MINIREVIEW

Zoonotic cryptosporidiosis

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Abstract

The widespread usages of molecular epidemiological tools have improved the understanding of cryptosporidiosis transmission. Much attention on zoonotic cryptosporidiosis is centered on *Cryptosporidium parvum*. Results of genotype surveys indicate that calves are the only major reservoir for *C. parvum* infections in humans. The widespread presence of human-adapted *C. parvum*, especially in developing countries, is revealed by recent subtyping and multilocus typing studies, which have also demonstrated the anthroponotic transmission of *C. parvum* subtypes shared by humans and cattle. Developing and industrialized countries differ significantly in disease burdens caused by zoonotic species and in the source of these parasites, with the former having far fewer human infections caused by *C. parvum* and little zoonotic transmission of this species. Exclusive anthroponotic transmission of seemingly zoonotic *C. parvum* subtypes was seen in Mid-Eastern countries. Other zoonotic *Cryptosporidium* spp. are also responsible for substantial numbers of human infections in developing countries, many of which are probably transmitted by anthroponotic pathways. The lower pathogenicity of some zoonotic species in some populations supports the occurrence of different clinical spectra of *Cryptosporidium* spp. in humans. The use of a new generation of molecular diagnostic tools is likely to produce a more complete picture of zoonotic cryptosporidiosis.

Introduction

Cryptosporidium spp. are common parasites of humans, domestic animals and wild vertebrates. Because of the wide host range of *Cryptosporidium* spp., cryptosporidiosis has been considered to be a zoonotic disease for some time. The role of animals, especially farm animals and domestic pets, in the transmission of human cryptosporidiosis is nevertheless not clear. This is largely because of the oocyst morphologic similarity between human-pathogenic and non-human-pathogenic species. Recently, molecular biologic tools have been developed to detect and differentiate *Cryptosporidium* at the species/genotype and subtype levels (Xiao & Ryan, 2004; Caccio, 2005). The use of these tools has made significant contributions to the understanding of the zoonotic potential of various *Cryptosporidium* spp., the disease burden and pathogenicity of zoonotic parasites, and the role of various animals in the transmission of human cryptosporidiosis (Hunter & Thompson, 2005; Smith *et al.*, 2007). These recent developments have enabled public health officials to better educate the public on the risk factors involved in the acquisition of cryptosporidiosis in vulnerable populations.

Epidemiologic evidence for zoonotic transmission

Cattle have been considered to be an important source of zoonotic cryptosporidiosis since the 1980s. Contact with infected calves has been implicated as the cause of many small cryptosporidiosis outbreaks in veterinary students, research technicians, and children attending agricultural camps and fairs (Preiser *et al.*, 2003; Smith *et al.*, 2004; Chalmers *et al.*, 2005b; Kiang *et al.*, 2006). Contamination of food or water by cattle manure has been identified as a cause of several foodborne and waterborne outbreaks of

cryptosporidiosis (Glaberman *et al*., 2002; Blackburn *et al*., 2006). In case–control studies, contact with cattle was implicated as a risk factor for human cryptosporidiosis in the United States, United Kingdom, Ireland, and Australia (Robertson *et al*., 2002; Goh *et al*., 2004; Roy *et al*., 2004; Hunter *et al*., 2004b). In the United States, the incidence of cryptosporidiosis is the highest in mid-western states where dairy farming is most intensive (Yoder & Beach, 2007). In the United Kingdom, cryptosporidiosis case numbers are higher in areas with a high estimate of *Cryptosporidium* oocysts applied to land from manure (Lake *et al*., 2007). Indeed, massive slaughtering of farm animals and restriction of farm visits during foot-and-mouth disease outbreaks reduced sporadic human *C. parvum* infections in large communities in the United Kingdom (Hunter *et al*., 2003; Smerdon *et al*., 2003). In contrast, few epidemiologic studies have implicated sheep as a source of human cryptosporidiosis (Duke *et al*., 1996).

The role of companion animals in the transmission of human cryptosporidiosis is less important. It is has been suggested for some time that dogs can be a significant source of human cryptosporidiosis (Enriquez *et al*., 2001; Robinson & Pugh, 2002; Shukla *et al*., 2006). This, however, was largely based on the observation of direct transmission of *C. parvum* from calves to humans and the erroneous belief that *C. parvum* is responsible for cryptosporidiosis in all mammals. Only a weak association between cryptosporidiosis in HIV+ persons and contact with dogs was found in the United States (Glaser *et al*., 1998) or between paediatric cryptosporidiosis and contact with dogs or cats in Guinea-Bissau and Indonesia (Molbak *et al*., 1994; Katsumata *et al*., 1998). In England, contact with dogs and cats was not found to be a risk factor for cryptosporidiosis (Goh *et al*., 2004), and in Australia it was actually a protective factor (Robinson & Pugh, 2002).

Cryptosporidium species and genotypes in humans

Cryptosporidium parvum was once considered to be the only *Cryptosporidium* species to infect humans. Genotyping tools based on DNA sequences of antigen and house-keeping genes identified genotypes 1 (the human genotype) and 2 (the bovine genotype) within the umbrella of *C. parvum* and these eventually became *Cryptosporidium hominis* and *C. parvum senso stricto,* both infectious for immunocompetent and immunocompromised persons (Xiao *et al*., 2004a, b; Caccio, 2005). The PCR techniques used do not amplify DNA from some more genetically different *Cryptosporidium* species. At the end of the 1990s, the use of small subunit (SSU) rRNA-based genotyping tools revealed the presence of *Cryptosporidium canis*, *Cryptosporidium felis*, and *Cryptosporidium meleagridis* in AIDS patients in the United States, Switzerland, and Kenya, in addition to the more frequently found *C. hominis* and *C. parvum* (Pieniazek *et al*., 1999; Morgan *et al*., 1999a, 2000a). This observation has been supported by data from France, Portugal, Italy, Thailand, and Peru (Alves *et al*., 2001; Guyot *et al*., 2001; Caccio *et al*., 2002; Tiangtip & Jongwutiwes, 2002; Gatei *et al*., 2002b).

