Prevalence and risk factors for cryptosporidiosis: Aglobal, emerging, neglected zoonosis

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Review article

Prevalence and risk factors for cryptosporidiosis: a global, emerging, neglected zoonosis

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Background: Cryptosporidiosis is a zoonotic disease caused by the important parasitic diarrheal agent *Cryptosporidium* spp. Cryptosporidiosis occurs in all classes of animals and man with a rapidly expanding host range and increased importance since the occurrence of human immunodeficiency virus/acquired immunodeficiency syndrome in man.
Objectives: To review the global picture of cryptosporidiosis in man and animals with emphasis on prevalence and risk factors.
Methods: Current relevant literature on cryptosporidiosis was reviewed.
Results: Cryptosporidiosis is widely distributed and the risk factors vary from one region to another with hygiene and immune status as important risk factors.
Conclusions: *Cryptosporidium* spp. associated mortality has not only been reported in immune-compromised patients, but also in immune-competent patients. Yet in many countries not much attention is paid to the control and prevention of this infection in animals and man. The neglect of this disease despite the serious threat it poses to animals, their husbandry, and humans, has led the World Health Organization to list it among globally neglected diseases. To control and prevent this infection more effort needs to be directed at controlling the risk factors of the infection in man and animals.

Keywords: Human and animal husbandry, cryptosporidiosis, neglected zoonosis

Cryptosporidiosis is a parasitic zoonotic disease affecting all terrestrial and most aquatic animals caused by 26 validated species (18 other species are not yet considered validated) of the genus *Cryptosporidium*. They are obligate intracellular parasites of man and animals on all continents except Antarctica. Cryptosporidiosis ranks 5th among the 24 most important food borne parasites globally [1-9]. There are 40 genotypes that have not yet been classified [7, 9]. *Cryptosporidium* species (spp.) are considered one of the most important parasitic diarrheal agents globally [10]. The disease usually manifests as a self-limiting diarrhea in immune-competent individuals, and as a progressively life-threatening diarrhea in immune-compromised patients such as those with human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), the young and the elderly; individuals undergoing cancer chemotherapy, and any other condition that compromises the immune system including simple malnutrition. The infection is increasingly becoming associated with travel [11]. The size of the inoculum does not have any apparent effect on the severity and duration of disease. As few as 10 oocysts are capable of causing severe infection with only partial immunity acquired after 2 weeks recovery from primary infection and rechallenge with the same organism [12].

A specific treatment has not yet been developed for cryptosporidiosis in man and animals, but nitazoxanide (Alinia) has shown encouraging results [13] and has been approved by the U.S. FDA for the treatment of cryptosporidiosis. Nitazoxanide has as yet not become generally available worldwide. However, effects of nitazoxanide in HIV/AIDS or immune-deficient patients are not any better than a placebo for treating cryptosporidiosis [9]. Paromomycin and other antibiotics such as spiramycin have been used, but their efficacy is in doubt [14]. Fortunately, cryptosporidiosis is a self-limited disease in healthy adults, and can be expected to subside with conservative measures and dietary manipulation.

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Despite the seemingly ubiquitous nature of cryptosporidiosis, sufficient attention has not been paid to it, prompting the WHO in 2004 to list it among globally "neglected diseases" which have a common link with poverty in most developing countries [15]. It can be deadly in malnourished or immune compromised individuals; particularly in under-developed countries with an HIV/AIDS endemic not able to manage a severely afflicted patient with sophisticated nutritional support until treating the primary underlying problem takes effect. This article highlights the global distribution, prevalence and risk factors of this ubiquitous parasite with special reference to Asia, and presents its neglected status around the world.

Cryptosporidium spp. belong to the Kingdom of Protozoa; phylum Apicomplexa; class Conoidasida; order Eucoccidiorida; Family Cryptosporidiidae, and Genus *Cryptosporidium* [16]. In 1895, Clarke reported parasitic forms that he described as "swarm spores lying upon the gastric epithelium of mice" [17], which may have been *Cryptosporidium muris*, which were later described by the renowned American parasitologist, E. E. Tyzzer as "a sporozoan found in the peptic glands of the common mouse" in 1907 [18]. Today, several species of *Cryptosporidium* have been described. They include *C. hominis, C. parvum, C.felis, C. andersoni, C. suis, C. canis, C. meleagridis, C. molnari, C. scophthalmi, C. scrofarum, C. bovis*, and *C. xiaoi*, infecting most species of animals and man [10, 19-22]. One of the latest species with probable worldwide distribution was initially named *C. cervine* genotype and infrequently as cervid, W4, or genotype 3. It is now recognized as a distinct species *C. ubiquitum* [23]. The advent of molecular biology and its methods has helped to identify and classify many species of *Cryptosporidium* spp., a rapid progress from the initial single species identified in 1907. The complete list of validated *Cryptosporidium* spp. based on morphological, biological, and molecular data of 2014 is shown in **Table 1**.

