia and neighboring countries by reviewing 23 published studies of *Cryptosporidium* and the etiology of diarrhea between 1986 and 2006. The prevalence of *Cryptosporidium* infection in humans ranged from 1% to 37% with a median of 4%, while in animals it was different for different species of animals and geographic locations of the studies. Most cases of cryptosporidiosis occurred among children less than 7 years of age, and particularly in the first two years of life. The seasonality of *Cryptosporidium* varied depending on the geographic locations of the studies, but it was generally most prevalent in the rainy season. The most commonly identified species was *Cryptosporidium parvum* while *C. hominis* was detected in only one study from Kuwait. The cumulative experience from Saudi Arabia and four neighboring countries (Kuwait, Oman, Jordan and Iraq) suggest that *Cryptosporidium* is an important cause of diarrhea in humans and cattle. However, the findings of this review also demonstrate the limitations of the available data regarding *Cryptosporidium* species and strains in circulation in these countries.

Cryptosporidium is a coccidian protozoan parasite of the intestinal tract that causes severe potentially fatal watery diarrhea in immunocompromised patients and self-limiting but often prolonged diarrheal disease in immunocompetent individuals.[1,2] It can also infect other animal species and thus may be zoonotic.[3,4] The infective form of *Cryptosporidium* is the thick-walled oocyst which is excreted in large numbers in the feces during acute infection. The oocyst is resistant to desiccation and most disinfectants.[5] Volunteer studies have demonstrated that the infective dose can be as low as one oocyst[5] and thus infection is easily spread person-to-person directly or indirectly.

Cryptosporidiosis is a significant cause of diarrheal diseases in both developing and industrialized nations,[6] but several epidemiologic studies have demonstrated that *Cryptosporidium* is more prevalent in developing countries (5% to >10%) than in developed countries (<1% to 3%).[7-9]

In temperate climates cryptosporidiosis accounts for only 1% to 4% of the cases of childhood diarrhea and is usually self-limiting.[5] It can, however, produce devastating diarrhea in HIV-infected individuals who have fewer than 200 CD 4+ lymphocytes/μL of blood.[10] In tropical environments however, cryptosporidiosis is much more prevalent accounting for 4% to 20% of the cases of childhood diarrhea, and children less than two years old have the greatest prevalence of cryptosporidiosis.[5,11] It is associated with high morbidity[8,12-14] and this probably reflects a poorer nutritional status in children in developing countries.[15] Transmission of *Cryptosporidium* spp via contaminated drinking water, outdoor and indoor recreational waters and municipal water is well documented.[16,17] Recently there has been a large water-borne outbreak involving over 800 inhabitants of Bani Hassan in Jordan apparently associated with contaminated drinking water.

Recent molecular epidemiologic studies of cryptosporidiosis have helped us to gain better understanding of the transmission of cryptosporidiosis in humans and the public health significance of *Cryptosporidium* spp. in animals and the environment.

Using genotyping tools, five species of *Cryptosporidium* (*C. hominis*, *C. parvum*, *C. meleagridis*, *C. felis, and C. canis*) have been shown to be responsible for most human infections.[6] The potential for zoonotic infection is a genuine problem since *Cryptosporidium* lacks species specificity.[18] Therefore, domestic and wild species of mammals and birds may be reservoirs of infection for susceptible human individuals, whether they are immunodeficient or immunologically competent.[19] Diarrheal disease is a frequent illness in developing countries, and contributes to the death of 4.6 to 6 million children annually in Asia, Africa and America.[20] Cryptosporidiosis has been recorded as a cause of diarrhea in veterinarians and animal handlers,[21] in bone-marrow transplant recipients,[22] in household contacts of infected patients,[4,23] in homosexual men,[24] in travellers,[25] in children in day care centers[26-29] and in patients with chronic diseases.[30]

Methods for detection of Cryptosporidium spp in feces usually involve microscopic examination of stained fecal smears (modified Ziehl-Neelsen, safranin methylene blue, auramine-phenol), antigen detection (immunofluorescence, ELISA) or genome detection (PCR amplification of the 18S rRNA gene).[5] Each varies in sensitivity and specificity and there is no universally accepted "gold-standard".

There are few published reports of studies on cryptosporidiosis in the Middle East. In Saudi Arabia, diarrheal disease is an important cause of morbidity in children but the contribution made to it by *Cryptosporidium* spp is largely unknown.

The aims of the present review were:

(1) To document the prevalence of *Cryptosporidium* spp in humans and animals in Saudi Arabia and neighboring countries.

