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REVIEW

Molecular Epidemiology of Human Cryptosporidiosis in Low- and Middle-Income Countries

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SUMMARY Cryptosporidiosis is one of the most important causes of moderate to severe diarrhea and diarrhea-related mortality in children under 2 years of age in low- and middle-income countries. In recent decades, genotyping and subtyping tools have been used in epidemiological studies of human cryptosporidiosis. Results of these studies suggest that higher genetic diversity of *Cryptosporidium* spp. is present in humans in these countries at both species and subtype levels and that anthroponotic transmission plays a major role in human cryptosporidiosis. *Cryptosporidium hominis* is the most common *Cryptosporidium* species in humans in almost all the low- and middle-income countries examined, with five subtype families (namely, Ia, Ib, Id, Ie, and If) being commonly found in most regions. In addition, most *Cryptosporidium parvum* infections in these areas are caused by the anthroponotic IIc subtype family rather than the zoonotic IIa subtype family. There is geographic segregation in *Cryptosporidium hominis* subtypes, as revealed by multilocus subtyping. Concurrent and sequential infections with different *Cryptosporidium* species and subtypes are common, as immunity against reinfection and cross protection against different *Cryptosporidium* species are partial. Differences in clinical presentations have been observed among *Cryptosporidium* species and *C. hominis* subtypes. These observations suggest that WASH (water, sanitation, and hygiene)-based interventions should be implemented to prevent and control human cryptosporidiosis in low- and middle-income countries.

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INTRODUCTION

Cryptosporidiosis is a major cause for diarrhea in young children in low- and middle-income countries. It has been recognized as one of the most important causes for moderate to severe diarrhea as well as diarrhea-related mortality in children less than 2 years in multiple recent studies (1–4). In South Asia and sub-Saharan Africa, *Cryptosporidium* infections contribute annually to nearly 2.9 to 4.7 million diarrheal cases in children under 2 years (5, 6). It is estimated that cryptosporidiosis-associated diarrhea caused over 48,000 deaths as well as 4.2 million disability adjusted life years (DALYs) in children less than 5 years in 2016 (7). Globally, although the mortality related to diarrhea in children under 5 years had declined by 60% from 2000 to 2016, diarrhea-associated morbidity showed a lower reduction of only 13% (8). The prevalence of pathogens unresponsive to conventional antibiotic treatments, such as *Cryptosporidium* spp. and rotavirus, might be responsible for the slow reduction in global diarrhea-associated morbidity.

Cryptosporidiosis is also an important cause of childhood malnutrition. Even when cryptosporidiosis is not associated with diarrhea, it can still cause severe malnutrition (9, 10). Lower weight, weight-for-age Z scores, height-for-age Z scores, and/or body mass index-for-age Z scores are found in children infected with *Cryptosporidium* spp. than in uninfected children (7, 10–15). Children having multiple episodes of cryptosporidiosis experience more severe stunting (10, 16). Therefore, cryptosporidiosis is an important cause of growth retardation. It has been suggested that *Cryptosporidium* spp. impair intestinal-epithelial barrier integrity through the induction of inflammatory responses in the small intestine and affect nutrient absorption through the destruction of intestinal epithelial cells (17–20). On the other hand, stunting at birth is associated with the occurrence of cryptosporidiosis (19, 21, 22).

Molecular epidemiological tools have been used extensively in characterizing *Cryptosporidium* spp. at species/genotype and subtype levels (23). While more molecular epidemiological studies of cryptosporidiosis have been conducted in developed countries, increasing numbers of studies are from low- and middle-income countries, leading to improved understanding of the epidemiology of cryptosporidiosis (6, 10, 24–38). In particular, these studies have led to the identification of anthropogenic factors involved in the acquisition of *Cryptosporidium* spp. in children and HIV-positive patients.

EPIDEMIOLOGICAL FEATURES OF CRYPTOSPORIDIOSIS IN LOW- AND MIDDLE-INCOME COUNTRIES

Due to higher endemicity, lower hygiene levels, and less-intensive animal farming, the epidemiological features of human cryptosporidiosis in low- and middle-income countries differ greatly from those in industrialized nations (Table 1). They include less-frequent occurrence of outbreaks, occurrence of infections at early age, more common association with HIV/AIDS, occurrence of multiple episodes of infections, and concurrence of other pathogens (39–41).

In low- and middle-income countries, cryptosporidiosis is mostly an infectious disease of young children. Pediatric cryptosporidiosis is mostly reported in children less than 2 years old (Fig. 1); recent birth cohort studies indicated as many as 77% of Bangladeshi children and 92.4% of Indian children experienced *Cryptosporidium* infection before the age of 2 years (9, 42). Data from the Global Enteric Multicenter Study (GEMS) conducted in several low-income countries also indicated that *Cryptosporidium* spp. are among the most important diarrhea-related pathogens in children under 2 years (2, 30, 31, 43). In one GEMS in children with moderate to severe diarrhea under 5 years in rural western Kenya, 88.7% of cryptosporidiosis cases occurred in children under 2 years (30). Another GEMS in Gambian children with moderate to severe diarrhea under 5 years found that 91.8% of diarrhea cases caused by *Cryptosporidium* spp. occurred in young children of 6 to 24 months (31). Similar results have also been found

TABLE 1 Differences in epidemiological features of human cryptosporidiosis between low- and middle-income countries and industrialized nations (23, 39, 103, 227)

Feature	Characteristic in:	
	Industrialized nations	Low- and middle-income countries
Endemicity	Low	High
Occurrence of outbreaks	High	Low
Susceptible population	All ages and immune statuses	Children and HIV-positive people
Infection in children	Late (>2 yrs)	Early (<2 yrs)
Major clinical symptoms	Diarrhea	Diarrhea and retarded growth
Asymptomatic infection	Low occurrence	High occurrence
Peak prevalence	Late summer and early autumn	Rainy season or cool months in the tropics
Major risk factors	International traveling, contact with animals or humans, swimming	Poor hygiene, overcrowding, diarrhea case in household

in MAL-ED (Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project) studies (4, 13). In one MAL-ED study conducted in eight countries of Africa, Asia, and South America, nearly 65% of children under 2 years experienced *Cryptosporidium* infection and 54% had *Cryptosporidium*-associated diarrhea (13). In contrast, pediatric cryptosporidiosis in children from industrialized nations occurs later (age over 2 years) than in low- and middle-income countries (under 2 years), which is likely the result of delayed exposures to contamination under better hygiene (44).

Cryptosporidiosis is also common in immunocompromised persons in low- and middle-income countries, especially HIV-positive patients (45–49). The prevalence of cryptosporidiosis in HIV-infected persons ranges from 5.6% to 25.7% in Africa, 3.7% to 45.0% in Asia, 5.6% to 41.6% in South America, and 2.6% to 15.1% in Europe (47). Higher infection rates and more severe clinical outcomes are seen in HIV-positive persons with $CD4^+$ cell counts lower than 200 cells/μl (48). Many recent studies have reported the occurrence of cryptosporidiosis in hemodialysis patients as well as renal transplant patients in low- and middle-income countries (50–59). In contrast, human cryptosporidiosis occurs in persons of various ages and immune statuses in industrialized nations, probably as a reflection of reduced immunity. In industrialized nations, improved hygiene and better drinking source water and wastewater treatment have probably led to reduced exposure to *Cryptosporidium* oocysts, resulting in reduced immunity (60, 61).