Table 1. Validated species of *Cryptosporidium*

S/No.	Species of *Cryptosporidium*	Major hosts	Zoonotic status	Reference
1.	*C. andersoni*	Cattle	Yes	[24]
2.	*C. baileyi*	Birds	No	[25, 26]
3.	*C. bovis*	Cattle	Yes	[27]
4.	*C. canis*	Dogs	Yes	[28]
5.	*C. cuniculus*	Rabbits	Yes	[29, 30]
6.	*C. erinacei*	Hedgehogs and horses	Yes	[31]
7.	*C. fayeri*	Marsupials	Yes	[32]
8.	*C. felis*	Cats	Yes	[33]
9.	*C. fragile*	Toads	No	[34]
10.	*C. galli*	Birds	No	[35]
11.	*C. hominis*	Humans	Most common species in humans	[36]
12.	*C. macropodum*	Marsupials	No	[37]
13.	*C. meleagridis*	Humans and birds	Yes	[4, 38]
14.	*C. molnari*	Fish	No	[39, 40]
15.	*C. muris*	Rodents	Yes	[41]
16.	*C. parvum*	Ruminants	Yes	[42]
17.	*C. ryanae*	Cattle	No	[43]
18.	*C. scrofarum*	Pigs	Yes	[44]
19.	*C. serpentis*	Snakes and lizards	No	[45, 46]
20.	*C. suis*	Pigs	Yes	[47]
21.	*C. tyzzeri*	Rodents	Yes	[48]
22.	*C. ubiquitum*	Primates, ruminants, and rodents	Yes	[49]
23	*C. varanii*	Lizards	No	[50]
24.	*C. viatorum*	Humans	Less common species in humans	[51]
25.	*C. wrairi*	Guinea pigs	No	[52]
26.	*C. xiaoi*	Sheep and goats	Yes	[53]

The following 18 species proposed by some researchers have not been validated: *C. crotali*, *C. vulpis*, *C. baikalika*, *C. ctenosauris*, *C. lampropeltis*, *C. amievae*, *C. agni*, *C. anserinum*, *C. rhesi*, *C. garnhami*, *C. nasorum*, *C. enteriditis*, *C. villithecum*, *C. curyi*, *C. saurophilum*, *C. scophthalmi*, *C. pestis*, and *C. ducismarci* [9].

The life-cycle of *Cryptosporidium* spp. is mostly similar to that of other coccidia (e.g. *Eimeria* and *Isospora*) affecting mammals and divided into 6 stages:

1. Excystation, which involves the release of infective sporozoites;
2. Merogony, which is the asexual multiplication that takes place within the cells of the host;
3. Gametogony, which is the formation of microgametes and macrogametes;
4. Fertilization, which is the fusion of the microgametes and macrogametes;
5. Oocyst wall formation, which is needed to form an environmentally resistant stage responsible for transmission of infection from one host to another; and
6. Sporogony, which is responsible for the formation of infective sporozoites within the oocyst wall.

An important distinction in the life-cycle of *Cryptosporidium* spp. is that each intracellular stage of *Cryptosporidium* spp. resides within a parasitophorous vacuole located in the microvillous region of the host cell, but that of *Eimeria* and *Isospora* are usually found in parasitophorous vacuoles perinuclear within the host cells. The oocysts of *Cryptosporidium* spp. undergo sporogony within the host cells releasing already infective sporozoites in the feces, whereas oocysts of other coccidia need optimum environmental conditions to sporulate and become infective [54]. The sporulated oocysts of *Cryptosporidium* spp. containing 4 sporozoites are excreted in the feces and perhaps other routes such as respiratory secretions especially in birds and children that may suffer from respiratory cryptosporidiosis [55, 56].

Human cryptosporidiosis

Accurate data on human cases of cryptosporidiosis are lacking from many countries where it is underdiagnosed and underreported. In recent years cryptosporidiosis has been found to not only affect the gastrointestinal tract, but also cause respiratory symptoms in man [6]. Probably the most famous outbreak of cryptosporidiosis was the outbreak in Milwaukee, USA, in 1993 that affected about 403,000 people, showing symptoms such as vomiting, watery diarrhea, stomach cramps, and fever [57]. The water treatment plant in Milwaukee was implicated in the outbreak in which there was a 100 fold increase in isolation of *Cryptosporidium* spp. compared with other enteric pathogens with a median duration of, supportive treatment, and an illness of 9 (range, 1–55) days. The Milwaukee outbreak could have been averted by possibly reducing delays in identifying and publicizing the known risk [58]. Different studies have shown the limitation of normal filters and standard water processing procedures in controlling *Cryptosporidium* spp. because of their minute size and high resistance to normal methods and agents to purify water for human consumption [59-62]. Outbreaks in health facilities, such as hospitals, have also been reported [63].