Even immunocompetent persons can be infected with zoonotic species other than *C. parvum*. Molecular characterization of over 2000 specimens in the United Kingdom identified 22 cases of *C. meleagridis*, six cases of *C. felis*, and one case of *C. canis* (McLauchlin *et al*., 2000; Leoni *et al*., 2006). Ninety-nine cases of *C. meleagridis,* 22 cases of *C. felis* and two cases of *C. canis* infections were identified by another group among 13 112 cases in England and Wales (Nichols *et al*., 2006). Most of the infected persons were not immunocompromised. HIV-seronegative children in Lima, Peru (Xiao *et al*., 2001), and children in Kenya had these *Cryptosporidium* species (Gatei *et al*., 2006). Over 20 other cases of *C. meleagridis* infection have been described in immunocompetent persons in other industrialized and developing countries (Tables 1 and 2). In Peru, where a significant proportion of infections are due to zoonotic *Cryptosporidium*, there was no significant difference between children and HIV+ adults in the distribution of *C. hominis, C. parvum, C. meleagridis, C. felis*, and *C. canis* (Xiao *et al*., 2001; Cama *et al*., 2003).

It is likely that other *Cryptosporidium* species can infect humans under certain circumstances. *Cryptosporidium muris*-like oocysts were found in two healthy Indonesian girls (Katsumata *et al*., 2000). A putative *C. muris* infection was reported in an immunocompromised patient in France based on sequence analysis of a small fragment of the SSU rRNA (Guyot *et al*., 2001). However, the sequence was more similar to *Cryptosporidium andersoni* (2-bp differences in a 242-bp region) than to *C. muris* (8-bp differences in the region). Several confirmed *C. muris* infections were documented in AIDS patients in Kenya and Peru, both by PCR-restriction fragment length polymorphism (RFLP) and sequencing of the SSU rRNA gene (Gatei *et al*., 2002a, 2006; Palmer *et al*., 2003), and a putative human *C. muris* infection was seen in India (Muthusamy *et al*., 2006). More human cases have been associated with the *Cryptosporidium* cervine genotype, which was reported in 10 patients in Canada, seven in the United Kingdom, three in the United States, and one in Slovenia (Ong *et al*., 2002; Blackburn *et al*., 2006; Feltus *et al*., 2006; Leoni *et al*., 2006; Nichols *et al*., 2006; Soba *et al*., 2006; Trotz-Williams *et al*., 2006). Other *Cryptosporidium* species found in humans include *C. suis* in an HIV+ patient in Lima, Peru, and two patients in England (Xiao *et al*., 2002; Leoni *et al*., 2006; Nichols *et al*., 2006), a *C. suis*-like parasite in two patients in Canada (Ong *et al*., 2002), a *C. andersoni*-like parasite in three patients in England (Leoni *et al*., 2006) and one patient in

Table 1. Distribution of common human-pathogenic *Cryptosporidium* species in humans in industrialized countries

Location	Patient type	Sample size	*C. hominis*	*C. parvum*	*C. meleagridis*	*C. felis*	*C. canis*	Mixed species	Reference
Portugal	HIV+adults	29	7	16	3	3			Alves *et al*. (2003)
Portugal	HIV+adults?	9	2	5	2				Almeida *et al*. (2006)
Spain	Children and HIV+adults	105	69	34	1	1			Llorente *et al*. (2007)
England	Children and adults	2414	1005	1354	22	6	1	21	McLauchlin *et al*. (2000), Leoni *et al*. (2006)
England	Children and adults	1622	726	896					Sopwith *et al*. (2005)
England	Children and adults	1263	563	662					Hunter *et al*. (2003)
England and Wales	Children and adults	191	115	76					Hunter *et al*. (2004b)
England and Wales	Children and adults	2251	936	1315					Smerdon *et al*. (2003)
England and Wales	Children and adults	13112	6594	5981	99	22	2	65	Nichols *et al*. (2006)
Scotland	Children and adults	136	71	64	1				Mallon *et al*. (2003)
N. Ireland	Children and adults	39	5	34					Lowery *et al*. (2001)
France	HIV+adults and other immunocompromised	46	14	22	3	6			Guyot *et al*. (2001)
France	HIV+adults	13	6	7					Bonnin *et al*. (1996)
France	HIV+adults and others	64	35	16	8	5			Coupe *et al*. (2005)
France	Unknown	54	20	26	2?	6?			Ngouanesavanh *et al*. (2006)
Switzerland	HIV+adults	13	2	7	1	3			Morgan *et al*. (2000a)
Switzerland	Children	14	11	3					Glaeser *et al*. (2004)
Switzerland	Unknown	9		9					Fretz *et al*. (2003)
Denmark	Various	44	25	18	1				Enemark *et al*. (2002)
The Netherlands	HIV- adults?	10	10						Caccio *et al*. (1999)
The Netherlands*	Mostly children	41	29	9					Ten Hove *et al*. (2007)
Czech Republic	Children	9		9					Hajdusek *et al*. (2004)
Slovenia	Children and adults	29	2	26					Soba *et al*. (2006)
Iran	Children and HIV+adults	15	4	11					Meamar *et al*. (2007)
Turkey	Children	4		4					Tamer *et al*. (2007)
Kuwait	Children	62	3	58				2	Sulaiman *et al*. (2005)
Taiwan	HIV+adults	4	2		1	1			Hung *et al*. (2007)
Japan	All	19	13	3	3				Yagita *et al*. (2001)
Japan	Unknown	5	3	2					Abe *et al*. (2006)
South Korea	Unknown, rural area	7	7						Park *et al*. (2006)
Australia	All		83%	17%					Morgan *et al*. (2000b)
Australia	Unknown	22	16	6					Chalmers *et al*. (2005b)
New Zealand	Unknown	423	198	223					Learmonth *et al*. (2004)
Canada†	Children and adults	150	108	29	2				Ong *et al*. (2002)
Canada	Immunocompetent persons	11	4	6					Trotz-Williams *et al*. (2006)
USA	HIV+adults	10	5	1		3	1		Pieniazek *et al*. (1999)
USA	HIV+adults	29	18	8		3			Xiao *et al*. (2004a)
USA	All	178	119	25					Xiao *et al*. (2004b)
USA	All	49	1	44					Feltus *et al*. (2006)