Cryptosporidiosis in children is often associated with diarrhea, nausea, vomiting, abdominal cramps, low-grade fever, headache, and fatigue (60, 62). The diarrhea can be watery and voluminous but usually resolves within 1 to 2 weeks without treatment. However, the median duration of postdiarrheal shedding was about 39.5 days (95%

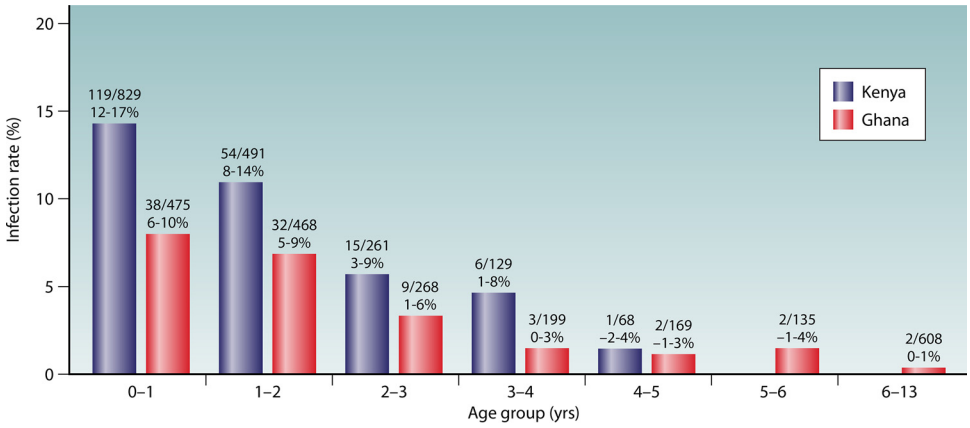

FIG 1 Age pattern of pediatric cryptosporidiosis in Kenya and Ghana (30, 128). Numbers above the bars denote the number of *Cryptosporidium*-positive cases/total number of children studied in each age group (the first line) and the 95% confidence intervals of the infection rates (the second line).

confidence interval [CI], 30.6 to 49 days) in one study (63). The occurrence of diarrhea or other symptoms, however, was detected in only approximately one-third of *Cryptosporidium*-infected children in community-based studies conducted in low- and middle-income countries (42). While multiple reasons, such as prior exposure to *Cryptosporidium* infection and receiving colostrum, might be involved, results of a recent study in Bangladesh suggest that host genetics could play a potential role. A genetic variant within protein kinase C alpha (PRKCA) was associated with a higher risk of symptomatic cryptosporidiosis during the first year of life (64). Even subclinical cryptosporidiosis has significant adverse effects on children, as they may experience retarded growth (7, 10, 15, 65). Unlike in low- and middle-income countries, both children and adults with cryptosporidiosis in developed countries often have diarrhea (39, 60).

Cryptosporidium infections in low- and middle-income countries result mainly from poor hygiene and sanitation (66). Cohort, case-control, and cross-sectional studies have identified multiple risk factors in human cryptosporidiosis in low- and middle-income countries (Table 2). Among them, poor hygiene is the most common risk factor, followed by contact with animals, overcrowding, poor drinking water, young age, and household diarrhea. However, different studies have identified different risk factors. For example, a recent molecular epidemiological study of cryptosporidiosis in four sub-Saharan African nations has identified contact with *Cryptosporidium*-positive household members (risk ratio [RR] = 3.6; 95% CI, 1.7 to 7.5) or neighboring children (RR = 2.9; 95% CI, 1.6 to 5.1) rather than having positive animals (RR = 1.2; 95% CI, 0.8 to 1.9) as the risk factors (33). Contact with animals, especially calves, was a common risk factor for human cryptosporidiosis in many but not all studies (33, 66–69). It is interesting to find that animal contact was protective for *Cryptosporidium* infection in children in Mozambique (70). One study in Cameroon found that breastfeeding (odds ratio [OR] = 0.18; 95% CI, 0.04 to 0.90) was protective for *Cryptosporidium* infection in children within 6 months (71). In an investigation of a cryptosporidiosis outbreak in Botswana, hospitalization and mortality in children were associated primarily with non-breastfeeding (72). However, prolonged breast feeding (>2 years) (OR = 2.18; 95% CI, 1.02 to 7.32) was a risk factor for pediatric cryptosporidiosis in Malaysia (73). In Zambia, male gender (OR = 2.5; 95% CI, 1.13 to 5.70), divorce (OR = 14.8; 95% CI, 1.58 to 138.4), and sharing water sources among neighbors (OR = 5.7; 95% CI, 1.15 to 27.9) were major risk factors for *Cryptosporidium* infection in HIV-positive persons (38). Although divergent risk factors for human cryptosporidiosis have been identified in different studies, poor hygiene was the major one in low- and middle-income countries, while swimming, contact with diarrheal persons/animals, and international travelling were the major ones in industrialized nations (39, 66, 74, 75).

Although cryptosporidiosis is highly endemic in low- and middle-income countries, it rarely causes outbreaks there, probably due to the high level of population immunity (66). A few outbreaks of human cryptosporidiosis, however, have been reported in Mexico, Brazil, Botswana, Jordan, and China, imposing additional burdens on the stretched public health system (72, 76–78). In contrast, human cryptosporidiosis in industrialized nations is best known for foodborne, waterborne, and animal contact-associated outbreaks (79, 80).

UNIQUE DISTRIBUTION OF *CRYPTOSPORIDIUM* SPECIES IN HUMANS IN LOW- AND MIDDLE-INCOME COUNTRIES

Although humans and other vertebrates are common hosts of *Cryptosporidium* spp., most species have host specificity (81). Currently, over 40 *Cryptosporidium* species have been recognized in mammals, birds, reptiles, amphibians, and fish (82). There are also many *Cryptosporidium* genotypes of unknown species status. Due to the existence of host specificity, only one to four *Cryptosporidium* species/genotypes are frequently found in one host species. For example, dogs are mostly infected with *C. canis*, cats with *C. felis*, rabbits with *C. cuniculus*, humans with *C. hominis* and *C. parvum*, sheep and goats with *C. parvum*, *C. ubiquitum*, and *C. xiaoi*, and cattle with *C. parvum*, *C. bovis*, *C. ryanae*, and *C. andersoni* (82).

TABLE 2 Recent studies on the risk factors for human cryptosporidiosis in low- and middle-income countries

Location	Type of study	Sample size	Study population	Major risk factor	Reference
Asia					
China	Case-control	1,366	Patients with and without HIV	Contact with animals	115
	Cross-sectional	1,635	Children and adults	Overcrowding, contact with animals, infection with hepatitis B virus	228
	Cross-sectional	321	Children	Poor hygiene, poor drinking water	229
	Cross-sectional	1,637	Children with and without diarrhea	Poor hygiene	230
Indonesia	Case-control	4,368	Patients with and without diarrhea	Contact with animals, overcrowding, rainfall	231
Malaysia	Cross-sectional	276	Children	Low birth wt, overcrowding, breastfeeding	73
	Cross-sectional	135	Children	Old age, poor hygiene	232
Philippines	Cross-sectional	137	Children and adults	Location, poor drinking water, open defecation	233
Cambodia	Cross-sectional	498	Children	Malnutrition, chronic medical diagnoses, contact with animals	130
Bangladesh	Case-control	272	Children with and without diarrhea	Young age, nonbreastfeeding, stunting	234
	Cohort	392	Children	Malnutrition	9
	Cohort	203	Children	Overcrowding	13
India	Case-control	580	Children with and without diarrhea	Overcrowding, stunting	235
Pakistan	Cross-sectional	425	Children with diarrhea	Poor hygiene, diarrhea, environmental factors	95
Iran	Cross-sectional	171	Children with and without diarrhea	Low birth wt, less breastfeeding, male gender	236
	Case-control	480	Healthy persons and hemodialysis patients	Poor hygiene, diarrhea, education level, young age	51
Lebanon	Cross-sectional	249	Children	Young age, digestive symptoms, diarrhea, fever	237
	Cross-sectional	412	Patients and children	Having meals outside home, diarrhea	238
Africa					
Ethiopia	Cross-sectional	520	HIV/AIDS patients	Contact with animals	67
	Cross-sectional	393	Children with and without diarrhea	Young age	157
Libya	Case-control	505	Children with and without diarrhea	Contact with animals, foreign workers from Africa, poor hygiene, poor drinking water	239
Egypt	Case-control	100	Children with and without diarrhea	Poor hygiene, contact with animals, diarrhea	139
Kenya	Case-control	1,778	Children with and without diarrhea	Young age	30
Uganda	Cross-sectional	108	Children and adults	Poor drinking water	240
Malawi	Case-control	96	Children with and without diarrhea	Contact with animals, poor hygiene, diarrhea	241
Nigeria	Cross-sectional	692	Children with and without diarrhea	Young age, stunting	242
	Cross-sectional	180	Children	Young age, diarrhea	243
South Africa	Case-control	180	Adults with or without HIV or diarrhea	Poor hygiene, contact with animals, poor socioeconomic state	140
Mozambique	Cross-sectional	985	Children with diarrhea	Nampula Province, underweight	70
Zambia	Cross-sectional	222	Children with diarrhea	Rainfall, breastfeeding	244
	Cross-sectional	326	HIV/AIDS patients	Sex, marital status, sharing water sources among neighbors	38
Angola	Cross-sectional	351	Children	Young age	150
Gambia	Case-control	4,907	Children with and without diarrhea	Poor drinking water, contact with animals, overcrowding	31
Ghana	Cross-sectional	50	Children and adults with HIV	Poor drinking water	245
Guinea-Bissau	Case-control	250	Children with and without diarrhea	Contact with animals, poor hygiene, male gender	246
Cameroon	Cross-sectional	112	Children	Nonbreastfeeding, poor drinking water	71
Sub-Saharan Africa	Cross-sectional	1363	Children	Contact with humans	33
Americas					
Cuba	Case-control	215	Children with and without diarrhea	Poor hygiene, contact with animals	247
Guatemala	Cohort	130	Children with and without diarrhea	Lack of toilet, contact with animals	248
	Cross-sectional	100	Children with gastroenteritis	Poor hygiene, female gender	249
Mexico	Cross-sectional	403	Children with diarrhea	Malnutrition, nonbreastfeeding	250
	Cross-sectional	173	Children without diarrhea	Poor drinking water, contact with animals	11
	Cross-sectional	132	Children without diarrhea	Poor drinking water, overcrowding, poor hygiene, diarrhea	251
Venezuela	Cross-sectional	515	Children and adults	Poor hygiene, overcrowding, young age	252
Brazil	Cohort	189	Children with and without diarrhea	Low birth wt, overcrowding	253
	Cross-sectional	445	Children with diarrhea	Young age, poor hygiene, diarrhea, rainfall, male gender	254
Peru	Cohort	368	Children with and without diarrhea	Lack of toilet, warm season	255