Prevalence and risk factors

Africa

Young children are in some of the most high risk groups for cryptosporidiosis in various African countries. The overall prevalence of cryptosporidiosis in children aged 0 to 15 years in the arid region of Borno State, Nigeria was reported to be 42.9% [1]. The children were found to be exposed to the infection through unhygienic environments and use of contaminated water facilities. It is generally known that undernourished and HIV seropositive children are more likely to have cryptosporidiosis than well-nourished normal host children. However in Jos, Nigeria; it was found that none of a group of HIV positive and undernourished children excreted oocysts in their faeces. However, 3.8% of children aged 0–5 years in a control group, consisting of HIV seronegative children, excreted oocysts in their stool [64]. This finding is important and suggests that children are easily infected by oocysts irrespective of their HIV status, and may remain relatively asymptomatic. The public health implications of this infection are further complicated by possible contamination of vegetables and other food items by oocysts. This can have serious implications for a country with a considerable number of immunocompromised HIV/AIDS patients and others with suppressed immunity [65]. The presence of various parasites in vegetables is a problem worldwide [66]. Socioenvironmental predictors of cryptosporidiosis in two communities in Nigeria include: presence of younger children in community (odds ratio (OR) = 1.889, $P < 0.0001$, 95% confidence interval (CI) = 1.568–2.274), presence of diarrhea (OR = 2.66, $P < 0.0001$, 95% CI = 1.733–4.100), younger age group (OR = 1.283, $P = 0.004$, 95% CI = 1.085–1.520), married status (OR = 2.463, $P = 0.028$, 95% CI = 1.100–5.513), lack of formal education (OR = 2.993, $P < 0.0001$,95% CI = 1.872–4.786), and farming occupation (OR = 1.392, $P = 0.002$, 95% CI = 1.135– 1.703). Regular hand washing (OR = 0.399, $P < 0.0001$, 95% CI = 0.283–0.535) was protective [67].

A study of 442 stool samples from children aged <5 years found a prevalence of 12.2% from 4 provinces in South Africa. It included a first report from South Africa of a *Cryptosporidium* sp. rarely reported in humans, *C. meleagridis*. This implies a tendency towards expanding hosts by different species of this parasite [68].

In most African countries the high poverty level, coupled with relatively high HIV prevalence rates, has made cryptosporidiosis an important public health problem. Economic burdens and poor sanitary facilities have helped the infection to continue spreading among the population. This apparent neglect of attention to this important emerging zoonotic disease, suggests that microscopic diagnosis is often missed because technicians search first, and often only, for better known other diarrhea-causing parasites.

Asia

Cryptosporidiosis cases have been reported in Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. In Bangkok, among the *Cryptosporidium* spp. that have been isolated from HIV patients are *C. parvum*, *C. hominis*, *C. meleagridis*, *C. canis*, *C. felis*, *C. muris*, and *C. parvum* bovine genotype 5 [69, 70, 71]. However, in Malaysia, *C. parvum* were found to be rare in the past [72], but have become common recently being 84.3% of *Cryptosporidium* spp. isolates [73]. This may show that the parasite is adapting to infecting many more hosts or that diagnosis and identification technology is improving.

Cryptosporidiosis is widespread in Southeast Asia in both humans and animals [74]. For instance, in Thailand, a study revealed that 11% and 6% of river and ocean water collected from various locations in Thailand were contaminated with *Cryptosporidium* spp. [75]. In a comparative study of water contamination in Malaysia and Thailand, it was shown that recreational water in Malaysia was more significantly contaminated with *Cryptosporidium* spp. oocysts than in Thailand [76]. A team of researchers from Kuala Lumpur National Zoo reported the presence of a coccidian parasite among birds. They postulated that the birds may appear asymptomatic and become vectors of *Cryptosporidium* spp. oocysts [77]. Viability and infectivity of *Cryptosporidium* spp. is retained after passage through an avian host and is quite resilient in the environment [78].

In India, a study found that both HIV and non-HIV patients attending a hospital had a prevalence of 38.60% and 2.52% respectively, showing a high prevalence in HIV patients [79]. Among the HIV patients 20.8% had an infection with *Cryptosporidium*. Cryptosporidiosis was also common in patients undergoing renal transplants. *C. hominis*, *C. parvum*, and mixed infections were detected in 50/71 (70.4%), and this was associated with higher stool frequency and a watery stool. A high parasite loads, vomiting and nausea was more frequently associated with *C. hominis* than with *C. parvum* [80]. In the rural areas of Bangladesh, calf handlers showed a prevalence of 3.2% for *Cryptosporidium* spp. [81].

Cryptosporidiosis in Asia appears to be associated with urbanization and rapid increase of population. Water sources are insufficient and not well maintained and open to contamination by animals and birds [21].