(2) To estimate the disease burden.

(3) To examine the age distribution of the cases.

(4) To determine the seasonality of cryptosporidiosis.

(5) To compare the importance of *Cryptosporidium* spp as a cause of diarrhea relative to other enteropathogens.

METHODS

Articles were identified for this review from a multilingual *MEDLINE* search for publications from 1976 to 2006 using the keywords *Cryptosporidium*, and the name of each of the following countries: Saudi Arabia, Kuwait, Iraq, Jordan, Bahrain, Qatar, Yemen, Oman and United Arab Emirates. In addition, the *Annals of Saudi Medicine* and the *Saudi Medical Journal* were handsearched for papers on diarrheal diseases and *Cryptosporidium*.

The studies were grouped into three categories: studies targeting human populations, studies targeting animal populations and studies identifying *Cryptosporidium* species and typing and these were analyzed separately. For each study, the prevalence of *Cryptosporidium* infection was examined initially in patients and compared with controls where a control group was included. Age profile and seasonality were also examined where sufficient data were available. Finally, we reviewed studies in which molecular characterization, typed species and subtyping allele families were available to examine the distribution of the different *Cryptosporidium* species and strains in circulation.

RESULTS

Description of Studies

We found 23 papers published from the region between 1986 and 2006. The prevalence of *Cryptosporidium* infection among humans was addressed by 15 papers,[10,31-44] while the prevalence among animals was addressed by two papers.[42,45] In addition, 5 papers identified the circulating species and reported the molecular characterization of the parasite.[6,36,46-48] One paper reported an outbreak of caprine cryptosporidiosis in the Sultanate of Oman and another examined the prophylactic value of paromomycin in the outbreak.[49,50] Finally, one paper described a case of cryptosporidiosis in a child in Kuwait.[51] The studies included five from Saudi Arabia[10,31,32,45,46] and the remainder from four neighboring countries: Kuwait,[6,33-35,51] Jordan,[36-40,44,47] Iraq[41-43,48] and The Sultanate of Oman.[49,50] Ten of these studies were hospital-based[6,31,33,34,36,40,41,43,48,51] four studies were designed to select inpatient cases only,[33,40,41,51] whereas both inpatients and outpatients were included in another four studies[31,34,36,43] and seven studies targeted hospital outpatients only.[10,32,35,39,44,46,48] In addition seven studies were entirely community-based (Table 1).[37,38,42,45,47, 49,50]

Study duration was variable, ranging from 3 months[10,34] to 38 months.[6] The median study duration was 12 months. The ages of the patients surveyed varied significantly, ranging from newborn (0-1 month)[31] to 87 years[38] and even within the same study the age groups ranged from 1 to 87 years.[38] Animal ages were reported only in the study from The Sultanate of Oman[49] and they ranged between two days to over one year.

Detection methods

In most studies fecal specimens were screened by examining stained fecal smears by bright field microscopy and the most common stains used were acid fast stains, (16 studies)[10,32,36-39,41-50] followed by trichrome, (7 studies)[33,34,37-40,44] and safranin methylene blue, (5 studies).[31,33-35,51] Fluorescent microscopy was used to examine fecal smears stained with auramine-phenol, (4 studies).[32,40,49,50] Other techniques such as a direct immunofluorescence assay (DFA) were used in three studies[35,36,47] while polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used in one study from Kuwait.[6] Different techniques used prior to the screening were sedimentation, sugar flotation concentration and direct wet mount preparations.

Prevalence and Seasonality

In humans the prevalence of cryptosporidiosis ranged from 1.0%[32] to 37.3%[36] and seemed to be higher in the studies that targeted infants and children under 7 years old (Table 1) while in animals it was different for different species of animals and the geographic locations of the studies (Table 2). The prevalence of cryptosporidiosis differed depending on the population surveyed. Outpatient studies showed significantly higher prevalences than those where inpatients were included. In addition, mixed inpatient and outpatient studies showed higher prevalences than the community-based studies. The range and median of the outpatient prevalence studies were 1 to 32% and 6.7% respectively, whereas the range and median of combined inpatient and outpatient studies were 1.15 to 37.3% and 5.5% respectively.