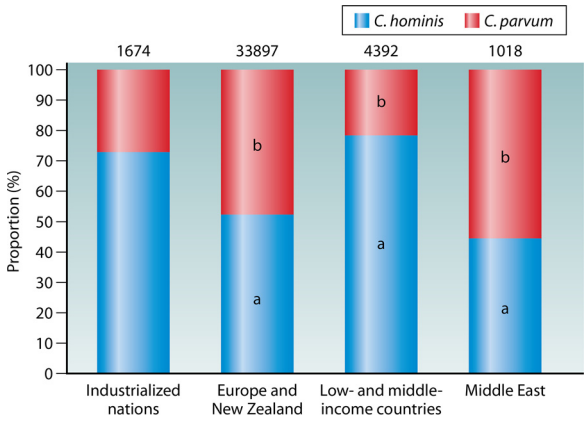

FIG 2 Proportion (%) of *Cryptosporidium parvum* and *Cryptosporidium hominis* in different areas and socioeconomic conditions. Numbers above bars denote sample size (*n*). In the bars, "a" indicates a significant difference in proportion of *C. hominis* between industrialized nations and the group under comparison ($P < 0.05$ by chi-square test), while "b" indicates a significant difference in proportion of *C. parvum* between industrialized nations and the group under comparison ($P < 0.05$).

Among the known *Cryptosporidium* species, *C. parvum* is one of the few species with a wide host range and also the most important zoonotic species in humans (82).

Over 20 *Cryptosporidium* species and genotypes have been reported in humans, many with fewer than a handful of cases (81). Among them, *C. parvum* and *C. hominis* are two major species, being responsible for over 90% of human cryptosporidiosis cases in most areas. Other less commonly detected species include *C. meleagridis*, *C. canis*, *C. felis*, *C. ubiquitum*, *C. cuniculus*, *C. viatorum*, *Cryptosporidium* chipmunk genotype I, and *C. muris* in the order of numbers of reported cases. The remaining ones have each been occasionally detected in several cases (82).

The distribution of *Cryptosporidium* species in humans is different between industrialized and low- and middle-income countries (Fig. 2). Molecular epidemiological studies of human cryptosporidiosis have recognized *C. hominis* as the dominant species in both children and HIV-positive patients in low- and middle-income countries (39). In contrast, *C. hominis* and *C. parvum* infections appear to be equally common in both immunocompromised and immunocompetent persons in European and Middle East countries as well as New Zealand (39, 75, 80, 83, 84). In some industrialized nations, such as the United States, Canada, Australia, and Japan, although most human cryptosporidiosis cases are caused by *C. hominis*, there is a high occurrence of *C. parvum* in rural areas (85–88). These results suggest that zoonotic infection is less common in low- and middle-income countries than in industrialized nations.

The distribution of other human-pathogenic *Cryptosporidium* species is also different between low- and middle-income countries and industrialized nations. Most human infections with *C. meleagridis*, *C. felis*, *C. canis*, *C. viatorum*, and *C. muris* have been reported in studies conducted in low- and middle-income countries or in persons who have traveled to these areas (10, 39, 67, 89, 90). In contrast, most human infections with *C. ubiquitum*, *C. cuniculus*, and chipmunk genotype I are from industrialized nations. In particular, *C. ubiquitum* and chipmunk genotype I contribute to substantial numbers of human *Cryptosporidium* infections in rural states in the United States, while *C. cuniculus* infections are reported mainly in the United Kingdom and New Zealand (83, 86, 91–94).

CHARACTERISTICS OF *C. HOMINIS* INFECTION IN HUMANS IN LOW- AND MIDDLE-INCOME COUNTRIES

Molecular epidemiological studies of *Cryptosporidium* infections in children have shown a dominance of *C. hominis* in low- and middle-income countries, accounting for an average of over 65% of *Cryptosporidium* cases. In some studies, the lack of *C.*

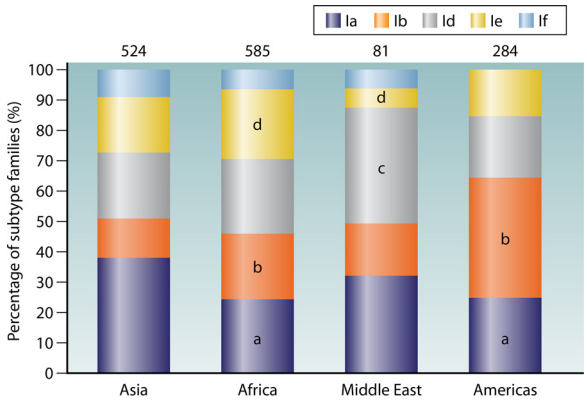

FIG 3 Distribution of common *Cryptosporidium hominis* subtype families among low- and middle-income countries in Asia, Africa, the Middle East, and the Americas. Numbers above bars denote sample size (*n*). In the bars, "a," "b," "c," and "d" indicate a significant difference in distribution of Ia, Ib, Id, and Ie between Asia and the group under comparison ($P < 0.05$ by chi-square test), respectively.

hominis was possibly caused by the use of genotyping tools targeting individual species (95) or a small number of *Cryptosporidium*-positive specimens (96, 97). The dominance of *C. hominis* could be due to the importance of environmental contamination and direct person-to-person transmission in cryptosporidiosis epidemiology. This was supported by the observation of a high rate of secondary infection and infection with the same subtype within families in a case-control study of *Cryptosporidium* transmission in Bangladeshi households (25). *Cryptosporidium hominis* is also a major species in HIV-positive patients in low- and middle-income countries. There is frequently a good agreement in the distribution of *Cryptosporidium* species between children and HIV-positive patients in the same country.

In low- and middle-income countries, the results of molecular characterizations of *C. hominis* isolates have highlighted the complexity of cryptosporidiosis epidemiology. Molecular analyses of *C. hominis* have revealed much higher numbers of subtype families in humans in low- and middle-income countries than in industrialized nations (98). Based on sequence analysis of the 60-kDa glycoprotein (*gp60*) gene, *C. hominis* is divided into five major subtype families with very divergent sequences, including Ia, Ib, Id, Ie, and If. Each *C. hominis* subtype family has many subtypes that differ from each other mostly in the number of trinucleotide repeats at the 5′ end of the gene sequence. All five subtype families are common in children and HIV-positive persons in most low- and middle-income countries examined. The complexity of transmission is further supported by the occurrence of multiple subtypes within the Ia, Ib, and Id subtype families in most areas of endemicity (25, 26, 29, 33, 62, 99–102). In comparison, much lower genetic diversity of *C. hominis* is seen in humans in industrialized nations. In European countries, subtype family Ib contributes to over 90% of *C. hominis* infections (80). The high heterogeneity of *C. hominis* in low- and middle-income countries is considered an indication of the high intensity of cryptosporidiosis transmission in areas of endemicity (103).

The distribution of common *C. hominis* subtype families varies among geographic areas (Fig. 3). In Asia, Ia is a major subtype family for *C. hominis* in humans, followed by Id, Ie, Ib, and If, in that order (25, 29); in Africa, the frequencies of Ia, Ib, Id, and Ie are about the same and significantly higher than that of If (33, 102, 104); in the Middle East, Id is most common, followed by Ia and Ib, with only limited occurrence of Ie and If (99, 100); in the Americas, Ib is the most common subtype family of *C. hominis*, followed by Ia, Id, and Ie, with the absence of If (24, 105). These differences in distribution of *C. hominis* subtype families possibly reflect variations in the transmission of *C. hominis* in humans among areas.