The Americas

The importance of contaminated vegetables as a risk factor for cryptosporidiosis was demonstrated by a study in Costa Rica. It consisted of 640 samples from 8 different vegetables normally consumed raw. They were analyzed for the presence of *Cryptosporidium* oocysts, fecal coliforms, and *Escherichia coli*. The study found that whereas *Cryptosporidium* oocysts were absent in cabbage, they were found in 5.0% (4 samples) of cilantro (coriander) leaves, 8.7% (7 samples), of cilantro roots, and 2.5% (2 samples) of lettuce. A 1.2% contamination rate was detected in samples of other vegetables (radish, tomato, cucumbers, and carrot) with a greater percentage of oocysts found during the rainy season; but only in cilantro leaves and lettuce. Positive linear correlation was established between the presence of oocysts of *Cryptosporidium* and fecal coliforms and *E. coli* [82]. This is a major concern considering the increasing number of immune-compromised individuals in this developing country and the neglect of the threat of cryptosporidiosis in food used for human consumption. Some other food items like milk may also be infected with viable oocysts, but the simple process of pasteurization of milk has long been shown to be sufficient to inactivate oocysts [83]. The process of cooking food and boiling water has long been shown to destroy oocysts and prevent infection [84].

The USA continued to battle elevated incidence rates for cryptosporidiosis nationally with a total of 9,313 and 8,008 cases reported in 2011 and 2012 respectively; with children aged 1–4 years having the highest number reported cases (6.6 per 100,000 population). Next most frequently infected were the elderly, aged ≥80 years (3.4 per 100,000), and 75–79 years (3.3 per 100,000); with women having higher cryptosporidiosis rates in both age groups than men. However, rates were higher among boys <15 years old and higher among women and girls ≥15 years old [41]. Sex is usually not significantly associated with cryptosporidiosis infection [85-87].

People in Brazil and other countries in South America suffer from cryptosporidiosis; especially children and the immunocompromised. Children with diarrheal episodes because of Cryptosporidia continued to suffer from excessive and protracted diarrheal illness for about 2 years. Children in Brazil, who had no *Cryptosporidium* induced diarrhea soon after birth, did not show further increased diarrheal illnesses [88]. *Cryptosporidium* infection was found to cause stunted growth of children. Presumably because of the protracted periods of persistent diarrhea. This is particularly important because of the lack or poor efficacy of currently available drugs. Children in densely populated or crowded suburbs were at greater risk of symptomatic infection. It was found that *Cryptosporidium* oocysts were identified in 7.4% and more frequently in children with consistent diarrhea (16.5%), than in those with acute (8.4%) or no (4.0%) diarrhea ($P < 0.001$) [89].

Europe

According to the European Centre for Disease Prevention and Control (ECDC), there was an unprecedented increase in cryptosporidiosis in the United Kingdom, The Netherlands, and Germany in late summer/autumn of 2012. In the same year, 2173 cases of cryptosporidiosis were reported in England and Wales, which was 1.5 fold higher than in the previous year and is the greatest since 2003. The most commonly isolated *Cryptosporidium* sp. was *C. hominis*. Although the number of cases reported in Germany is lower than in England, it was a 1.6 fold increased since 2007 [90].

The suggested reasons for this increase include climatic changes, such as heavy rainfall, contaminated drinking water, and better reporting. Nevertheless, there was no direct evidence of secondary transmission from parents to children. Moreover, specific causes of *Cryptosporidium* spp. infection were not identified, despite case interviews.

The prevalence of Cryptosporidia in Northern Spain was on average 1% in children and 3% in cattle [91]. The virtually simultaneous presentation of infection in both humans and animals gives credence to the assertion of this being a zoonotic disease.

In Ostersund, Sweden in November 2010, about 45% of the inhabitants were affected by cryptosporidiosis caused by *C. hominis* from contaminated public water supply [36]; similar to the Milwaukee outbreak of 1993 in the USA. The outbreak was characterized by rapid onset of symptoms and high attack rate, especially among young and middle aged persons. Identified risk factors where: family member, amount of water consumed daily, and gluten intolerance. The exact amount of pathogen needed to trigger a water borne infection is still unknown, but is likely to be low.

Australia

In Western Australia in 2012, there were 18 notified cases of human cryptosporidiosis through contamination of a swimming pool with viable oocysts [22].

In 2001, an outbreak of cryptosporidiosis in Northern Tasmania was highly associated with human exposure to cattle. Within one month, there were 48 cases of cryptosporidiosis reported with high prevalence seen among people who attended an agricultural fair [92]. In New South Wales, 1141 people became infected with *Cryptosporidium* spp. in 2009 because of contaminated public swimming pools [93].

Prevalence rates of cryptosporidiosis in Australia are a major public health problem and higher than in other developed countries. Although cryptosporidiosis was also associated with rainfall, cases of it have been reported to occur in hot and dry areas like Brisbane.

In rural areas, cases of cryptosporidiosis are related to a high density of cattle [94]. The most important *Cryptosporidium* spp. identified in humans in Australia include: *C. hominis*, *C. parvum*, *C. meleagridis*, *C. fayeri*, *C. andersoni*, and *C. bovis* [7].