Cryptosporidium infection was more common in children less than 7 years of age. Data from eight studies showed that the prevalence of cryptosporidiosis was higher in children less than 7 years old,[10,31,32,35,36,40-42,44] and 4 of these studies showed that the highest prevalence was among children less than 2 years of age.[10,32,35,40]

The seasonal variation in cryptosporidiosis was reported in five studies only. Two studies from Kuwait, which has high temperatures during the summer with a very dry climate and a short cool winter, showed that the highest prevalence was during winter (March and April)[33] or from January to April.[35] The other three studies were from Jordan, which has a relatively wet rainy season from November to April and very dry weather for the rest of the year with uniformly hot dry summers and cool variable winters. The maximum prevalence in the first study, which was done in Irbid City, was undertaken from January to May in the rainy season,[36] while in the two remaining studies, which were done in Badia, the maximum prevalence was reported in the warm months from May to September.[38,39]

Cryptosporidium species and strains identified

The most commonly identified species was described as *Cryptosporidium parvum*, which has been reported from Dammam, Saudi Arabia,[46] Kuwait,[6] Irbid, Jordan,[36] Basra, Iraq[48] and Bani-Kenanah in Jordan (Table 3).[47] *Cryptosporidium hominis* was reported in one study from Kuwait only.[6] Light and immunofluorescent microscopy were used to identify *Cryptosporidium* species in these studies except in the study from Kuwait where advanced molecular tools were used, namely PCR, RFLP and DNA sequencing. It is not possible to assign cryptosporidia to species on the basis of microscopic morphology alone.

In the last study,[6] four subtype allele families (IIa, IId, IIc and IIf) of *Cryptosporidium parvum* were identified and 3 (Id, Ie and Ib) of *Cryptosporidium hominis*. An atypical outbreak of caprine cryptosporidiosis occurred in the Sultanate of Oman in goats ranging in age from two days to adulthood, on a well-managed closed farm.[49] None of the other animals on the farm, including sheep, cows and buffalo were affected. Morbidity approached 100 per cent in goats less than six months of age. Despite intensive supportive care, 238 goats, ranging in age from two days to over one year, died. Cryptosporidia were detected in large numbers in the intestinal contents of dead animals and in faecal smears of animals with diarrhea.

In another study from the Sultanate of Oman, the prophylactic value of paromomycin (an aminoglycoside antibiotic analogous in structure to neomycin)[52] was examined in the same outbreak of caprine cryptosporidiosis.[50]

DISCUSSION

In the 23 studies addressing *Cryptosporidium* infections in Saudi Arabia and neighboring countries, *Cryptosporidium* infection in humans ranged between 1%[32] and 37.3%,[36] while in animals it was different for different species of animals and the geographic locations of studies. It appears that the prevalence of cryptosporidiosis in humans is lower than in animals.[42] Interestingly, the prevalence differed even within Irbid, a city in Jordan, where the prevalence varied from 1.5%[40] to 37.3%.[36] This may be due to methodological differences, as bright field microscopy only was used in most of the studies with its low detection rate compared

Table 1. Cryptosporidium detection rates in Saudi Arabia and neighboring countries.

Country	Period	Detection methods	Number of patients	Age of patients	Number of control	Age	Setting	Prevalence in patients (%)	Prevalence in control (%)	Seasonality	Reference
Saudi Arabia	3/00-5/00	S, DWM, BFM (AFS)	63	17% <1 y	190	<5 y	(O)	32	4.7	NR	(10)
Saudi Arabia	1990	S, BFM (SM-B)	174	25-59 mo	50	0-120 mo	H (I,O)	1.15	0	NR	(31)
Saudi Arabia	11/86-5/87	DWM, S, BFM (AFS), FM (AP)	209 * 112 **	2 y	0	0-12 y >12 y	(O)	1 0	0	NR	(32)
Kuwait	1/88-6/99	DWM, S, BFM (SM-B), TSSP	2205	5-96 mo	0	2 wk to 12 y	H (I)	1.6	0	Winter Mar, Apr	(33)
Kuwait	mid-Jan to mid-Apr 89	S, DWM, BFM (SM-B), TSSP	738 * 413 **	1.25-8 y	0	NR	H (I,O)	1.36 0	0	NR	(34)
Kuwait	9/95-8/97	S, BFM (SM-B), DFA	3549	>2 y	500	3 mo to 13 y	(O)	1.43	0	Winter Jan to Apr	(35)
Jordan	11/00-9/01	DWM, SFC, BFM (AFS), DFA	300	5-7 y	0	0 to 12 y	H (I,O)	37.3	0	Jan to May, the rainy season	(36)
Jordan	9/92-3/93	DWM, S, SFC, BFM (AFS, TSSP)	1000	<9 y	0	6 to 14 y	CB	4	0	NR	(37)
Jordan	9/99-9/01	DWM, S, SFC, BFM (AFS,TSSP)	200	mean 7.5 y	0	1 to 14 y 15 to 87 y	CB	5 3	0	Spring	(38)
Jordan	NR	DWM, S, BFM (AFS, TSSP)	180	NR	100	12 – 84 y	(O)	8.3	0	Warm mo May-Sep	(39)
Jordan	5-8/93	S, BFM (TSSP), FM (AP)	265	<1 y	0	< 5y	H (I)	1.5	0	NR	(40)
Iraq	11/97-5/98	S, BFM (AFS)	40	46- 55 y	175	2 y - 60 y	H (I)	5	1.14	NR	(41)
Iraq	NR	S, BFM (AFS)	60	<6 y	175	4-62 y	CB	5	1.14	NR	(42)
Iraq	1-12/00	S, BFM (AFS)	205	26-35 y	175	2 mo- 65 y	H (I,O)	9.7	1.1	NR	(43)
Jordan	7/92-9/93	DWM, SFC, BFM (TSSP, AFS)	300	<3 y	300	6 mo-6 y	(O)	6.7	1.7	NR	(44)