Geographical segregation is seen in the distribution of subtypes within some of the common subtype families. For instance, two major subtypes are seen within the subtype family Ib: IbA9G3 and IbA10G2. The former is common in Jordan, Tanzania,

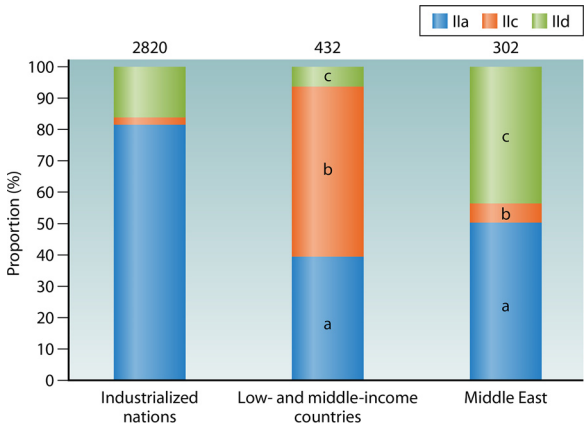

FIG 4 Proportion (%) of common *Cryptosporidium parvum* subtype families in different areas and socioeconomic conditions. Numbers above bars denote sample size (*n*). In the bars, "a," "b," and "c" indicate a significant difference in proportion of IIa, IIc, and IId between industrialized nations and the group under comparison ($P < 0.05$ by chi-square test), respectively.

Uganda, Kenya, Bangladesh, and India, while the latter is common in Peru, Jamaica, Colombia, Argentina, and Brazil as well as South Africa. Other subtypes, such as IbA13G3, IbA10G1, IbA11G2, and IbA12G3, were reported only in limited regions. This geographic segregation in *C. hominis* subtypes has been confirmed by multilocus sequence type (MLST) analysis of specimens from several countries (106).

CHARACTERISTICS OF *C. PARVUM* INFECTION IN HUMANS IN LOW- AND MIDDLE-INCOME COUNTRIES

Cryptosporidium parvum contributes to ~20% of cases of human cryptosporidiosis in low- and middle-income countries. As with *C. hominis*, there are multiple subtype families within *C. parvum* at the *gp60* locus. Some of the *C. parvum* subtype families are host adapted, which is useful in tracking the sources of *C. parvum* infections in humans. For example, the IIa subtype family is commonly found in dairy calves, the IId subtype family is found mostly in lambs and goat kids, while the IIc subtype family is almost exclusively a human pathogen (82). Although there are more subtype families in *C. parvum* than in *C. hominis*, only 1 or 2 subtype families are responsible for most human *C. parvum* infections in one particular area.

The distribution of common *C. parvum* subtype families varies greatly among different geographic regions and socioeconomic conditions (Fig. 4). In low- and middle-income countries, IIc contributes to over half the disease burden due to *C. parvum*, followed by IIa, while the contribution of IId is limited. The IIa subtypes identified in humans in low- and middle-income countries, however, were mostly from the few studies conducted in Malaysia and Ethiopia (67, 107, 108), except for a recent one in China (28), where IIa subtypes are rare in animals (109–113). In Middle East countries, some of which are highly industrialized, the disease burdens of IId and IIa are significantly higher than that of IIc. In contrast, IIa is responsible for over 80% of *C. parvum* infections in industrialized countries, whereas IId subtypes are seen mostly in New Zealand and Europe, and IIc infections are associated with travel to low- and middle-income countries (75, 80, 83, 98). The difference in distribution of *C. parvum* subtype families among geographic regions and socioeconomic conditions is probably a reflection of differences in infection sources and transmission routes.

The subtype diversity of *C. parvum* in humans is much higher in low- and middle-income countries than in industrialized nations (Table 3; Fig. 5). As presented in Table 3, analysis of the subtype diversity using the Simpson and Shannon-Wiener indexes showed the highest subtype diversity of *C. parvum* in Asia, followed by Africa, the Middle East, Europe, Oceania, South America, and North America. In Africa, as many as nine subtype

TABLE 3 Subtype diversity of *Cryptosporidium parvum* in humans in divergent geographic regions

Location	No. of cases of indicated subtype of *C. parvum*[a]													Simpson index	Shannon-Wiener index
	IIa	IIb	IIc	IId	IIe	IIf	IIg	IIh	IIi	IIl	IIm	IIn	IIo		
Asia	40	5	25	17	8	0	0	0	0	0	6	2	4	0.7678	1.6957
Africa	93	8	132	9	31	0	1	1	5	0	2	0	0	0.6578	1.3215
Europe	822	1	38	111	2	0	1	0	0	1	0	16	2	0.3019	0.6390
Oceania	1,387	0	20	384	4	0	0	0	0	0	0	0	1	0.3578	0.5973
Middle East	151	0	19	132	0	1	0	0	0	0	0	0	0	0.5579	0.9016
South America	6	0	61	0	0	0	0	0	0	0	0	0	0	0.1631	0.3015
North America	96	0	7	0	0	0	0	0	0	0	0	0	0	0.1267	0.2483

[a]Numbers represent cases of each subtype family in corresponding regions.

families are recognized, including IIa to IIe, IIg, IIh, IIi, and IIm. Among them, IIc is the most common subtype family. This is followed by the IIe subtype family, which appears to be another anthroponotic subtype family of *C. parvum*. The occurrence of the remaining subtype families is sporadic. The IIa subtype family, however, appears to be common in AIDS patients in Ethiopia, together with some occurrence of the IId subtype family (67).

In Asia, up to eight subtype families have been reported, namely, IIa to IIe, IIm, IIn, and IIo. Among them, the IIa and IIc subtype families are the most common. They are followed by the IId and IIe subtype families. The common occurrence of the IIa subtype family, however, is mostly attributable to two reports in Malaysia and China (28, 108). The Chinese report was contradictory to other reports, which mostly reported the IId subtype family in the country (27, 114, 115). In fact, IIa subtypes are absent from dairy calves in China, which are exclusively infected with IId subtypes (109). Other *C. parvum* subtype families such as IIe, IIm, and IIo have been only occasionally reported in humans in Asia (6, 26, 32, 116, 117).

In the Middle East, the genetic diversity of *C. parvum* in humans is much lower. Although four subtype families are recognized, two of them have very low frequency. Among them, IId contributes to over half of the *C. parvum* infections. The importance of IId in human infections in Middle East countries may be related to the importance of small ruminants, which are commonly infected with *C. parvum* IId subtypes (118). This is followed by IIa, which accounts for almost all the remaining *C. parvum* infections there. In contrast, IIc and IIf subtype families were reported in only a few cases in the area (99, 100, 119–121).

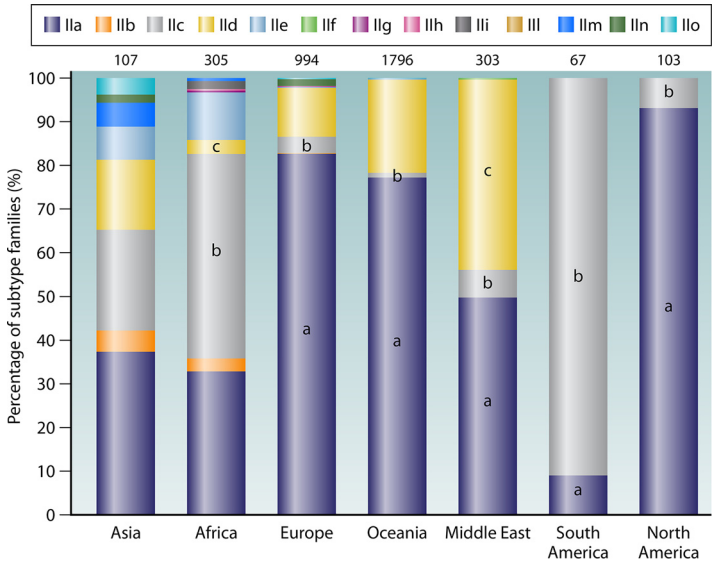

FIG 5 Distribution of *Cryptosporidium parvum* subtype families in humans in Asia, Africa, Europe, Oceania, the Middle East, South America, and North America. Numbers above bars denote sample size (*n*). In the bars, "a," "b," and "c" indicate a significant difference in distribution of IIa, IIc, and IId between Asia and the group under comparison ($P < 0.05$ by chi-square test), respectively.