Animal cryptosporidiosis

Cryptosporidiosis has been reported from different species of animals worldwide. These include fish, reptiles, mammals, and birds with varying prevalence rates and sometimes seasonal fluctuations. The economic impact of cryptosporidiosis in livestock is becoming clearer with more studies showing it has significant economic impact with clinical signs that may vary from symptomatic to deadly [95]. Cryptosporidiosis has been shown to have negative effects on animal live weights, growth rates, meat quality and dressing percentage in lamb [96]. Moreover, infection leads to economic losses resulting from retarded growth of animals, mortality of animals, and increase in labor and veterinary care assistance, even after the recovery of animals [95].

Prevalence and risk factors

Africa

Cryptosporidiosis has been reported in birds in Zaria, Nigeria with a prevalence of 5.3% in wild birds, 6.6% in exotic birds, 9.5% in local birds, and an overall prevalence in birds of 7.4%. The ease of contact with oocysts by kept birds. Scavenged feed was one of the main reasons given for the possible higher prevalence of oocysts [2]. *Cryptosporidium* spp. were found in water buffaloes in Egypt using modified Ziehl–Neelsen staining and DNA sequencing of the small subunit rRNA. *C. parvum* and *C. ryanae* were found the predominant species with *C. ryanae* being most prominent. This suggests that in water buffaloes this new species, *C. ryanae* may be more important than *C. bovis* and *C. andersoni* [97]. *Cryptosporidium* spp. infection has been reported in animals from different regions and countries in Africa with varying prevalence rates and risk to man. The widespread distribution of the infection in both domestic and wild animals is of public health concern and its presence in water bodies, such as rivers, ponds and other water sources used by both animals and humans implies that the infection can be easily spread [10, 98-101].

Asia

Iran

A study in Iran demonstrated the importance of considering cryptosporidiosis as a differential diagnosis in infections of lambs and goat kids by showing a significant infection of cryptosporidiosis according to age groups; with the highest rate of infection found in animals 1 month of age. Diarrheic fecal samples had a significantly higher prevalence than the nondiarrheic samples. Overall prevalence of cryptosporidium oocysts was 10.24% and 18.86% in lambs and kids respectively [102]. The importance of wild rats as reservoirs of *C. parvum* was shown in a study in Iran where 27.3% of rats were positive for *C. parvum* using nested polymerase chain reaction (PCR); highlighting the public health implications of this infection in areas where there is contact between humans and rats [103]. In another study, the prevalence of *Cryptosporidium* spp. in sheep in different regions of Iran was 11.3% with significant difference in prevalence based on age and sex [104].

Malaysia

In a study of cryptosporidiosis in Malaysia, a case fatality of 40% was reported in a dairy farm where inadequate nutrition and lack of hygiene were implicated in the occurrence [105]. Among domestic animals, dairy cattle are one of the most prone to cryptosporidiosis [19, 106, 107]. In another more recent study in Malaysia, a prevalence of 3.2% was reported for asymptomatic *Cryptosporidium* spp. infection in cattle with *C. bovis* and *C. ryanae* reported in 4 out of 6 farms studied [108].

China

The first description and report of *C. andersoni* in horses in 2015 was from China. This has expanded the host range for this species and showed possibility of cross transmission of this species between cattle and horses especially when grazed together [109]. In a study on avian cryptosporidiosis, 2579 fecal samples were collected from 21 prefectures in Henan, China. The overall infection rate was 10.6% (163/1542) in layer chickens (10 out of 17 farms), 3.4% (16/473) in broilers (five out of 29 farms), and 16.3% (92/564) in Peking ducks (4 out of 8 farms), respectively. The highest prevalence rates were seen in 31-day-old to 60-day-old layer chickens (24.6%) and 11-day-old to 30-day-old Peking ducks (40.3%). *C. baileyi* and *C. meleagridis* were the species identified with

C. baileyi being predominant [110]. This has zoonotic implications because of the closeness of man to poultry and because *C. meleagridis* is the third most common *Cryptosporidium* spp. parasite in humans [111]. Cryptosporidiosis is suspected to be endemic in dogs across China even though only few extensive studies had been conducted. From 84 fecal samples taken from cats, dogs and from waste water of zoo drainage channels, in a study in Shanghai, China, an infection rate of 7% was reported [112]. From 545 fecal samples taken from yaks in nine different counties of central western region of China, the prevalence of *Cryptosporidium* spp. was 4.0% and sequence analysis of the small subunit rRNA (SSU rRNA) gene of the *Cryptosporidium* spp. isolates confirmed the species as *C. parvum* (n = 12), *C. bovis* (n = 6), *C. ryanae* (n = 3), and *C. ubiquitum* (n = 1). These findings may implicate yaks as possibly playing a role in the transmission of zoonotic cryptosporidiosis in China and shows the predominance of *C. parvum* in China over other species [113]. The relatively new species, *C. xiaoi* was the dominant species found in samples taken from 12 goat farms across 4 provinces (Guangdong, Hubei, Shandong, and Shanghai City) with a prevalence ranging from 2.9% to 25.0%. Other species identified were *C. parvum* and *C. ubiquitum* with goat kids more susceptible than adult goats [114].