*Including three unamplified.

†Includes nine specimens with the cervine genotype.

Malawi (Morse *et al*., 2007), the chipmunk genotype I (W17) in two patients in Wisconsin (Feltus *et al*., 2006), and the skunk genotype in one patient in United Kingdom (Nichols *et al*., 2006). The *C. hominis* monkey genotype has been found in two persons in the United Kingdom (Mallon *et al*., 2003b). Other new *Cryptosporidium* genotypes will likely be found in humans in future, but these parasites account for a very minor proportion of *Cryptosporidium* infections in humans.

Some unusual *Cryptosporidium* species may have a broad host range and might emerge as important pathogens in humans when socioeconomic and environmental changes favor the transmission. The avian pathogen *C. meleagridis* is increasingly recognized as an important human pathogen. In Lima, Peru, and Bangkok, Thailand, *C. meleagridis* is responsible for 10–20% of human cryptosporidiosis cases (Xiao *et al*., 2001; Gatei *et al*., 2002b; Cama *et al*., 2003). Likewise, the increasing number of humans infected with

Table 2. Distribution of common human-pathogenic *Cryptosporidium* species in humans in developing countries

Location	Patient type	Sample size	*C. hominis*	*C. parvum*	*C. meleagridis*	*C. felis*	*C. canis*	Mixed species	Reference
India	HIV+adults	48	31	9	1	5			Muthusamy *et al*. (2006)
India	Children	50	47	0		1		2	Gatei *et al*. (2007)
India	Children	58	47	7	1 (?)	3			Ajjampur *et al*. (2007)
Thailand	4 HIV+children, 25 HIV+adults	29	24		3	1			Tiangtip & Jongwutiwes (2002)
Thailand	HIV+adults	34	17	5	7	3	2		Gatei *et al*. (2002b)
China	Children	5	5	0					Peng *et al*. (2001)
Kenya	HIV+adults	24	14	8	1				Gatei *et al*. (2003)
Kenya	Children	175	153	15	1	2	3		Gatei *et al*. (2006)
Malawi	Children	43	41	2					Peng *et al*. (2003b)
Malawi	Children	39	25	10	2			1	Morse *et al*. (2007)
Uganda	Mostly HIV+children	76	56	14	3			3	Tumwine *et al*. (2005)
Uganda	Children	444	326	85	5			19	Tumwine *et al*. (2003)
South Africa	HIV+children	21	16	5					Leav *et al*. (2002)
South Africa	All	44	36	8					Samie *et al*. (2006)
Haiti	HIV+adults	49	31	16	1?	1?			Ngouanesavanh *et al*. (2006)
Venezuela	HIV+adults	10	8	1			1		Certad *et al*. (2006)
Colombia	HIV+adults	6	3	2		1			Navarro-i-Martinez *et al*. (2006)
Guatemala	Children	15	14	1					Xiao *et al*. (2004b)
Peru	HIV+adults	302	204	34	38	10	12		Cama *et al*. (2003)
Peru	Children	85	67	8	7	1	2		Xiao *et al*. (2001)
Peru	Children	5	4	1					Cordova Paz Soldan *et al*. (2006)
Brazil	Children	42	24	18					Bushen *et al*. (2007)
Chile	Children	4	2	2					Neira-Otero *et al*. (2006)

the cervine genotype might be related to its wide range of mammalian hosts (Feng *et al*., 2007a).

Cryptosporidium species and genotypes in animals

There is extensive genetic variation within the genus *Cryptosporidium* (Fig. 1). In addition to the 16 accepted species, nearly 50 *Cryptosporidium* genotypes have been described in animals and new genotypes are continually being discovered (Xiao *et al*., 2004a; Feng *et al*., 2007a). Several well-known genotypes in recent years have been elevated to species status as other biologic data have become available. Phylogenetically, *Cryptosporidium* species and genotypes form mostly two groups: those found primarily in the intestine and those in the stomach. Each group contains parasites of mammals, birds and reptiles (Fig. 1). Some other more primitive parasites, such as fish genotypes and the chipmunk genotype II (Ryan *et al*., 2004; Feng *et al*., 2007a), are placed outside these two groups (Fig. 1).

With few exceptions, most species and genotypes are host-adapted in nature, having a narrow spectrum of natural hosts. Thus, one *Cryptosporidium* species or genotype usually infects only a particular species or a group of related animals. Surveys conducted in cattle, sheep, pigs, kangaroos, squirrels, wild mammals, Canada geese, and reptiles have shown that most animal species are infected with only a few host-adapted *Cryptosporidium* species or genotypes (Guselle *et al*., 2003; Jellison *et al*., 2004; Power *et al*., 2004; Zhou *et al*., 2004a, b; Xiao *et al*., 2004c; Ryan *et al*., 2005; Langkjaer *et al*., 2007; Feng *et al*., 2007a, b). The existence of host-adapted *Cryptosporidium* species or genotypes indicates that cross-transmission of *Cryptosporidium* among different groups of animals is probably limited. Nevertheless, host- adaptation is not strict host specificity. Cross-species transmission occurs occasionally when animals share a similar habitat, such as the transmission of the *Cryptosporidium* skunk genotype among skunks, raccoons, squirrels, and opossums (Feng *et al*., 2007a).