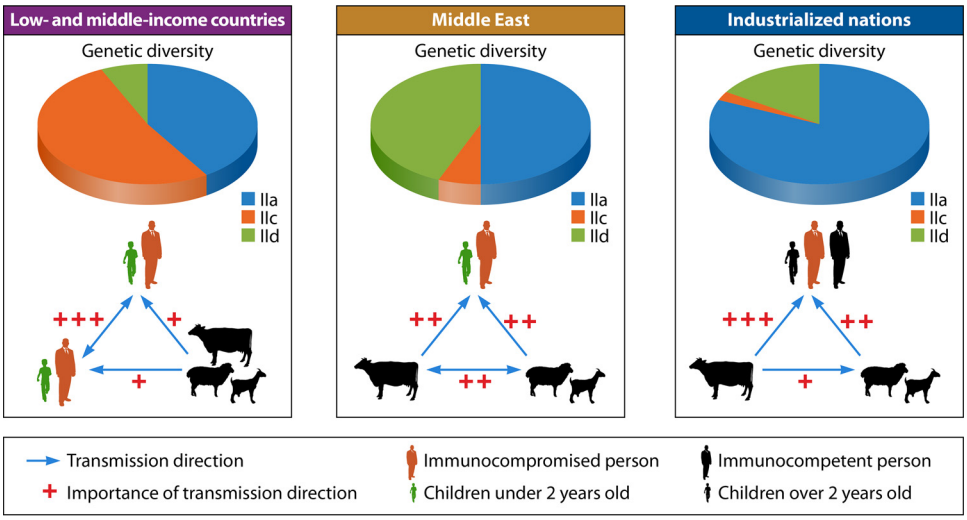

FIG 6 Differences in transmission of major subtype families of *Cryptosporidium parvum* in humans between low- and middle-income countries and industrialized nations. The blue arrows indicate major directions of transmission, and the red plus symbols indicate their importance in cryptosporidiosis epidemiology. The relative distribution of the major subtype families is indicated in the pie chart.

In South America, only IIc and IIa have been reported in humans. Although IIc is more common than IIa there, there is an increasing occurrence of IIa in humans in recent years, especially in Colombia and Mexico, which geographically is located in North America (24, 122). The occurrence of IIa subtypes there reflects their common occurrence in dairy calves (123). The IIc subtype family, however, remains the dominant *C. parvum* in humans in urban areas in South America (105, 122, 124, 125).

The dominance of the IIc subtype family in humans in low- and middle-income countries suggests that anthroponotic transmission plays a major role in cryptosporidiosis in this area (Fig. 6). This is especially the case in African and Asian countries and urban areas in South America, where the anthroponotic IIc subtype family is especially common in low-income countries with poor sanitation and in HIV-positive persons (126). In many Asian and African countries, the occurrence of IIc subtypes in humans is in concurrence with IIe, another anthroponotic *C. parvum* subtype family (26, 32, 33, 67, 104, 127–130). In addition to them, several other subtype families were also found (127, 128, 131). In contrast, the common occurrence of IIa and IId subtypes in Middle East countries suggests that zoonotic transmission of *C. parvum* might play a significant role in cryptosporidiosis there. This is in agreement with the common occurrence of IIa and IId subtypes in calves, lambs, and goat kids in these countries (132–138). Indeed, animal contact has been identified as a risk factor for pediatric cryptosporidiosis in Egypt (139). Zoonotic transmission appears to be important in some countries elsewhere, such as Ethiopia in Africa and Malaysia in Asia, where in addition to IIa and IId, anthroponotic transmission of IIc occurs simultaneously (67, 108). In the Ethiopian study, calf contact was identified as a risk factor for infection with the IIa subtype family (67). This is one of the rare occasions in low- and middle-income countries where zoonotic transmission of *C. parvum* has been explicitly implicated in playing a significant role in cryptosporidiosis epidemiology. These findings indicate that although anthroponotic transmission contributes to the majority of *C. parvum* infections in humans in low- and middle-income countries, zoonotic transmission is increasingly recognized in some countries where the disease is endemic. This is probably related to the increased direct or indirect contact with farm animals as part of the property relief efforts that have been under way for some years (68, 140, 141).

In the desert country Botswana, one major outbreak of diarrhea in 2006 after heavy rains and floods had led to hundreds of deaths and thousands of infections in children less

than 5 years old. It was mainly caused by cryptosporidiosis. Based on the results of molecular epidemiological investigations, *C. parvum* and *C. hominis* were found in 30 cases examined, with almost equal distribution (72). A total of five subtype families of *C. hominis* were found. In contrast, only two IIc subtypes (IIcA5G3a and IIcA5G3b) were found among the *C. parvum*-positive samples (L. Xiao, unpublished data). These data indicate that the source of contamination during the outbreak was probably of human origin. Poor sewage treatment or lack of sewage treatment might have contributed to the occurrence of the outbreak (72).

CHARACTERISTICS OF OTHER *CRYPTOSPORIDIUM* SPECIES IN LOW- AND MIDDLE-INCOME COUNTRIES

In addition to *C. hominis* and *C. parvum*, other species, including *C. meleagridis*, *C. canis*, *C. felis*, *C. viatorum*, and *C. muris,* are significant causes of human cryptosporidiosis in low- and middle-income countries (10, 24, 26, 32, 67, 103). In industrialized nations, infections with these species are frequently associated with foreign travel, as autochthonous infections with them are rare (83, 89, 142, 143). Several other species associated with zoonotic cryptosporidiosis in industrialized nations, such as *C. ubiquitum*, *C. cuniculus*, and *Cryptosporidium* chipmunk genotype I, are rarely detected in humans in low- and middle-income countries.

Cryptosporidium meleagridis is traditionally considered an avian species but has been found in children and HIV-positive patients in many low- and middle-income countries. In some recent studies conducted in Nigeria, Mozambique, Tunisia, Madagascar, Ghana, Bangladesh, Thailand, and Colombia, *C. meleagridis* was a prevalent species and contributed to 9% to 92% of the 22 to 94 cryptosporidiosis cases examined in each study (10, 25, 26, 33, 99, 129, 144). In one recent study of molecular epidemiology of cryptosporidiosis in two areas in Bangladesh, over 100 *C. meleagridis* infections were identified. *Cryptosporidium meleagridis* was found in 13% of *Cryptosporidium* infections in the urban area and 90% of *Cryptosporidium* infections in the rural area (10). *Cryptosporidium meleagridis* was also found at a high frequency (20 of 92 *Cryptosporidium*-positive cases) in HIV-positive patients in one study in Bangkok, Thailand (26). In one small-scale study in China, only *C. meleagridis* was found in children with diarrhea (96).

A *gp60*-based subtyping tool is available for the genetic characterization of *C. meleagridis* (145). Eight subtype families (IIIa to IIIh) and over 30 subtypes have been reported in humans (23, 145). In one study of *C. meleagridis* infections in HIV-positive patients in Bangkok, Thailand, nine subtypes were identified (26). Some human infections with *C. meleagridis* are possibly caused by zoonotic transmission, judged by the occurrence of IIIbA26G1R1b and IIIbA22G1R1c in both diarrheic children and farmed chickens in Hubei, China (96, 146). The results of one MLST analysis of *C. meleagridis* from children, AIDS patients, and birds in Peru did not find obvious host segregation in subtypes, suggesting that zoonotic transmission of *C. meleagridis* between humans and birds is possible (147). Seven of the 55 human *C. meleagridis* cases in the study, however, had coinfection with *C. hominis*, indicating that at least some of the *C. meleagridis* infections in humans were of anthroponotic origin.

The MLST characterization of *C. meleagridis* identified two major groups (group 1 and group 2) of *C. meleagridis* subtypes (147). They correspond to types 1 and 2 at the small-subunit (SSU) rRNA locus and IIIb and IIIc subtype families at the *gp60* locus. As they also have different nucleotide sequences at the MSC6-5 and RPGR loci, they probably represent two segregated *C. meleagridis* populations (147). Thus far, the biological significance of the two *C. meleagridis* populations is not clear. In the Peruvian study, group 1 was found in both chickens and humans, and 2 of the 14 multilocus subtypes of *C. meleagridis* in the group were found in both AIDS patients and birds, suggesting that indeed zoonotic transmission might be involved. In contrast, group 2 was found only in humans. Nevertheless, the number of avian isolates characterized was small. Population genetic analysis of the MLST data suggests a clonal population of *C. meleagridis* in the study community (147).

Cryptosporidium canis is the only *Cryptosporidium* species found in dogs in most molecular epidemiological studies of cryptosporidiosis in companion animals (148). It has been commonly reported in humans in low- and middle-income countries. For most studies, only a few cases were positive for *C. canis*, but unusually high infection rates (>10% of cryptosporidiosis cases) were reported in children in Cambodia and Angola as well as HIV-positive patients in Thailand and Venezuela (26, 130, 149, 150). In Venezuela, all the *C. canis*-positive patients kept dogs during the survey, indicating a possible occurrence of zoonotic transmission, although no survey of dogs was done (149). Although zoonotic transmission between humans and dogs has been identified using a genotyping tool (151), the transmission from pet dogs to humans is considered a low risk (20). Currently, no subtyping tools are available for *C. canis*, which has seriously impeded our understanding of the transmission of *C. canis* between humans and dogs. In a multilocus characterization of *C. canis* specimens from 12 HIV-infected persons from Lima, Peru, three were coinfected with *C. hominis*, indicating that some of the *C. canis* infections in humans were probably of anthroponotic origins (152).