Myanmar

There is a dearth of literature on the epidemiology of cryptosporidiosis in Myanmar. However, a few studies conducted showed that it is widely distributed in animals where studied. The overall prevalence reported in cattle in the Mandalay region was 56 of 400 cattle. Calves under 6 months had a significantly higher risk of cryptosporidiosis (OR = 2.27, CI = 1.11–4.66, $P = 0.02$). Grazing (OR = 3.78, CI = 2.35–6.06, $P = < 0.001$) and drinking water from a pond or river (OR = 0.25, CI = 0.16–0.37, $P = < 0.001$) were significantly associated with the risk of *Cryptosporidium* spp. infection in cattle [115]. This study confirms already known risk factors for cryptosporidiosis as a life threatening infection in young animals with sporulated oocysts that can contaminate small and large bodies of water [116].

India

India reported varying prevalence of *Cryptosporidium* spp. infection in domestic and wild animals [117]. *Cryptosporidium* spp. infection was associated with hydrocephalus [118]. This raises the question of the possibility of vertical transmission, although some previous investigators have not agreed [119, 120]. However, an experimental study in mice demonstrated vertical transmission of *Cryptosporidium* spp. infection [121]. In a study of prevalence and risk factors associated with young livestock in India, the overall prevalence was 16.2% of the animals studied with *Cryptosporidium* spp. infection prevalence of 16.3% in cattle calves, 24.2% in buffalo calves, 1.8% in lambs, 3.5% in kids, and 19.1% in piglets. Infection was found to be significantly associated with age, sex, season, and diarrhea [122].

Pakistan

There have been several reports of *Cryptosporidium* spp. infections, especially in *Bovine* spp., from different parts of Pakistan. A prevalence of 10.5% in cattle was reported from Lahore on dairy farms run by the Government. It is also higher than on military and private dairy farms. The highest prevalence was during the summer. A higher prevalence was detected using PCR than microscopy, but the difference was not significant [123]. The treatment of calves using azithromycin was effective, but using cotrimoxazole and kalvangi (*Nigella sativa*, also known as black cumin) was ineffective [124]. In another study in Lahore, overall, 25.6% calves were found to be shedding *C. parvum* with a prevalence of 27.2% in cows and 24% in buffalo calves [125]. In small ruminants, a prevalence of 18.7% in goats and 21.3% in sheep has been reported. It was more prevalent (40%) in lambs. Among positive animals, 75% of goats and 71.9% of sheep were having diarrhea. In the same study, 200 water samples were collected for analysis and found 10.5% overall prevalence. Water samples contained 28% *C. parvum* oocysts in canal water, 8% in tap water, and 4% in underground water, whereas no oocyst was found in mineral water bottles, making it the safest source of water for human consumption [126].

Japan

Hedgehogs are popular pets in Japan. But they have been found to harbor two zoonotic *Cryptosporidium* spp.: *C. parvum* and *C. erinacei* (which are known as the hedgehog genotype). In the same study, *Cryptosporidium* horse genotype was identified in a four-toed hedgehog (*Atelerix albiventris*) and *C. serpentis* lizard genotype, in geckos *(Teratoscincus scincus)* by sequencing analysis of partial SSU rRNA and actin genes. This was the first report of *Cryptosporidium* spp. isolates in pet birds in Japan [127]. Murakoshi et al. [128] showed that *C. parvum* 1 (CSpV1), a member of the family *Partitiviridae*, was capable of infection by *C. parvum*.

Thailand

Cryptosporidiosis is widespread and associated with diarrhea among HIV/AIDS patients. In a study of 108 dairy cattle farms in the Nong Pho region of central Thailand, 31.5% of farms were contaminated with *Cryptosporidium* spp. [129]. To estimate the prevalence of cryptosporidiosis in water buffalo in northeast Thailand, 600 samples from 287 farms in 6 provinces were investigated using DMSO-modified acid-fast staining and PCR. Individual animal prevalence was 5.7% and herd level prevalence was 8.7% in provinces located around Sakhon Nakhon in the northern part of the region having the highest prevalence. Farms with more than 5 buffalo had a higher prevalence (30%) compared to farms with 5 or less (16.2%), with *C. parvum* making up 88.2% of infections while the remaining 11.2% of infections were from *C. ryanae* [130]. To determine the spread of the parasites in the Thailand, Koompapong et al. collected fecal samples from seagulls (*Chroicocephalus brunnicephalus* and *Chroicocephalus ridibundus*), domestic pigeons (*Columba liviadomestica*), dogs, and cats from different locations. The results showed *C. meleagridis* in pigeons, *Cryptosporidium* avian genotype III in seagulls, *C. canis* in dogs, and *C. felis* in cats. The prevalence was 2.1% (2/95) for dogs in a Temple and 2.5% (2/80) for cats. This was the first report of *C. meleagridis* in domestic pigeons and *Cryptosporidium* avian genotype III in seagulls [131]. Long-tailed macaques (*Macaca fascicularis*) that reside among human communities in Thailand and come into regular contact with man showed a low prevalence of 1% for *Cryptosporidium* spp. monkey genotype. Although this prevalence is low in monkeys in Thailand, it portends risks of human infection because of frequent human contacts and the low number of oocysts require for human infection [132].