Cryptosporidium parvum has received the most attention in zoonotic transmission of cryptosporidiosis. This was largely due to the fact that *C. parvum* is a major human pathogen and was traditionally considered to infect all mammals. Genetic characterizations of *Cryptosporidium* specimens from various animals, however, have mostly failed to detect this parasite in wild mammals (Zhou *et al*., 2004b; Feng *et al*., 2007a). It is now generally accepted that *C. parvum* (referred to previously as the bovine genotype)

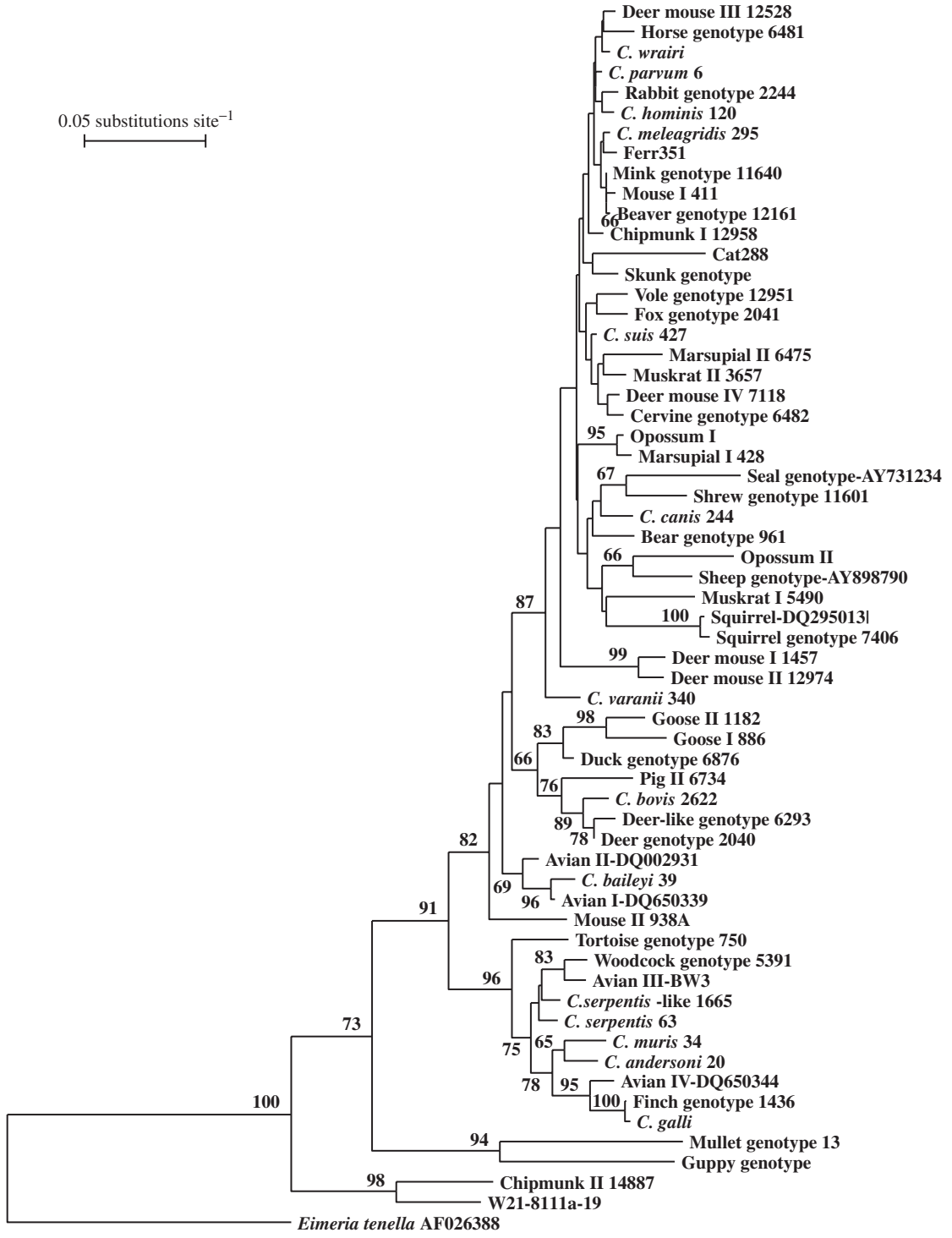

Fig. 1. Genetic relationship among named *Cryptosporidium* species and genotypes inferred by a neighbor-joining analysis of the partial (~375 bp) SSU rRNA gene. Values on branches are percent bootstrapping using 1000 replicates. Numbers following species or genotypes are isolate identifications or GenBank accession numbers used in the construction of the phylogenetic tree. A few other genotypes with shorter sequences are not included.

primarily infects ruminants and humans, even though natural infections have been found occasionally in other animals such as mice and raccoon dogs (Morgan *et al.*, 1999b; Matsubayashi *et al.*, 2004).

Even though cattle have been considered to be a major host for *C. parvum*, only preweaned calves are frequently infected with this species. Most *Cryptosporidium* infections in postweaned calves are due to *C. bovis* and the deer-like genotype, which can be frequently found in yearlings and adult cattle. *Cryptosporidium andersoni* is first found in juveniles but more frequently in yearlings and adults (Santin *et al.*, 2004; Fayer *et al.*, 2006b; Langkjaer *et al.*, 2007; Feng *et al.*, 2007b). *Cryptosporidium bovis* and the deer-like genotype are genetically related and the age pattern of the host is very similar for both parasites, even though the deer-like genotype is usually less common. Thus, only preweaned calves are major contributors of zoonotic *C. parvum*.