Similar to *C. canis* in canine animals, *C. felis* is the dominant *Cryptosporidium* species in cats and other felines (148). It is commonly reported in humans in low- and middle-income countries. Possible transmission of *C. felis* between cats and humans has been reported (153). In Peru, some of the *C. felis*-infected AIDS patients were coinfected with *C. hominis* and *C. meleagridis*, suggesting that not all *C. felis* infections in humans are the result of zoonotic transmission (152). Recently, a subtyping tool based on sequence analysis of the *gp60* gene has been developed for *C. felis*. It was used in the confirmation of two cases of zoonotic transmission of *C. felis* in Sweden (154). Thus far, it has been used in the characterization of human specimens from China, India, Ethiopia, Kenya, Nigeria, Jamaica, and Peru, suggesting potential host adaption as well as geographic isolation in *C. felis* (155).

Cryptosporidium viatorum was first reported in travelers back to Britain from India (89) and has been reported in humans in India, China, Ethiopia, Nigeria, and Colombia (32, 34, 67, 104, 125, 156–158). In particular, a high prevalence of *C. viatorum* (>10% of cryptosporidiosis cases) was recognized in children and HIV-positive persons in Ethiopia and Colombia (67, 125, 157). A subtyping tool based on sequence analysis of the *gp60* gene is available for *C. viatorum* (159). Thus, far, four subtype families have been identified, including XVa, XVb, XVc, and XVd, but only XVa subtypes have been identified in humans (159). Most XVa subtypes have only three copies of the TCA repeat in the trinucleotide repeat region of the *gp60* gene. As there are minor sequence differences downstream from it, eight subtypes (namely, XVaA3a to XVaA3h) are recognized among them (23, 34, 159). Recently, these four *C. viatorum* subtype families, namely, XVa (XVaA6, XVaA3g, and XVaA3h), XVb (XVbA2G1), XVc (XVcA2G1a and XVcA2G1b), and XVd (XVdA3), have been reported in wild rats in Australia and China (160–162). Previously, *C. viatorum* was thought to be an anthroponotic species (163). As subtypes XVaA3g and XVaA3h have been found in both humans and wild rats, *C. viatorum* infections are probably of the rat origin (34, 143, 161). This is also supported by the occurrence of another rat intestinal *Cryptosporidium* species, *C. occultus*, in humans in low- and middle-income countries (34, 164). These two species are rarely detected in humans in industrialized nations, probably a reflection of better hygiene there.

Cryptosporidium muris is another *Cryptosporidium* species in rats and some other rodents but has been found in humans in a few studies in Kenya, Nigeria, Thailand, India, Saudi Arabia, Colombia, and Peru (24, 42, 144, 165–171). In agreement with this, macaque monkeys in China are commonly infected with *C. muris* (172). Unlike other human-pathogenic *Cryptosporidium* spp., *C. muris* is a gastric pathogen with a much longer patent period (173). A *Cryptosporidium* species related to it, *C. andersoni*, has also been found in some human cases (24). Two studies reported a high prevalence of *C. andersoni* in immunocompetent children and adults in China (174, 175). A multilocus subtyping tool is available for characterizing the transmission of *C. muris* and *C. andersoni* (176).

Except for the five species mentioned above, other human-pathogenic species such

as *C. ubiquitum*, *C. cuniculus*, and *Cryptosporidium* chipmunk genotype I are seldom reported in low- and middle-income countries (39). *Cryptosporidium ubiquitum* is commonly found in the United States. Subtyping analysis of *C. ubiquitum* isolates from humans, animals, and water based on sequence analysis of the *gp60* gene indicated that *C. ubiquitum*-infected lambs and contaminated drinking water were likely the sources for human infections (93). *Cryptosporidium cuniculus* was first reported in rabbits in the United States but is a common human pathogen in the United Kingdom and New Zealand, leading to one large outbreak of human cryptosporidiosis in the United Kingdom (177, 178). *Cryptosporidium* chipmunk genotype I was first found in rodents in the United States (179). Subtype analysis revealed that isolates from humans and wild animals shared high genetic identity at the *gp60* locus, supporting the occurrence of zoonotic transmission in humans (92).

CONCURRENT INFECTIONS WITH MIXED *CRYPTOSPORIDIUM* SPECIES, MULTIPLE EPISODES OF INFECTIONS, AND SECONDARY TRANSMISSION

One consequence of the high prevalence and diversity of *Cryptosporidium* spp. in humans in low- and middle-income countries is the concurrence of mixed *Cryptosporidium* species. Most of the mixed infections are caused by *C. hominis* and *C. parvum* (Table 4). The clinical significance of coinfections with multiple *Cryptosporidium* species is not clear. In one study in India, while the distribution of *Cryptosporidium* species was similar between symptomatic and asymptomatic children, a much higher occurrence (8.7% of the cryptosporidiosis cases compared with 0.6%) of mixed infections with *C. hominis* and *C. parvum* was seen in symptomatic children (42). This indicates that coinfection with two or more *Cryptosporidium* spp. might have deleterious effects on children.

Restriction fragment length polymorphism (RFLP) analysis of PCR products is widely used in the detection of mixed *Cryptosporidium* species. Using this approach, the concurrence of *C. hominis* in 14 of 95 *C. parvum*-infected children and of *C. andersoni* in one *C. muris*-infected child was identified in a recent study in India (42). Another study in Egypt identified coinfection of *C. parvum* in 3 of 10 *C. hominis*-infected children (139). Coinfections of *C. parvum* and *C. hominis* were also identified in HIV-positive patients in Argentina, Brazil, and Mozambique (105, 129). Concurrence of *C. hominis* and *C. meleagridis* was identified in children and migrant workers in Tunisia and Qatar (99, 180). Coinfections of *C. hominis* and *C. canis*/*C. felis* were also identified in HIV-infected patients in Peru (151).

The occurrence of mixed *Cryptosporidium* species may be more common than believed, as shown in some studies in which multiple molecular tools were used in the identification and characterization of *Cryptosporidium* spp. With the application of species-specific quantitative PCR (qPCR) in a study conducted in Bangladesh, coinfection with *C. parvum* or *C. hominis* was identified in 1 and 13 of 100 *C. meleagridis*-infected children, respectively. Coinfection with *C. hominis* was further identified in one of five *C. parvum*-infected children (10). The use of a similar approach identified the concurrence of *C. parvum* in 5 of 124 *C. hominis*-infected children in Gambia (31). Coinfection with *C. hominis* was identified in 7 of 55 *C. meleagridis*-positive children and AIDS patents in Peru (147). Thus, accurate identification of coinfections with multiple *Cryptosporidium* species can improve our understanding of the transmission of zoonotic *Cryptosporidium* species in humans.

Children in low- and middle-income countries can experience multiple episodes of cryptosporidiosis, possibly reflecting short-lived or incomplete protection against *Cryptosporidium* infection after the primary infection (39, 181). In a longitudinal birth cohort study conducted in Bangladesh, 118 of 302 *Cryptosporidium*-positive children had two to four episodes of infections before reaching the age of 2 years, with no significant decreases in parasite burden during repeated infections (9). In another 3-year birth cohort study in India, 81% (322/397) of children with cryptosporidiosis experienced multiple episodes of infections, with no reduction in the severity of diarrhea during repeated infections (42). Unexpectedly, there was no species-specific protection against reinfections (16, 42, 124). Protective immunity, however, could exert effects at

TABLE 4 Concurrent infections with mixed *Cryptosporidium* species in low- and middle-income countries in recent studies[a]