Turkey

Several workers have reported varying prevalence of cryptosporidiosis in Turkey. In one study of 307 calves, *C. parvum* was the only *Cryptosporidium* sp. found using nested PCR to amplify fragments of the *Cryptosporidium* SSU rRNA gene with a prevalence of 3.9% [133]. In the east and southeast of Turkey, using immuno-chromatographic rapid tests, the prevalence of *Cryptosporidium* spp. was 21.8% in diarrheic and healthy calves [134]. The first report of the various subtypes of *C. parvum* in Turkey revealed *C. parvum* IIa (12/13), IId (1/13) subtype family and IIaA15G2R1 (10/13), IIaA16G3R1 (2/13), IIdA15G1 (1/13) subtypes/subgenotypes were seen in cattle while *C. parvum* IIaA15G2R1 (9/10) and HaA16G3R1 (1/10) were determined in calves. *C. parvum* IIaA16G3R1 (2/3) and IIdA15G1 (1/3) were determined in cows. The subtype family of *C. parvum* IIa (8/8) along with the *C. parvum* subtype IIaA15G2R1 (7/8) were regularly seen in diarrheic calves [135]. Various water sources investigated in Turkey, which could be sources of drinking water for humans and animals, revealed 5.2% prevalence for *C. parvum* [136].

Middle East

In the Middle East, *Cryptosporidium* spp. infection is known to be prevalent in domestic and wild animals. In a study in Iraq, the prevalence of *Cryptosporidium* spp. infection was 61% in camels and 56% in the camel breeders [137]. This raises again the important issue of cross transmission of this parasite from animals to humans and from humans to animals. Considering that the camel, known to be hardy against parasitic infections [138, 139], could have this high prevalence in both camels and humans caring for them, shows the hardiness of this protozoan parasite and its ability to adapt and survive in several different hosts.

North America

Cryptosporidiosis has been reported from the USA and Canada from different species of animals including ruminants, birds, marine, and wild animals. The widespread nature of *Cryptosporidium* spp. infecting animals in both developing and developed countries reveals the seeming ubiquitous nature of this parasite. The annual burden of illness attributed to *Cryptosporidium* spp. was 113,344 [140]. Lack of or limited subtyping tools make it difficult to determine the role of zoonotic transmission of

Cryptosporidium chipmunk genotype I, but in a study of *Cryptosporidium* chipmunk genotype I isolates, it was shown to be genetically similar from humans and wild life, suggesting zoonotic transmission may play a role in human infections. Many other reports of cryptosporidiosis in North America are available [141-145].

South America

In a study in Chile, using Ziehl–Neelsen and auramine staining techniques, *Cryptosporidium* spp. infection was present in calves on milk farms with 57.9% of all the animals testing positive with the Ziehl–Neelsen stain, while 55.6% of all the animals turned out positive in the auramine stain test. The McNemar test indicated no significant difference between both diagnostic techniques ($P > 0.05$). The kappa index showed proper concordance between tests ($\kappa = 0.73$) [146]. Colombia first reported *Cryptosporidium* spp. in cats in 2006 and the infection is considered wide spread in various animal species in Colombia [147]. There are several reports of cryptosporidiosis from this region using different methods [148-151].

Europe

Cryptosporidium spp. has been reported from different animals across Europe. Control in livestock farms have been very difficult; especially in dairy cattle farms, which are usually intensively managed. This makes the spread of the infection easy because of increased contact between animals and their droppings, which may contain viable oocysts [152]. A study in roe deer (*Capreolus capreolus*) in Galicia (northwest Spain) two species of *Cryptosporidium* spp. were identified (*C. bovis* and *C. ryanae*) with a prevalence of 4.2% and infection was more in juvenile than adult animals, but the difference was not significant. The mean intensity of infection ranged between 5 and 225 oocysts/g [153].There are several reports of cryptosporidiosis from Europe [152, 154, 155], which should be consulted for detailed information.