Cryptosporidium parvum has only been detected in small numbers in other farm animals. Studies conducted in Australia and the United States suggest that *C. parvum* infection is not common in sheep, which are more often infected with the *Cryptosporidium* cervine genotype and other genotypes (Ryan *et al.*, 2005; Santin *et al.*, 2007). However, lambs are sometimes naturally infected with *C. parvum* and direct transmission of *C. parvum* from lambs to children was confirmed for at least one small outbreak of cryptosporidiosis by subtyping (Chalmers *et al.*, 2005b). Possible transmission of *C. parvum* among humans, calves, and zoo ruminants in Lisbon, Portugal, was supported by subtyping (Alves *et al.*, 2003). Although *C. parvum* was detected in a few horses, its prevalence is not known (Grinberg *et al.*, 2003; Hajdusek *et al.*, 2004; Chalmers *et al.*, 2005a) and horses are known to be infected with a *Cryptosporidium* horse genotype (Ryan *et al.*, 2003).

Cryptosporidium parvum has been detected in a few dogs in Italy (Giangaspero *et al.*, 2006), but most studies indicated that dogs are almost exclusively infected with *C. canis* (Morgan *et al.*, 2000c; Satoh *et al.*, 2006; Huber *et al.*, 2007; Rimhanen-Finne *et al.*, 2007). Likewise, most cats are infected with *C. felis*, although *C. muris* were also found in two cats (Pavlasek & Ryan, 2006; Santin *et al.*, 2006; Fayer *et al.*, 2006a; Rimhanen-Finne *et al.*, 2007). Because *C. canis* and *C. felis* are minor pathogens of humans, these genotyping data suggest that the role of dogs and cats in the transmission of human cryptosporidiosis is probably limited. Direct transmission of *C. canis* to humans, however, has been speculated in a recent report, in which two children and one dog in the same household were shown to be infected with *C. canis* during the same period (Xiao *et al.*, 2007b).

One *Cryptosporidium* with a noticeable broad host range is the cervine genotype. Because its initial finding in storm runoff in a feral area, it has been found in domestic and wild ruminants (sheep, mouflon sheep, blesbok, nyala, and deer), rodents (squirrels, chipmunks, woodchucks, beavers, and deer mice), carnivores (raccoons), and primates (lemurs and humans) (Xiao *et al.*, 2000; Perz & Le Blancq, 2001; Ong *et al.*, 2002; da Silva *et al.*, 2003; Ryan *et al.*, 2003, 2005; Blackburn *et al.*, 2006; Feltus *et al.*, 2006; Leoni *et al.*, 2006; Nichols *et al.*, 2006; Soba *et al.*, 2006; Trotz-Williams *et al.*, 2006; Feng *et al.*, 2007a). Because it is the most common *Cryptosporidium* found in pristine water, it is likely the some other wild mammals are also hosts (Jiang *et al.*, 2005).

A few human-pathogenic *Cryptosporidium* spp. have been found in unusual hosts. For example, *C. hominis* was detected in several calves and sheep in the United Kingdom, United States, Australia, and India (Giles *et al.*, 2001; Ryan *et al.*, 2005; Smith *et al.*, 2005; Feng *et al.*, 2007b), *C. suis* was found in a calf in the United States (Fayer *et al.*, 2006b) and a few lambs in Australia (Ryan *et al.*, 2005), *C. meleagridis* was seen in one dog in Czech Republic and one deer mouse in the United States (Hajdusek *et al.*, 2004; Feng *et al.*, 2007a), and the *C. canis* dog genotype was seen in a fox (Zhou *et al.*, 2004b). The role of these animals in the transmission of these species to humans is probably minimal. Mechanical carriage of *C. hominis* and *C. parvum* oocysts has been reported in a few Canada geese. However, Canada geese are normally infected with two unique *Cryptosporidium* genotypes: goose genotypes I and II (Zhou *et al.*, 2004a).

Zoonotic cryptosporidiosis in industrialized countries

Over the last decade, extensive studies have been conducted to examine the transmission of human cryptosporidiosis in industrialized nations using both genotyping and subtyping tools. Among the five common *Cryptosporidium* species in humans, *C. parvum* and *C. hominis* are responsible for $>$ 90% of human cases of cryptosporidiosis in most areas (Xiao & Ryan, 2004). Geographic differences exist in the disease burdens attributable to these two species. Results of a series of large scale studies showed that *C. parvum* and *C. hominis* are speonsible for 96–98% of sporadic cases in England and Wales, with *C. parvum* responsible for slightly more infections than *C. hominis* (McLauchlin *et al.*, 2000; Chalmers *et al.*, 2002; Leoni *et al.*, 2006). This may also be the case in some other parts of the Europe (such as Northern Ireland, France, Switzerland, Portugal, Slovenia, and the Czech Republic) and New Zealand (Table 1). In contrast, *C. hominis* in general is responsible for more infections than *C. parvum* in the United States, Canada, Australia, Japan (Peng *et al.*, 1997; Morgan *et al.*, 1998; Sulaiman *et al.*, 1998; Ong *et al.*, 1999, 2002; Xiao *et al.*, 2004b). Interestingly, in the highly urbanized Kuwait City, almost all cryptosporidiosis cases in children are caused by *C. parvum*

(Sulaiman *et al.*, 2005), which may also be the case in Iran and Turkey (Meamar *et al.*, 2007; Tamer *et al.*, 2007). This geographic difference in the distribution of *C. parvum* and *C. hominis* in humans is true in both immunocompetent and immunocompromised individuals. Immunocompromised persons in these countries seemingly have slightly more infections caused by *C. meleagridis*, *C. canis*, and *C. felis* than immunocompetent persons (Table 1).