Location	Study population	No. of isolates	Mixed infections (*n*)	Genotyping technique(s)	Reference
Asia					
India	Children	50	*C. hominis* and *C. meleagridis* (2)	SSU rRNA-based PCR-RFLP	256
	Immunocompromised children	53	*C. hominis* and *C. meleagridis* (5), *C. hominis* and *C. parvum* (2)	SSU rRNA-based PCR-RFLP, *gp60*-based PCR and sequencing	117
	Immunocompromised patients	71	*C. hominis* and *C. parvum* (2)	Species-specific DHFR-based PCR and qPCR	50
	Children	473	*C. hominis* and *C. parvum* (14), *C. andersoni* and *C. muris* (1)	SSU rRNA-based PCR-RFLP	42
Bangladesh	Children	268	*C. hominis* and *C. parvum* (1), *C. hominis* and *C. meleagridis* (13), *C. parvum* and *C. meleagridis* (1)	SSU rRNA-based pan-*Cryptosporidium* qPCR	10
Cambodia	Children patients	38	*C. hominis* and *C. parvum* (1)	SSU rRNA-based qPCR and multiplex qPCR	130
Qatar	Adults	38	*C. hominis* and *C. parvum* (4), *C. parvum* and *C. meleagridis* (3)	SSU rRNA-based PCR-RFLP	180
Saudi Arabia	Children	35	*C. hominis* and *C. parvum* (1)	SSU rRNA-based and COWP-based PCR-RFLP	166
Africa					
Tunisia	HIV^+ patients	42	*C. hominis* and *C. meleagridis* (1)	SSU rRNA-based PCR-RFLP	99
Egypt	Diarrheal patients	18	*C. hominis* and *C. parvum* (3)	COWP-based PCR-RFLP	257
	Children	14	*C. hominis* and *C. parvum* (3)	SSU rRNA-based PCR-RFLP	139
Ethiopia	HIV^+ patients	140	*C. hominis* and *C. parvum* (1)	SSU rRNA-based PCR-RFLP	67
Mozambique	HIV^+ patients	9	*C. hominis* and *C. parvum* (1)	SSU rRNA-based PCR-RFLP	129
Gambia	Children	280	*C. hominis* and *C. parvum* (5)	TaqMan array card-based qPCR	31
Nigeria	Children	77	*C. hominis* and *C. parvum* (4)	SSU rRNA-based PCR-RFLP	258
	Children	44	*C. hominis* and *C. parvum* (4)	SSU rRNA-based PCR-RFLP	242
	HIV^+ patients	4	*C. hominis* and *C. meleagridis* (1)	SSU rRNA-based PCR-RFLP	259
Kenya	Diarrheal children	151	*C. hominis* and *C. parvum* (1)	SSU rRNA-based PCR-RFLP	260
Malawi	Diarrheal children	43	*C. hominis* and *C. parvum* (5)	SSU rRNA-based and COWP-based PCR-RFLP	261
Uganda	Diarrheal children	444	*C. hominis* and *C. parvum* (18)	COWP-based PCR-RFLP	262
Americas					
Brazil	HIV^+ patients	26	*C. hominis* and *C. parvum* (1)	SSU rRNA-based PCR-RFLP	105
Argentina	HIV^+ patients	15	*C. hominis* and *C. parvum* (2)	SSU rRNA-based PCR-RFLP	105
Peru	Children	156	*C. hominis* and *C. parvum* (2), *C. canis* and *C. meleagridis* (1)	SSU rRNA-based PCR-RFLP	124
	Children and HIV^+ patients	55	*C. hominis* and *C. meleagridis* (7)	SSU rRNA-based PCR and MLST	147

[a]HIV^+, HIV positive; DHFR, dihydrofolate reductase; COWP, *Cryptosporidium* oocyst wall protein gene.

the subtype level, as multiple episodes of *C. hominis* infection in children were more likely to be caused by different subtype families in a longitudinal birth cohort study conducted in Peru (124). Similar findings were obtained in another birth cohort study in Bangladesh; although four children experienced repeated infections with *C. hominis*, subtyping analysis revealed that they were caused by heterogeneous subtypes (29).

As one of the risk factors involved in the acquisition of cryptosporidiosis is contact with *Cryptosporidium*-positive patients, secondary transmission of *Cryptosporidium* spp. in households is expected (33, 182). One case-control study of *Cryptosporidium*-infected children and their family members in Bangladesh demonstrated that the secondary infection rates were 35.8% (19/53) in urban case families and 7.8% (5/64) in rural case families. This was confirmed by results of subtype analysis of the *C. hominis* and *C. parvum* involved (25). The differences in rates of secondary transmission between the urban and rural study sites were attributed to differences in the dominant *Cryptosporidium* species (*C. hominis* versus *C. meleagridis*) and transmission routes (anthroponotic versus zoonotic) in the two communities. *Cryptosporidium meleagridis* appears to be less infectious than *C. hominis* (25). In a multicountry study conducted in sub-Saharan Africa, identical *gp60* subtypes of *C. parvum* or *C. hominis* were detected among two or more contacts in 36% of the 108 initial *Cryptosporidium*-positive cases followed, indicating a common occurrence of secondary transmission of *Cryptosporidium* spp. (33). Among them, the *C. hominis* subtype IeA11G3T3 was involved in a cluster that

lasted over 32 days with 13 infected subjects in two neighboring households, while the *C. hominis* subtype IfA14G1 was detected in a cluster that lasted over 18 days with 11 infected subjects in two neighboring households.

CRYPTOSPORIDIUM GENETICS AND VIRULENCE

The clinical implications of different *Cryptosporidium* species and subtypes in humans are not yet clear. Studies of genotyping analyses indicated that *C. hominis* and *C. parvum* likely behaved differently in humans, with the former causing more severe clinical manifestations (183). Earlier studies in urban slums in Peru and Brazil found that children infected with *C. hominis* had higher oocyst shedding intensity and longer duration than those infected with *C. parvum* and other species (124, 184, 185). Similar results were also obtained in immunocompromised patients in India (50). Children infected with *C. hominis* showed significantly more severe diarrhea than those infected with other species in South India (186). In one pediatric study in Kuwait, *C. hominis* infections showed more severe fever and diarrhea than *C. parvum* infections (121). In a study conducted in Ethiopia, AIDS patients with *C. hominis* infections had both diarrhea and vomiting, while those with *C. parvum* infections had only diarrhea (67). Similarly, in immunocompromised patients in India, nausea and vomiting were more frequently found in *C. hominis* infections than in *C. parvum* infections (50). *Cryptosporidium hominis* also appears to be more virulent than *C. meleagridis*. In a study conducted in two communities in Bangladesh, diarrhea was present in approximately 30% of *C. hominis* infections but nearly absent in *C. meleagridis* infections (10).

Due to the differences in pathogenicity, *C. hominis* infection is expected to have more deleterious nutritional effects on infected children than *C. parvum* infection. In Brazil, in children under 3 months, the height-for-age Z scores (HAZ) showed significant declines with infection of *C. hominis* or *C. parvum*, but in children of 3 to 6 months following infections, only *C. hominis*-infected children showed continuous decline in HAZ scores, especially for asymptomatic infections (185). Similar results have also been found in children in India, where most infections were caused by *C. hominis*, and children with sequential infections had significantly lower HAZ scores and long-term effects on growth (16). In Sonora, Mexico, malnutrition was significantly associated with *Cryptosporidium* infection, especially for *C. hominis* (122). In one recent birth cohort study conducted in two areas in Bangladesh, however, although the dominant *Cryptosporidium* species were different between urban (*C. hominis*) and rural (*C. meleagridis*) areas, they had similar effects on HAZ scores and child growth (10).

Even within the same *Cryptosporidium* species, the clinical manifestations of cryptosporidiosis can differ among subtypes. In Peruvian children infected with *C. hominis*, IbA10G2 was associated with diarrhea, nausea, vomiting, and general malaise, while other subtypes were associated only with diarrhea (124). This indicates that IbA10G2 is likely more virulent than other subtypes in *C. hominis*. This is partially support by the fact that almost all autochthonous *C. hominis* infections in Europe are caused by this subtype (187). In India, most cases with subtype Ib had vomiting and/or appetite loss, while all cases with Ia and Id showed chronic diarrhea (32). Differences in the severity of diarrhea have also been found between Ia and Id subtype families of *C. hominis* (77, 121).