S: sedimentation, DWM: direct wet mount, BFM: bright field microscope, FM: fluorescent microscope, DFA: direct immunofluorescent assay, SFC: sugar flotation concentration, H: hospital-based, I: inpatient, O: outpatient, CB: community-based, * children, ** adults, SM-B: safranin methylene blue, AP: auramin-phenol, TSSP: trichrom stool smear preparation, AFS: acid fast stain (modified Ziehl-Neelsen, modified Kinyoun's), NR: not reported.

to DFA which is more sensitive. For example, in Irbid the detection rate was 37.3% in the study where DFA was used together with bright field microscopy,[36] while in an other study in the same city where bright field microscopy alone was used, the detection rate decreased to 1.5%.[40]

The finding that most *Cryptosporidium* infections occur among children less than 7 years of age is consistent in most studies in the region and is comparable with the reports from other parts of the world.[53-55] It is possible that the infection rate in these studies would have been higher if more than one stool specimen had been collected from each child because of the intermittent nature of oocyst excretion with this parasite.[56,57] Outpatient studies showed significantly higher prevalences than those where inpatients were included, which may have resulted from the presence of *Cryptosporidium* oocysts in asymptomatic children, some of whom could be considered carriers who act as important reservoirs of the organism and finally a potential source of infection.

Seasonal variations in prevalence have been noted in some studies.[33] Several factors could account for seasonal variations in the occurrence of cryptosporidiosis, including factors affecting the numbers of oocysts present in the environment such as rainfall or agricultural practices, factors affecting oocyst survival, such as humidity or temperature, and factors promoting exposure to oocysts such as contact with animals or attendance at child care centers. However, in most studies, the highest numbers of cases were detected during the rainy season.[58,59] In Kuwait for example the climate is characterized by long dry hot summers (40-50 °C) and short warm winters. There is no rainy season in Kuwait as such. The highest prevalence was during winter (March and April)[33] or from January to April.[35] While in Jordan, which has a relatively moist rainy season from November to April and very dry weather for the rest of the year with hot dry uniform summers and cool variable winters, the maximum prevalence was from January to May. The highest prevalence was during the rainy season in Irbid[36] but in the warm months from May to September in Badia.[38,39]

Few studies have tried to identify the infecting species and *Cryptosporidium parvum* was the most prevalent species identified, but this was with one exception by microscopy alone. *Cryptosporidium hominis* was identified in a study from Kuwait[6] where RFLP was used. Because the majority of these studies were done between 1986 to 1998 no advanced molecular tools were used to identify the infecting species and the researchers depended completely upon microscopy and direct im-

Table 2. Cryptosporidium detection rates among animals in Saudi Arabia and neighboring countries.

Country	City	Period	Duration	Animal type	Detection methods	Number of animals	Prevalence	Reference number
Saudi Arabia	Al-Ahsa region	Oct 2002 to Oct 2003	13 mo	White-cheeked bulbuls	BFM (AFS)	42	28.6 %	(45)
Iraq	Basrah	NR	NR	Domestic animals	S, BFM (AFS)	198	13.6 %	(42)

BFM: bright field microscope, AFS: acid fast stain (modified Ziehl-Neelsen, modified Kinyoun's), S: Sedimentation, NR: not reported

Table 3. Cryptosporidium species identified and subtyping.