Major differences in the transmission routes may be responsible for the differences in the *Cryptosporidium* species distribution. This is supported by results of studies in the United Kingdom, which reported that *C. hominis* infection was more common in patients with a history of foreign travel (McLauchlin *et al.*, 2000; Goh *et al.*, 2004; Hunter *et al.*, 2004b; Hunter *et al.*, 2007). Indeed, restriction of farm visits and culling of farm animals during a foot and mouth disease outbreak in England have greatly reduced the occurrence of cryptosporidiosis due to *C. parvum* (Hunter *et al.*, 2003; Smerdon *et al.*, 2003). It is possible this and other factors such as drinking water treatment improvement may have permanently changed the transmission of cryptosporidiosis in North West England (Sopwith *et al.*, 2005). In recent years, *C. hominis* has been more prevalent than *C. parvum* in humans in England and Wales (Nichols *et al.*, 2006).

Not surprisingly, geographic differences in the distribution of *Cryptosporidium* species can occur within a country (McLauchlin *et al.*, 1999, 2000; Learmonth *et al.*, 2004). Thus, *C. hominis* infection is generally more common in urban areas and *C. parvum* is more common in rural areas. It seems likely, but remains unproven, that the high prevalence of *C. parvum* in humans in these areas may be due in part to the intensive husbandry practiced for ruminants and the associated high concentrations of young animals at these feeding operations. In the United States, even though *C. hominis* is usually more common than *C. parvum* in humans (Zhou *et al.*, 2003; Xiao *et al.*, 2004b), most human cryptosporidiosis cases in the dairy state Wisconsin are attributable to *C. parvum* (Feltus *et al.*, 2006).

Seasonal differences in the distribution of *C. parvum* and *C. hominis* have been reported. In the United Kingdom and New Zealand, the spring increase in the cryptosporidiosis cases reported was mostly due to *C. parvum* whereas the autumn increase was largely due to *C. hominis* (McLauchlin *et al.*, 2000; Learmonth *et al.*, 2003, 2004; Hunter *et al.*, 2004b), suggesting that seasonal differences in the relative importance of specific transmission routes might exist. It was speculated that the increase in *C. parvum* in spring was due to lambing, calving, and farm runoff from spring rains, and the autumn *C. hominis* peak in these countries was likely the result of increased recreational water activities and international travel during late summer and early autumn (Goh *et al.*, 2004; Hunter *et al.*, 2004b).

What proportion of *C. parvum* infections in humans are attributable to zoonotic transmission remains unclear, as the source of *C. parvum* in humans can be of bovine or of human origin. Results of subtyping studies at the 60 kDa glycoprotein (GP60) locus support the occurrence of zoonotic transmission in industrialized nations. One major GP60 *C. parvum* subtype family, IIa, is common in humans in rural areas in the United States and in Europe (Glaberman *et al.*, 2002; Alves *et al.*, 2003, 2006; Stantic-Pavlinic *et al.*, 2003; Chalmers *et al.*, 2005b; Feltus *et al.*, 2006). Many of the IIa subtypes found in humans have also been found in calves in the same area. For example, in Portugal, one *C. parvum* subtype in humans, IIaA15G2R1, is the predominant *C. parvum* subtype in calves and zoon ruminants (Alves *et al.*, 2003, 2006). In Wisconsin, where patients were almost exclusively infected with *C. parvum* (Feltus *et al.*, 2006), many of the subtypes found in humans were found previously in calves in neighboring Michigan and Ontario (Peng *et al.*, 2003a; Trotz-Williams *et al.*, 2006). Likewise, in Northern Ireland, even though calves are infected with many subtypes in the *C. parvum* subtype family IIa, most of the common subtypes have been found in human outbreak or sporadic cases (Glaberman *et al.*, 2002; Thompson *et al.*, 2007). In an apple-cider-associated outbreak of cryptosporidiosis in 2003 in Ohio, all patients had *C. parvum*, with either subtype IIaA15G2R1 or IIaA17G2R1 (Blackburn *et al.*, 2006). One of the two *C. parvum* subtypes detected in patient specimens, IIaA17G2R1, was found in the implicated apple cider (Blackburn *et al.*, 2006). This subtype is rare in eastern United States, having only been reported in some calves in Ohio and Vermont (Xiao *et al.*, 2007a). Thus, cattle were attributed as the likely source of apple contamination with *Cryptosporidium* oocysts.

Another less common bovine *C. parvum* subtype family, IId, may also be responsible for some zoonotic infections. In southern Europe (Portugal, Italy, Serbia and Hungary), although IIa subtypes were the dominant *C. parvum* in calves, IId subtypes were found occasionally (Alves *et al.*, 2003, 2006; Wu *et al.*, 2003; Misic & Abe, 2007; Plutzer & Karanis, 2007). Four of the IId subtypes, have been found in HIV+ persons in Portugal (Alves *et al.*, 2003, 2006). About half of the *C. parvum* infections in children in Kuwait City are caused by IId subtypes, although the transmission appears to be anthroponotic in origin (Sulaiman *et al.*, 2005). IId subtypes of *C. parvum*, nevertheless, have never been found in calves or humans in the United States, Canada, Australia, and the United Kingdom (Glaberman *et al.*, 2002; Peng *et al.*, 2003a; Chalmers *et al.*, 2005b; Trotz-Williams *et al.*, 2006; Thompson *et al.*, 2007; Xiao *et al.*, 2007a). All these are further indicators of differences in the role of zoonotic parasites in the transmission of *C. parvum* among geographic areas.