To understand the differences in clinical symptoms and pathogenicity among *C. hominis* subtype families, population genetics and comparative genomics analyses have been used in the characterization of isolates. In Peru, genetic recombination was identified in the virulent subtype IbA10G2 by using comparative sequence analysis of 53 isolates at 32 genetic loci across chromosome 6. Using linkage disequilibrium and recombination analyses, limited genetic recombination was identified exclusively in the *gp60* gene of IbA10G2, a major subtype responsible for the outbreaks of human cryptosporidiosis in industrialized nations. Intensive transmission of the virulent subtype IbA10G2 possibly had led to genetic recombination with other subtypes. In addition, selection for the IbA10G2 type sequence was detected in a 129-kb region around the *gp60* gene, which had led to reduced sequence variation within the 129-kb region

in the IbA10G2 subtype, reflecting the possible involvement of the gene or other linked genes in pathogenicity (188). This was supported by comparative genomics analysis of IbA10G2 isolates and other *C. hominis* subtypes in the United States, which revealed the occurrence of genetic recombination in IbA10G2 at the 5′ and 3′ ends of chromosome 6 and in the *gp60* region, indicating that genetic recombination likely contributed to the emergence of these hypertransmissible subtypes (189). Comparative genomics analysis of the virulent IbA10G2 and other *C. hominis* subtypes in Europe has identified a loss-of-function mutation in the gene (*cgd6_210*) encoding COWP9 in chromosome 6 in all subtypes except IbA10G2. As expected, phylogenetic analysis of IbA10G2 and other *C. hominis* subtypes based on 743 coding sequences indicated that all the IbA10G2 genomes formed a unique clade in spite of the existence of some heterogeneity among the IbA10G2 isolates (190). Genetic recombination in *C. hominis* appears to be more common in low- and middle-income countries. A comparative genomics analysis of 32 *C. hominis* isolates from a longitudinal cohort study of children in a Bangladeshi community identified high rates of genetic recombination in the genomes, with the area around the *gp60* gene being one of the seven highly polymorphic regions. Genetic recombination was confirmed by the decay of linkage disequilibrium in the *C. hominis* genome over <300 bp. Because of the common occurrence of genetic recombination, the relatedness of *C. hominis* genomes was not segregated by *gp60* subtype (29). More *Cryptosporidium* species and subtypes should be sequenced to better understand the population structure and genetic determinants of virulence and high transmissibility in some *Cryptosporidium* species and subtypes (85, 191).

IMPLICATIONS FOR WASH (WATER, SANITATION, AND HYGIENE)-BASED INTERVENTION OF CRYPTOSPORIDIOSIS IN LOW- AND MIDDLE-INCOME COUNTRIES

The results of molecular epidemiological studies suggest that anthroponotic transmission plays a major role in the transmission of *Cryptosporidium* spp. in humans in low- and middle-income countries (103). Since cryptosporidiosis in these countries occurs mostly in children under 2 years (2–4), targeted intervention should be implemented to control the occurrence of cryptosporidiosis in this population. This intervention should be implemented regardless of the occurrence of diarrhea and other clinical symptoms, as subclinical cryptosporidiosis can induce malnutrition and growth retardation (10).

Water, sanitation, and hygiene (WASH)-based interventions have been used effectively in the prevention and control of diarrheal diseases (192). WASH is a collection of integrated prevention and control strategies for infectious diseases which aim to improve the provision of water (e.g., safe water source), sanitation (e.g., clean toilets), and hygiene (e.g., frequent handwashing) (193–195). Application of the WASH-based interventions, such as clean drinking water, toilets for sanitation, and handwashing with soaps for hygiene, can reduce the occurrence of diarrhea and thus has been recommended as a measure to interrupt the environmental transmission of enteric pathogens such as *Cryptosporidium* spp. (48, 196–199). It is estimated that WASH intervention can reduce infections with diarrhea by 15 to 50%, and up to 40% nonemergency cases can be eliminated by handwashing with soaps (200–202). In children less than 5 years in low-income countries, application of WASH interventions has led to a 27 to 56% reduction in diarrhea occurrence (203, 204). Among them, handwashing appears to be the most effective long-term WASH intervention (205). It has been shown to reduce the occurrence of giardiasis in young children in rural Bangladesh (206).

WASH-based interventions may be effective against cryptosporidiosis in low- and middle-income countries (81). The risk factors associated with cryptosporidiosis occurrence, including poor hygiene, unclean drinking water, open defecation, overcrowding, and diarrhea in household (66), are key targets of WASH interventions. Therefore, good personal hygiene practices are known to reduce the transmission of *Cryptosporidium* spp. and other intestinal parasites in children (207). This is further supported by the negative correlation between the occurrence of the *C. parvum* IIc subtype family in

HIV-positive individuals and the percentage of the population with access to improved sanitation (126). The use of a point-of-use drinking water filter was shown recently to reduce the occurrence of *Cryptosporidium* infection in children in Rwanda (208).

FUTURE PERSPECTIVES

Data from molecular epidemiological studies of human cryptosporidiosis have significantly improved our understanding of the transmission of *Cryptosporidium* spp. in low- and middle-income countries. We now have a better understanding of the infection sources of *Cryptosporidium* spp. in children and immunocompromised persons. We also have a better appreciation of the role of endemicity of cryptosporidiosis in the genetic diversity of *Cryptosporidium* spp., concurrence of multiple *Cryptosporidium* species, and multiple episodes of infections. The eminent association between cryptosporidiosis occurrence and poor hygiene has made WASH (water, sanitation, and hygiene)-based interventions an economical intervention measure against cryptosporidiosis in low- and middle-income countries.

The number of molecular epidemiological studies of cryptosporidiosis conducted in low- and middle-income countries is small, considering the fact that the disease exerts its highest toll there. Most of the data on the distribution of *Cryptosporidium* species and *C. parvum* and *C. hominis* subtypes in humans in low- and middle-income settings have been generated from only a handful countries in Asia and South America by established research groups. As a result, our understanding of cryptosporidiosis epidemiology may be skewed by the underrepresentation of low-income countries where *Cryptosporidium* transmission is most intensive and risk factors for infections might be different (66). We have yet to take advantage of the recent large scale of global disease burden and mortality studies through genetic characterizations of *Cryptosporidium* spp. from these well-designed epidemiological investigations (6, 31). As molecular characterizations of specimens from longitudinal birth cohort studies have provided a wealth of data on the development of species- and subtype-specific immunity, differences in the virulence of *Cryptosporidium* species and subtypes, and intrafamilial transmission of *Cryptosporidium* spp. (9, 10, 29, 42, 124), these studies should be expanded to African nations. We also need to assess vigorously the effectiveness of existing WASH-based interventions for the prevention and control of cryptosporidiosis in humans in low- and middle-income countries (192, 209, 210). Improved hygiene education is urgently needed to enable longer lasting and improved WASH behaviors (211–214). As cryptosporidiosis is a major cause of malnutrition, the development and assessment of nutritional interventions are also urgently needed (72, 206).

The application of advanced molecular tools such as comparative genomics analyses could increase significantly the depth of research in molecular epidemiology of human cryptosporidiosis. The development of procedures for whole-genome sequencing of *Cryptosporidium* spp. in clinical specimens without pathogen isolation and passage in laboratory animals has increased the availability of whole-genome sequence data from major human-pathogenic *Cryptosporidium* species. Comparative analyses of these data have begun to shed light on the genetic determinants for host adaptation in some common *C. parvum* subtype families and the high virulence in some *C. hominis* subtype families. These studies have identified genetic recombination as the driving force for the emergence of host-adapted and virulent subtypes (85, 191, 215). Thus far, the number of comparative genomics studies has only been small in low- and middle-income countries (29).

The recent development of genetic manipulation tools for *Cryptosporidium* spp. promotes the identification and validation of new drug targets and development of new interventions against cryptosporidiosis (216, 217). Thus far, nitazoxanide remains the only drug approved by the U.S. Food and Drug Administration for treating cryptosporidiosis (218). With the application of CRISPR/Cas9 techniques, one *Cryptosporidium* PI (4)K inhibitor was identified as a candidate drug against cryptosporidiosis (219). Another study applying the CRISPR/Cas9 tool showed that *C. parvum* salvages purine nucleotides through a single pathway, providing another target for the development of treatments

for this pathogen (220). Comprehensive studies combining genetic, biochemical, and chemical techniques indicated that bicyclic azetidines can kill *C. parvum* in mice by inhibiting the phenylalanyl-tRNA synthetase of parasites (221). The identification of these new targets should greatly facilitate the development of new drugs against cryptosporidiosis. The recent development of genetic tagging and conditional protein degradation systems might also facilitate studies on the genetic determinants of virulence in *C. hominis* and the identification of vaccine candidates in the *Cryptosporidium* proteome (222, 223).

Understanding the reasons for the dominance of *C. parvum* in humans and the common occurrence of its zoonotic subtype families IIa and IId in some areas would require the use of the "one health" approach. Thus far, the transmission of *C. parvum* IIa and IId subtypes in the Middle East and some other Muslim countries is poorly understood. This is largely due to the lack of genetic characterization of *Cryptosporidium* spp. in farm animals, especially ruminants, in these areas. Systematic sampling of both humans and ruminants in the same area, comparative analysis of *C. parvum* subtypes from humans and animals residing in the same households, and genotyping and subtyping of *Cryptosporidium* spp. in drinking source water would shed light on the infection sources and transmission routes of *C. parvum* in these areas. This would require collaboration among public health researchers, veterinarians, and environmental scientists, which has been advocated as a new measure for the prevention and control of zoonotic cryptosporidiosis (224–226).

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