Country	City	Species identified	%	Subtyping	Technique	Reference No.
Saudi Arabia	Dammam	*C. parvum*	30	-	S, BFM (E, I, AFS)	(46)
Kuwait	Kuwait	*C. parvum*	94	4 subtype allele families (IIa, IId. IIc, IIf)	SSU rRNA-based PCR-RFLP, 60-KD a glycoprotein-based DNA sequencing tool.	(6)
		C. hominis	5	3 subtype allele families (Id, Ie, Ib)		
Jordan	Irbid	*C. parvum*	37.3	-	DWM, SFC, BFM (AFS), DFA	(36)
Iraq	Basra	*C. parvum*	1	-	S, BFM (AFS)	(48)
Jordan	Bani-Kenanah	*C. parvum*	2	-	BFM (AFS), DFA	(47)

DFA: direct immunoflourescent assay, BFM: bright field microscope, RFLP: restriction fragment length polymorphism, E,I: eosin, iodine stain munofluorescent assay as a screening tool, which calls into question the accuracy of the results. But in the one study where molecular tools such as PCR and RFLP were used, *C. hominis* (5%) and *C. parvum* (95%) were detected.[6]

The distribution of *Cryptosporidium* genotypes in the population is very different worldwide. Studies conducted in Peru, Thailand, Malawi, Uganda, Kenya, and South Africa showed a predominance of *C. hominis* in children or human immunodeficiency virus-positive adults.[60-64] In contrast, most of the patients investigated in Kuwait were infected with *C. parvum*. The only other region where *C. parvum* is more prevalent in humans than *C. hominis* is Europe, where several studies have shown a slightly higher prevalence of *C. parvum* over *C. hominis* in both immunocompetent and immunocompromised persons.[65-68]

The differences in the distribution of *Cryptosporidium* genotypes in humans are considered an indication of differences in infection sources.[68-70] Thus, the predominance of *C. parvum* in a population has been considered to be the result of zoonotic transmission. Indeed, even in areas with a high percentage of infections due to *C. parvum*, massive slaughter of farm animals during foot-and-mouth disease outbreaks can result in a reduction of the proportion of human infections due to *C. parvum*.[71]

Recent subtyping studies have shown that not all *C. parvum* infections in humans are the result of zoonotic transmission.[65,72,73] Among the *C. parvum* GP60 subtype families identified, alleles IIa and IIc (previously known as Ic) are the two most common types. The former has been identified in both humans and ruminants, whereas the latter has been seen only in humans.[65,73,74] In one of the studies included in this review two Kuwaiti children were infected with an allele IIc subtype strain, indicating that anthroponotic transmission of *C. parvum* occurs in Kuwait. Nevertheless, the low proportion of infections due to *C. hominis* suggests that anthroponotic transmission of cryptosporidiosis in Kuwait is probably not as important as in other countries. It is important to note that the other valid taxonomic species have not yet been detected in the region.

Returning to the outbreak of caprine cryptosporidiosis in the Sultanate of Oman, and to determine the reasons for it, it has been noted that the outbreak started during the cooler rainy season and this environmental factor might have imposed a stress responsible for the epizootic. However the rainy season may be associated with other factors, such as the enhanced survival of the organism in the environment or the seasonal variability of antibody levels observed in goats. Jonson et al.[75] observed an increase in incidence of enteric and respiratory diseases in goats during the rainy season in north-east Brazil and associated it with lower levels of serum antibodies recorded during the wet season than during the dry hot season. It has also been reported that goats who do not receive colostrum or are separated from their mothers and fed artificially, are more likely to develop cryptosporidial infections.[76-78] The kids in the Omani study were all suckled by their mothers and there was no indication that they had not received adequate quantities of colostrum. No immediate source of the infection was apparent. The water supply was not tested for cryptosporidia, but it seemed unlikely to have been the source because no other animals were affected and the treated water supply for the animals was the same as that for human consumption. It was a closed herd and the possibility that the infection was brought in from outside could therefore be ruled out.

In conclusion, future studies should focus predominantly on those in the age group <7 years, as this is consistent with the findings of previous studies in the region and elsewhere. The period of future studies should be at least 12 months to be able to detect any seasonal variation. Wherever possible, molecular techniques should be used for typing *Cryptosporidium* in order to provide valuable information about all circulating *Cryptosporidium* species and strains in the region. Finally, we recommend that physicians be aware of *Cryptosporidium* as a cause of diarrhea in children and that procedures for the diagnosis of this parasite be included in the routine diagnostic procedure for diarrheal stool specimens in all laboratories. This is particularly important since there is now an effective drug, nitazoxanide, available for therapy.[79]

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