The use of a multilocus typing tool also identified the occurrence of zoonotic transmission in a case-control study in Wales and northwest England (Hunter *et al.*, 2007). At the ML1 locus, significantly more persons with *C. parvum* subtype ML1–242 had touched or handled farm animals than those with ML1–227. Similarly, at ML2, significantly more isolates with alleles between 223 and 237 were from patients who had touched or handled farm animals than were strains with alleles 193 and 197. At the GP60 locus, patients who had contact with farm animals yielded significantly greater product sizes than those who reported no animal contact before onset of illness (Hunter *et al.*, 2007).

Not all *C. parvum* subtypes are zoonotic. One study in Portugal showed that the genetic diversity of *C. parvum* was much higher in HIV+ persons than in calves or zoo ruminants, and of the three *C. parvum* subtype families, one (IIc) was not found in animals. The anthroponotic nature of the IIc subtype family has been demonstrated subsequently in comparative subtyping studies of human and bovine cryptosporidiosis in Portugal, United States, Canada, United Kingdom, and Australia, where IIc subtypes have only been found in humans. In urban areas in the United States, IIa subtypes are rarely seen in humans. Instead, the anthroponotic IIc subtype family is responsible for most human *C. parvum* infections in these areas (Xiao *et al.*, 2004a). In European countries such as Portugal and the United Kingdom, both IIa and IIc are fairly common in humans (Alves *et al.*, 2003, 2006).

Results of multilocus typing studies support the occurrence of anthroponotic *C. parvum*. PCR product length polymorphism analysis of three minisatellite and four microsatellite markers has identified two large groups of *C. parvum* in human and bovine specimens from Scotland, with one group exclusively found in humans and the other groups found in both humans and in calves (Mallon *et al.*, 2003a, b). A Similar finding was obtained more recently in England and Wales using three of the same microsatellite markers (Leoni *et al.*, 2007). Like the previous observation of greater *C. parvum* genetic diversity in humans than bovines in the GP60 gene in Portugal, humans in Scotland were infected with significantly wider spectra of *C. parvum* multilocus types than cattle. Thus, a significant fraction of human *C. parvum* infections may not have originated from bovine reservoirs (Grinberg *et al.*, 2007). In contrast, lower genetic diversity of *C. parvum* was observed in France in humans than in animals (Ngouanesavanh *et al.*, 2006). Although two populations of *C. parvum* were also seen in France, they were not restricted to a particular host (Ngouanesavanh *et al.*, 2006). It is not clear whether the omission of some more polymorphic markers such as GP60 in the French study has contributed to this different observation.

Zoonotic cryptosporidiosis in developing countries

The distribution of *Cryptosporidium* spp. in humans in developing countries is very different from that in most industrialized nations. All studies conducted so far have shown a dominance of *C. hominis* in humans in developing countries, responsible for 70–90% of infections (Peng *et al.*, 2001, 2003b; Xiao *et al.*, 2001; Leav *et al.*, 2002; Tiangtip & Jongwutiwes, 2002; Cama *et al.*, 2003; Gatei *et al.*, 2003, 2006, 2007; Tumwine *et al.*, 2003, 2005; Das *et al.*, 2006; Muthusamy *et al.*, 2006; Bushen *et al.*, 2007). In contrast, the disease burden attributable to *C. parvum* is much lower. This strongly suggests that zoonotic infection is much less common in developing countries than in industrialized countries. Children and HIV+ persons in developing countries, however, usually have a higher prevalence of *C. meleagridis*, *C. canis*, *C. felis*, and *C. muris*, with the cervine genotype seen rarely. In fact, most human *C. canis* infections have been reported in persons in developing countries. In Peru and Thailand, *C. meleagridis*, *C. canis*, and *C. felis* are responsible for 15–20% of *Cryptosporidium* infections in AIDS patients and children (Table 2).

Another unique feature of cryptosporidiosis in developing countries is the anthroponotic origin of *C. parvum*. Unlike European countries, Australia, and the United States, the zoonotic IIa subtypes are rarely seen in humans in developing countries. Instead, the anthroponotic IIc subtype family is responsible for most human *C. parvum* infections in these areas (Leav *et al.*, 2002; Peng *et al.*, 2003b; Xiao & Ryan, 2004; Xiao *et al.*, 2004b; Akiyoshi *et al.*, 2006). In some regions such as Lima, Peru, the IIc subtype family is the only *C. parvum* in humans, whereas in other developing countries such as Malawi and Kenya, another anthroponotic *C. parvum* subtype family, IIe, is also seen in humans (Peng *et al.*, 2003b; Xiao & Ryan, 2004; Xiao *et al.*, 2004b; Cama *et al.*, 2007). In Uganda, even though IIc subtypes are the dominant *C. parvum* in children, several new subtype families are present (Akiyoshi *et al.*, 2006). Most of the genotyping and subtyping studies were carried out in urban areas. A recent study in Malawi has shown a higher *C. parvum* infection rate in rural areas than in urban areas (Morse *et al.*, 2007). Unfortunately, subtyping was not carried out to determine the source of *C. parvum* in rural areas, even though an earlier study clearly demonstrated an almost exclusive anthroponotic transmission of cryptosporidiosis in the country (Peng *et al.*, 2003b).

Whether *C. meleagridis*, *C. canis*, *C. felis*, and *C. muris* are transmitted in developing countries by the zoonotic pathway remains to be decided. Using *C. hominis* and *C. parvum*-specific genotyping tools, the analysis of *C. canis*- and *C. felis*-infected specimens from HIV+ persons in Lima, Peru, revealed the concurrent presence of the *C. hominis* and

C. parvum IIc subtype family in 6 of 21 patients, indicating that infection with mixed *Cryptosporidium* spp. is more prevalent than believed previously. The concurrent presence of the human-specific *C. hominis* and *C. parvum* also suggests that many of the *C. canis* and *C. felis* infections in humans were transmitted through the anthroponotic rather than the zoonotic pathway (Cama *et al.*, 2006). There are no multilocus subtyping studies to determine whether there is any host segregation in *C. canis* or *C. felis*, although an earlier study of a small number of human and bird specimens failed to show this in *C. meleagridis* (Glaberman *et al.*, 2001).