Australia

The Australian livestock industry has been known to suffer from cryptosporidiosis caused by many genotypes that are undergoing ongoing study [7]. Different wild and domestic animals have been reported to be infected with *Cryptosporidium* spp. with varying prevalence rates [9, 156]. There was evidence of zoonotic transmission of *Cryptosporidium* spp. between cattle and humans in northern New South Wales [157]. In the Northern Territory of Australia a more recent study reported in 2016 that water buffalo (*Bubalus bubalis*), showed a prevalence of 30% and 12% of *Cryptosporidium* spp. in farmed and wild buffaloes respectively. The species reported were *C. parvum* and *C. bovis* using an 18S quantitative PCR (qPCR) and sequence analysis with *C. parvum* accounting for about 80% of infections in farmed buffaloes and 50% in wild buffalo [158]. In southeastern Australia, a prevalence of 2.8% was reported for *Cryptosporidium* spp. from animals in water catchment areas with 14 unique sequence types for each of pSSU and pgp60, representing *C. hominis*, *C. parvum*, *C. cuniculus* and *C. canis*, *C. fayeri*, *C. macropodum*, and *C. ubiquitum* in addition to six new pSSU sequence types. Nothing appears to be known about the zoonotic potential of the 35 new genotypes recorded for the first time, of *Cryptosporidium* spp. and *Giardia*, which have been associated with *Cryptosporidium* spp. and this will require further studies [159]. The prevalence of the infection in sheep, using quantitative multiplex PCR, in 474 fecal samples from 2 sales yards on 4 occasions and 96 effluent samples, was 6.5% with the zoonotic species *C. parvum* and *C. ubiquitum* accounting for 54.2% of the positive samples [160].

Treatment

Effective treatment of cryptosporidiosis for humans and animals has eluded us for many years. Several drugs and drug combinations such as rifaximin, azithromycin, and paromomycin have been tried against cryptosporidiosis with unsatisfactory or inconsistent and reproducible results. So far the most promising of all anti-cryptosporidial agents, appears to be nitazoxanide, which has been approved for treatment of *Cryptosporidiosis* in humans by the U.S. FDA, but is not yet widely commercially available and awaits larger post marketing reports. Fortunately, most normal human hosts recover with nutritional and supportive therapy. However, cryptosporidiosis still remains a life threatening disease in immune compromised hosts.

Prospects for control and eradication

Controlling *Cryptosporidium* spp. infection is challenging because of the biological features of the parasites, their wide distribution in nature, and that oocysts may remain active in harsh environments and are resilient to common detergents [161]. Chlorine is commonly used in control of harmful microorganisms [162]. However, *Cryptosporidium* spp. are resistant to usual concentrations of 0.2−1 mg/L used in communal drinking water [163, 164]. Sterilization processes using steam, ethylene oxide, Sterrad 100 (Johnson and Johnson, Norderstedt, Germany) and similar technologies can inactivate up to 3 logs or more of *C. parvum*. However, the only liquid disinfectant/sterilant that could do the same is 6% or 7.5% hydrogen peroxide. At lower concentrations or lower exposures, there is a lack of or incomplete inactivation. Other agents such as peracetic acid, sodium hypochlorite, a phenol, a quaternary ammonium compound, 2% glutaraldehyde, and ortho-phthalaldehyde did not completely inactive 3 logs of *C. parvum* [161, 165], chlorine dioxide, ozone (O_3), or ultraviolet light have been used to disinfect drinking water, but this is not generally practical. The ability of *Cryptosporidium* oocysts to remain viable even after 10 h of immersion in glutaraldehyde is a serious cause for concern, especially in hospitals, because endoscopic equipment, which may come in contact with *Cryptosporidium* ssp., cannot be immersed for this long in glutaraldehyde to avoid corrosion [166].

Although water filtration may work, flocculation can clump the fine particulates found in water. Coagulators such as aluminum sulfate, iron (II) sulphate, or iron (III) chloride can be used to neutralize the negatively charged oocysts, thus promoting their coagulation. Sedimentation and filtration provided an effective barrier for *Cryptosporidium* spp. [162]. Instead of using ineffective chemical means of water purification and very difficult filtration processes, there is a new trend towards reverse osmosis, membrane filtration, and electronic/radiation methods [167, 168]. In childcare centers, cryptosporidiosis can be prevented by frequent disinfection using hydrogen peroxide or ammonia. Extra care needs to be taken when handling diapers and toys [161]. In the absence of any viable vaccine against cryptosporidiosis, proper hygiene is paramount for the control and prevention of infection.

Conclusion

Cryptosporidiosis is an emerging global zoonosis that is still poorly understood and largely neglected. Reports are often sporadic or nonexistent. However, there are now enough reliable reports to be concerned. The mechanisms by which *Cryptosporidium* spp. are able to adapt to several hosts and its ability to withstand many adverse conditions is still insufficiently understood and studied. There are no conclusive studies concerning transplacental transmission of oocysts in animals and man despite detection of oocysts in newborn animals. The threat posed by a parasite that is rapidly evolving and expanding its host range should not be underestimated; especially considering that there is still no specific effective therapeutic drug available to cure infection. *C. parvum* appears to be the most important *Cryptosporidium* sp. because of its widespread geographical distribution, the number of animal species affected, and its zoonotic potential. Equally common in humans is *C. hominis*. In the absence of vaccines; proper hygiene, and consumption of food and water free from *Cryptosporidium* oocysts appear to be the only method at present, to prevent infection with cryptosporidiosis.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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