Pathogenicity of zoonotic *Cryptosporidium* spp. in humans

The clinical significance of various *Cryptosporidium* species and genotypes in humans is not yet clear. Biologically, *C. parvum* and *C. hominis* differ from each other in host specificity. *Cryptosporidium parvum* infects humans and calves in natural situations and mice in cross-transmission experiments, whereas *C. hominis* does not infect calves or mice readily (Peng *et al.*, 1997). In antibiotic pigs, *C. parvum* and *C. hominis* differ from each other in the prepatent period, infection site, and disease severity (Pereira *et al.*, 2002). In immunosuppressed Mongolian gerbils, no difference in oocyst shedding was observed between the two *Cryptosporidium* species (Baishanbo *et al.*, 2005). Human volunteers inoculated with a *C. hominis* isolate also had an infection course and symptoms similar to those infected with *C. parvum* isolates (Chappell *et al.*, 2006). The number of isolates tested for both species in these models is very small. It remains to be determined whether any observed differences were due to intrinsic biologic differences between the two species or variations in biologic characteristics at the isolate level.

Results of recent genotyping studies nevertheless support the theory that *C. hominis* and *C. parvum* behave differently in humans. In sporadic cases of cryptosporidiosis in the United Kingdom, samples with *C. hominis* were more likely scored microscopically for 2+ or 3+ than those with *C. parvum* (McLauchlin *et al.*, 1999). Similarly, in a longitudinally followed cohort of children in Peru, stools with *C. hominis* had a significantly higher mean oocyst score than those with the zoonotic genotypes (1.7 vs. 1.3 out of 3, $P = 0.02$). In addition, children with *C. hominis* had a significantly longer duration of oocyst shedding than those with the zoonotic genotypes (13.9 vs. 6.4 days, $P = 0.004$) (Xiao *et al.*, 2001). Likewise, oocyst shedding intensity was higher in Brazilian children infected with *C. hominis* than *C. parvum* (Bushen *et al.*, 2007).

In addition to the differences in host specificity and oocyst shedding, *C. parvum* and *C. hominis* differ from each other in pathogenicity and clinical presentations. In sporadic cryptosporidiosis in England, *C. hominis* but not *C. parvum* was associated with an increased risk of nonintestinal sequelae such as joint pain, eye pains, recurrent headache, dizzy spells, and fatigue, even though there were no significant differences between the two species in the presence and duration of diarrhea (Hunter *et al.*, 2004a). In AIDS patients in Lima, Peru, infections with *C. canis* and *C. felis* were more likely associated with diarrhea, and infections with *C. parvum*, *C. canis* and *C. felis* were associated with chronic diarrhea, and *C. parvum* was more likely associated with vomiting. In contrast, infections with *C. meleagridis* and *C. hominis*, especially its Ia and Ie subtype families, were more likely asymptomatic (Cama *et al.*, 2007). These results demonstrate that *C. hominis* and zoonotic *Cryptosporidium* spp. are linked to different clinical manifestations in different populations of humans.

In a Brazilian study, although there were no differences between *C. hominis* and *C. parvum* in the occurrence of diarrhea, these two species seemingly had different nutritional effects on infected children. Height-for-age (HAZ) *Z*-scores showed significant declines within three months of infection for children infected with either *C. hominis* or *C. parvum*. However, in the 3–6-month period following infection, only *C. hominis*-infected children continued to demonstrate declining HAZ scores and those with asymptomatic infection showed an even greater decline ($P = 0.009$). Thus, *C. hominis* was associated with greater growth shortfalls, even in the absence of symptoms (Bushen *et al.*, 2007).

Conclusions

Molecular diagnostic tools are being used increasingly in studies of zoonotic cryptosporidiosis. Significant progresses has already been made in the understanding of the zoonotic potential of *Cryptosporidium* spp. from animals, the human disease burden attributable to several zoonotic species, the contribution of various groups of animals to cryptosporidiosis transmission in humans, and the infection sources for the so-called zoonotic species. Data are emerging to show different spectra of clinical illness between *C. hominis* and zoonotic *Cryptosporidium* spp. in humans, and differences in cryptosporidiosis transmission between developing and industrialized countries, or between rural and urban areas in industrialized nations, especially the relevance of zoonotic transmission. The use of GP60-based subtyping and more recently multilocus subtyping and multilocus sequence typing tools has increased our appreciation of anthroponotic transmission of *C. parvum*, which is very important in developing countries and has becomes increasingly important in industrialized countries. The development of new subtyping tools for other more divergent

species will no doubt lead to better assessment of their infection sources in humans.

The use of genotyping and subtyping tools in well-designed case–control studies and longitudinal cohort studies has played a very important role in achieving this progress (Xiao *et al*., 2001; Hunter *et al*., 2004b, 2007; Bushen *et al*., 2007; Cama *et al*., 2007). Continued efforts in this area, especially more studies in developing countries and the utilization of new-generation typing tools, would provide the scientific data needed to better advice public health professionals, governmental officials, and the general public on the importance of zoonotic transmission of cryptosporidiosis, as a recent flurry of outbreaks of cryptosporidiosis, including a major one in Botswana, has attracted wide attention in the general news media. This would require close collaborations among epidemiologists, clinicians, molecular biologists, and parasitologists. Such an integrated approach will undoubtedly lead to better utilization of available molecular diagnostic tools and a better understanding of zoonotic cryptosporidiosis.

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Statement

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